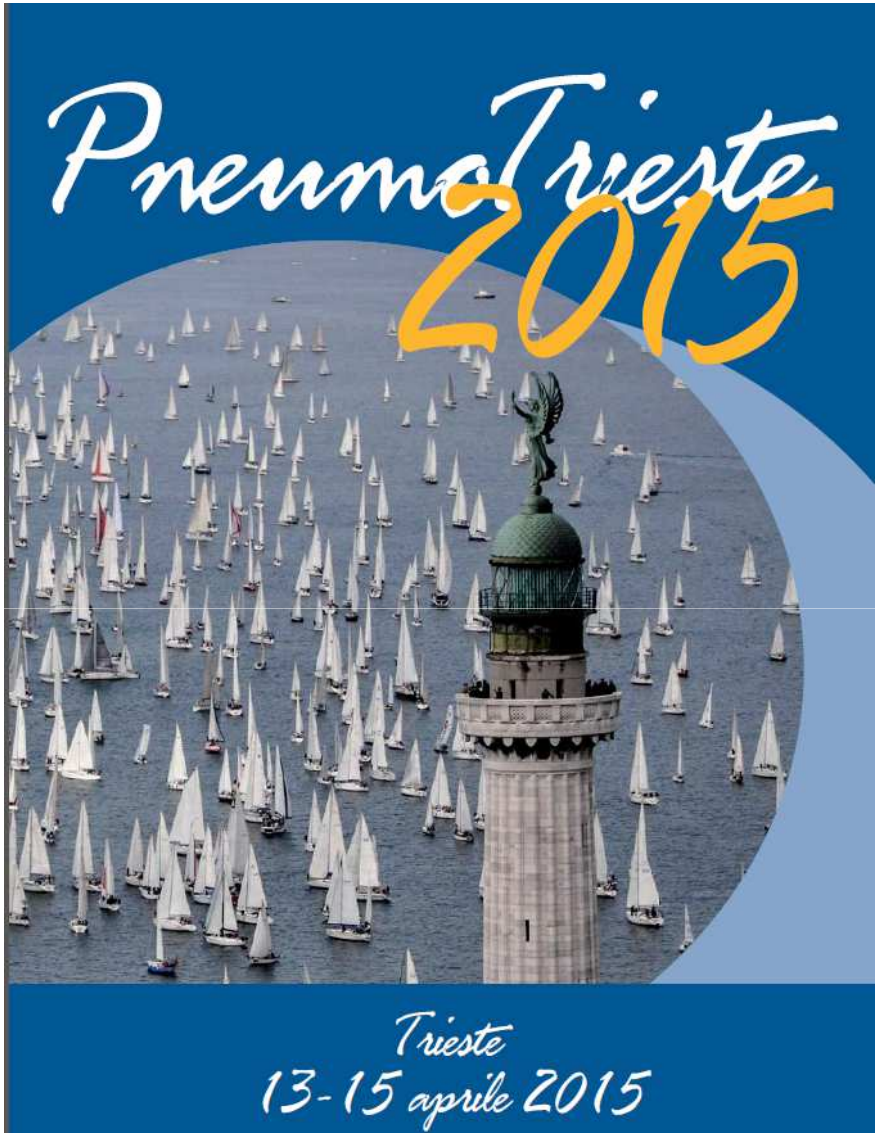


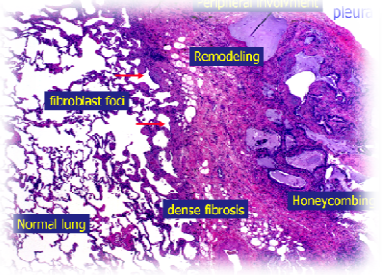
IPF AND SURROUNDINGS
Discussants: *S.Harari,*
C. Robalo Cordeiro

IPF
Pathogenesis

Prof. Marco Chilosi
UOC Anatomia e Istologia Patologica

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

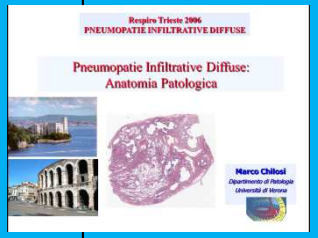
2002



2003

2004

2005



2006

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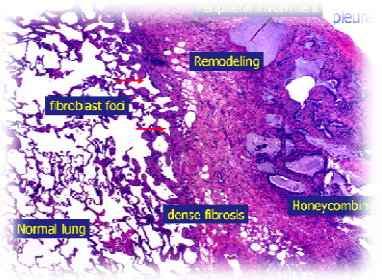
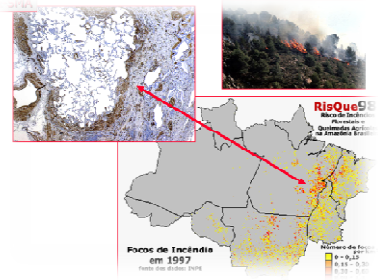
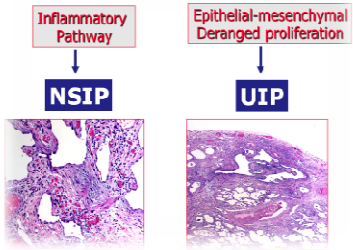
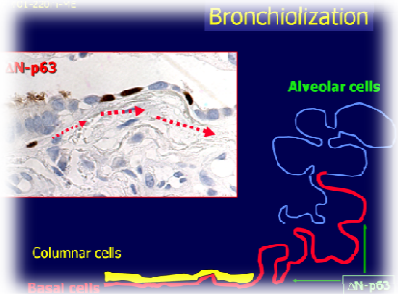
2009

2002









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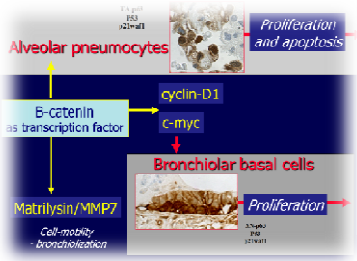

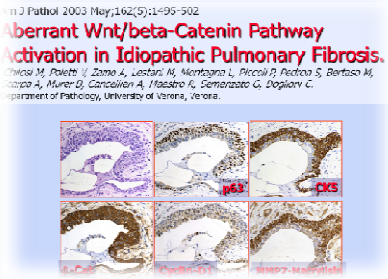

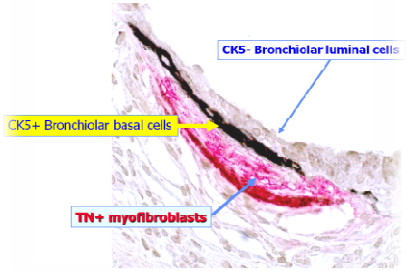

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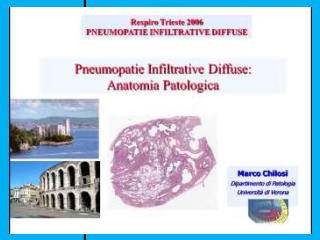

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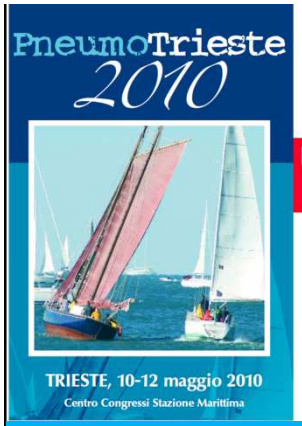


IPF and Lung Cancer: what are the links

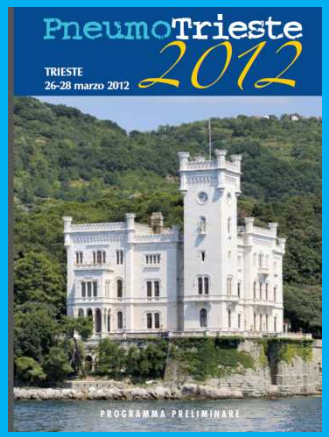
Marco Chilosi
Dipartimento di Patologia
Università di Verona

2010

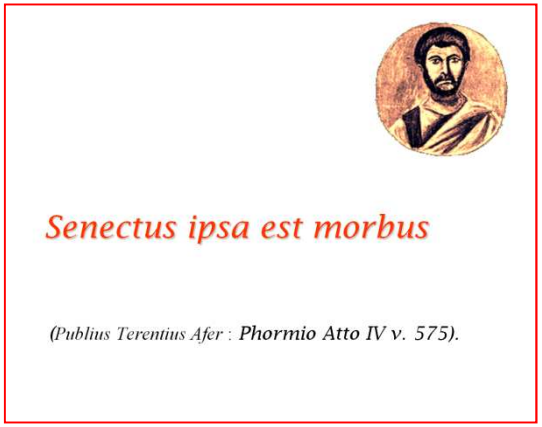
IPF:
is it a distinct
Biological entity?

Marco Chilosi
Dipartimento di Patologia
Università di Verona

2011

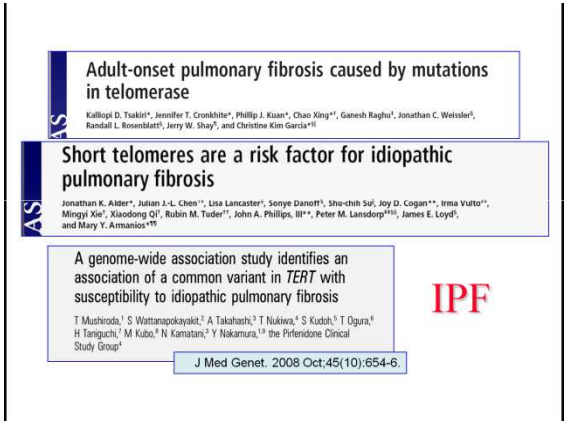


2012



Senectus ipsa est morbus

(*Publius Terentius Afer* : *Phormio Atto IV v. 575*).



Adult-onset pulmonary fibrosis caused by mutations in telomerase

Kalliopi D. Tsakiri*, Jennifer T. Cronkhite*, Phillip J. Kuan*, Chao Xing*†, Ganesh Raghu‡, Jonathan C. Weissler§, Randall L. Rosenblatt§, Jerry W. Shay¶, and Christine Kim Garcia*‖‖

Short telomeres are a risk factor for idiopathic pulmonary fibrosis

Jonathan K. Alder*, Julian J.-L. Chen††, Lisa Lancaster‡, Sonye Danoff§, Shu-chih Su‖, Joy D. Cogan**, Irma Vuto††, Mingyi Xie‖, Xiaodong Qi‖, Rubin M. Tuder††, John A. Phillips, III**, Peter M. Lansdorp‡‡§§, James E. Loyd§, and Mary Y. Armanios*¶¶

A genome-wide association study identifies an association of a common variant in *TERT* with susceptibility to idiopathic pulmonary fibrosis

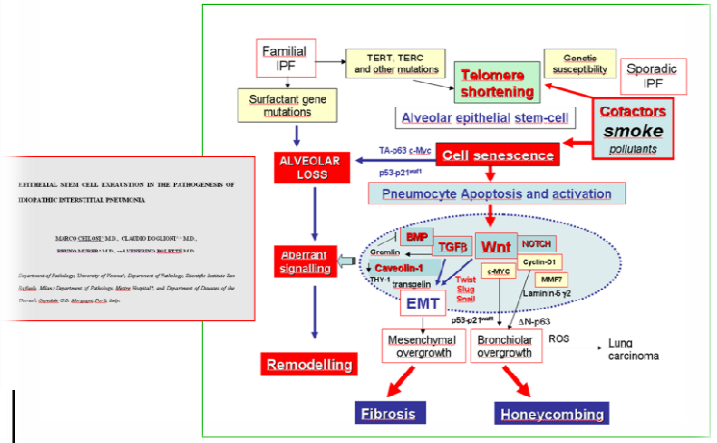
T Mushiroda,[1] S Wattanapokayakit,[2] A Takahashi,[3] T Nukiwa,[4] S Kudoh,[5] T Ogura,[6] H Taniguchi,[7] M Kubo,[8] N Kamatani,[2] Y Nakamura,[1,9] the Pirfenidone Clinical Study Group[1]

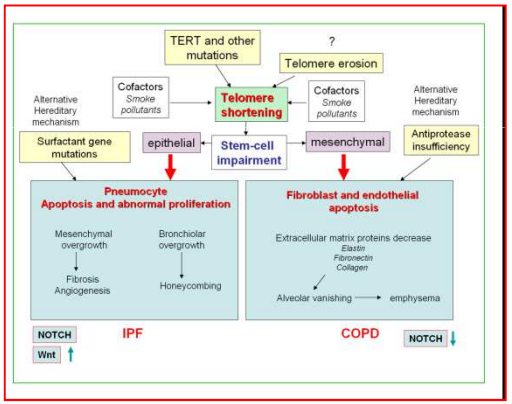
J Med Genet. 2008 Oct;45(10):654-6.

IPF

- **pathogenesis of IPF**

in press: *Sarcoidosis Vasc Diffuse Lung Dis. 2010*

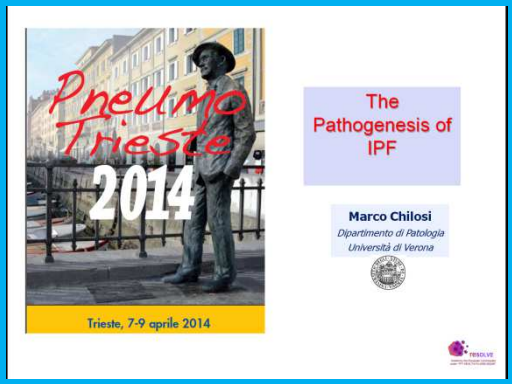




2013

The Pathogenesis of IPF

Marco Chilosi
Dipartimento di Patologia
Università di Verona



The Pathogenesis of IPF

Marco Chilosi
Dipartimento di Patologia
Università di Verona

2014

IPF pathogenesis

Stem cell exhaustion

Pulmonary disease determined by accelerated aging of lung parenchyma leading to abnormal tissue renewal with tissue remodelling, and progressive functional impairment.

Complications:

- *senescence related co-morbidities*
- *Acceleration with DAD features,*
- *Carcinoma development*

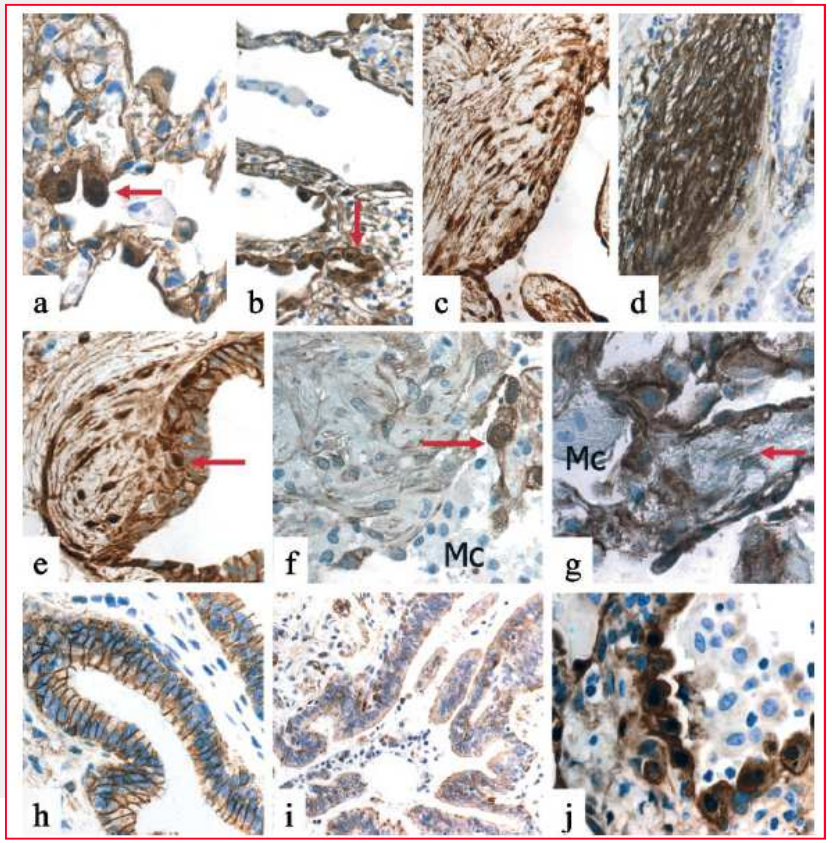
WNT
EMT
OIS
SASP
HONEYCOMBING

American Journal of Pathology, Vol. 162, No. 5, May 2003

Aberrant Wnt/β-Catenin Pathway Activation in Idiopathic Pulmonary Fibrosis

Marco Chilosi,* Venerino Poletti,† Alberto Zamò,* Maurizio Lestani,* Licia Montagna,* Paola Piccoli,* Serena Pedron,* Manuela Bertaso,* Aldo Scarpa,* Bruno Murer,‡ Alessandra Cancellieri,§ Roberta Maestro,¶ Gianpietro Semenzato,‖ and Claudio Doglioni**

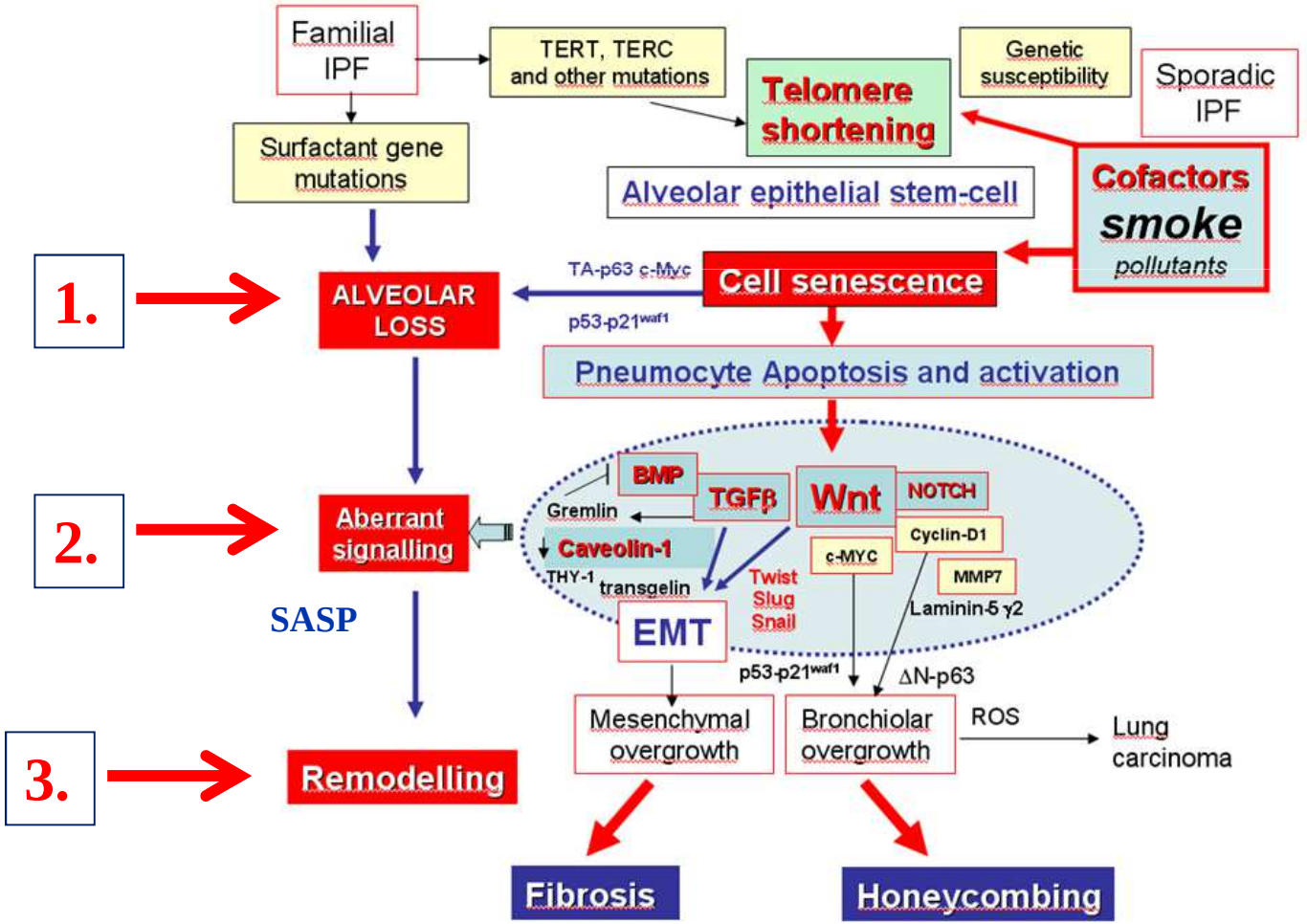
From the Department of Pathology, University of Verona, Verona; the Department of Pneumology,† Forlì City Hospital, Forlì; the Department of Pathology,‡ Mestre City Hospital, Mestre; the Department of Pathology,§ Maggiore Hospital, Bologna; the Department of Experimental Oncology,¶ Centro di Riferimento Oncologico Aviano National Cancer Institute, Aviano; the Department of Clinical and Experimental Medicine,‖ University of Padua, Padua; and the Department of Pathology,** Belluno City Hospital, Belluno, Italy*

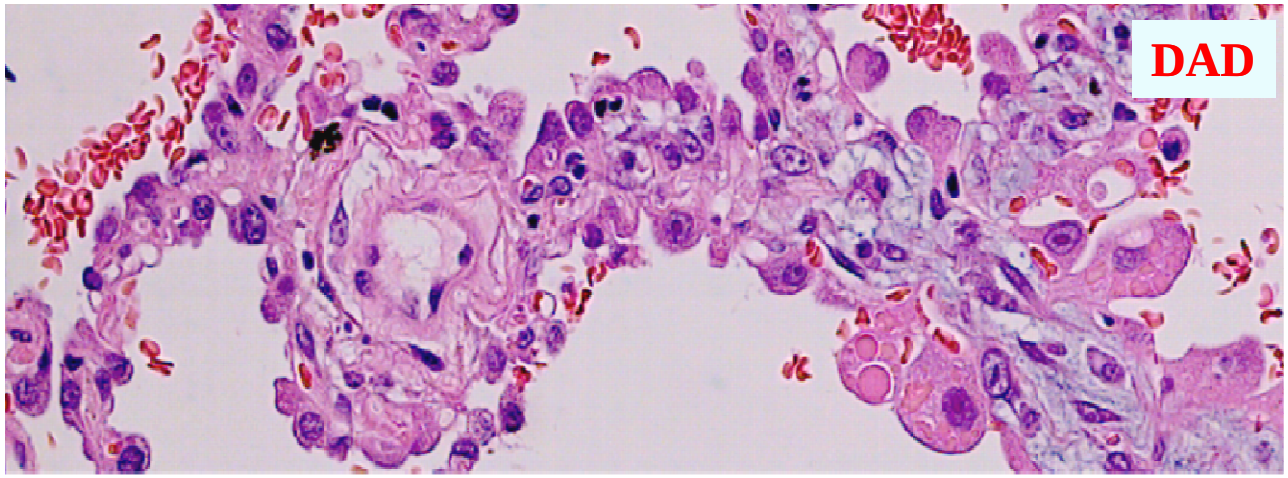


Sarcoidosis Vasc Diffuse Lung Dis. 2010

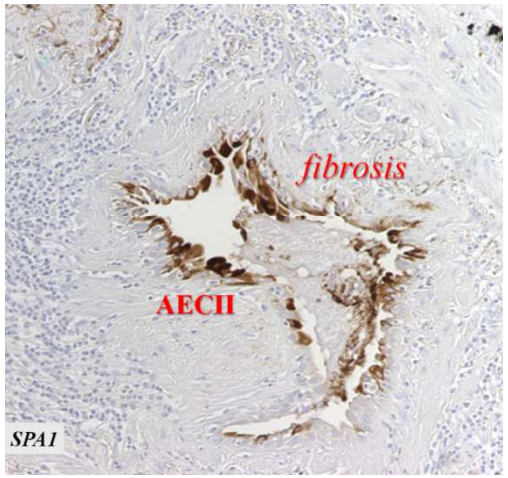
EPITHELIAL STEM CELL EXHAUSTION IN THE PATHOGENESIS OF IDIOPATHIC PULMONARY FIBROSIS

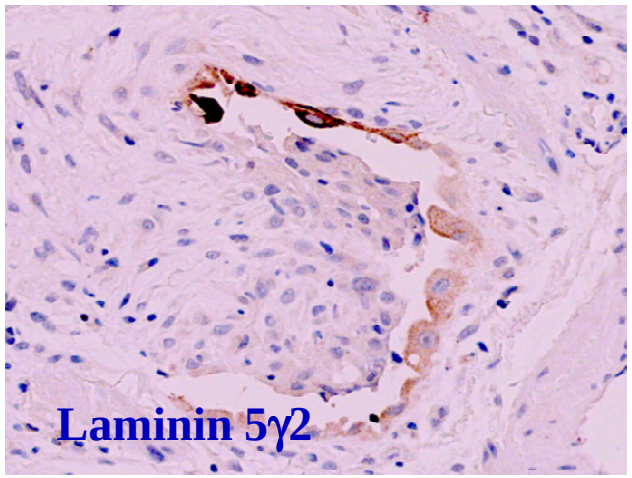
M. Chilosi[1], C. Doglioni[2], B. Murer[3], V. Poletti[4]





Pneumocyte





The Victim

Targeted Injury of Type II Alveolar Epithelial Cells Induces Pulmonary Fibrosis

Am J Respir Crit Care Med Vol 181. pp 254–263, 2010

Thomas H. Sisson[1], Michael Mendez[2], Karen Choi[1], Natalya Subbotina[1], Anthony Courey[1], Andrew Cunningham[1], Aditi Dave[1], John F. Engelhardt[3], Xiaoming Liu[3], Eric S. White[1], Victor J. Thannickal[1], Bethany B. Moore[1], Paul J. Christensen[2], and Richard H. Simon[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Hospital, Ann Arbor; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Veterans Affairs Medical Center, Ann Arbor, Michigan; and [3]Department of Anatomy and Cell Biology, University of Iowa, Iowa City, Iowa

Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

VERONA, TERNI; AND FORLÌ, ITALY

Aging

Replicative senescence and Telomere attrition

Genetic

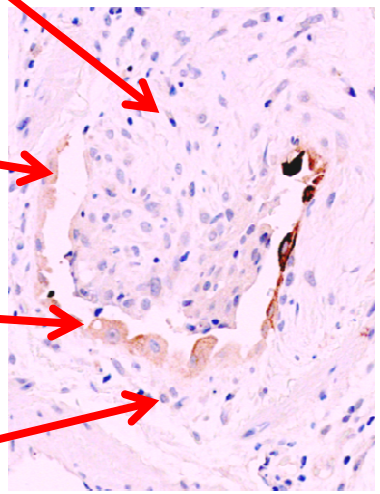
Telomerase gene mutations
Surfactant gene mutations
Endoplasmic reticulum stress

Smoking, pollutions:

Oxidative stress, ROS, NOX4

Anatomy

Mechanical stress



IPF

Epithelial Stem cell exhaustion

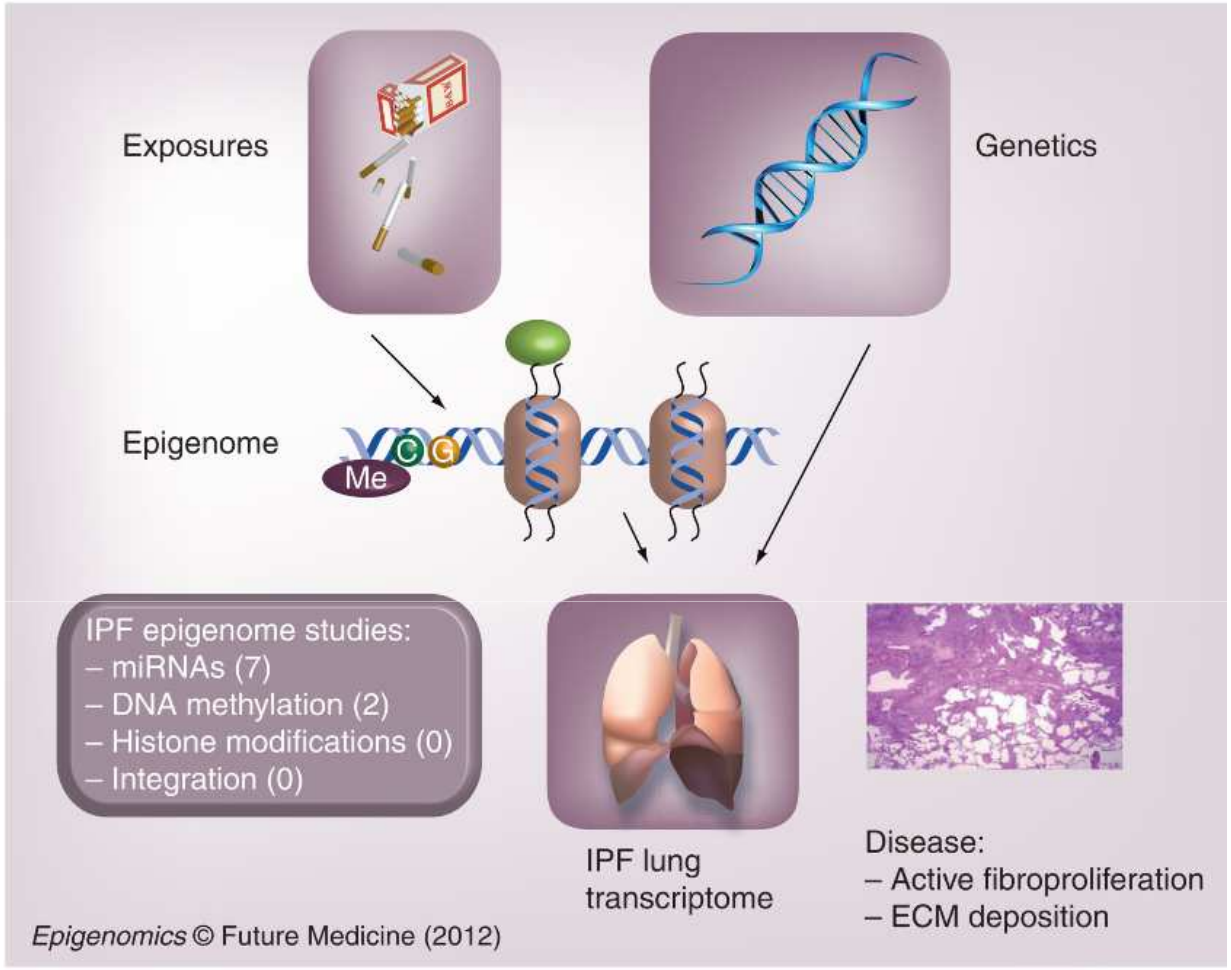


Figure 1. The idiopathic pulmonary fibrosis transcriptome is influenced by both environmental and genetic factors

The epigenome links environmental exposures to gene-expression changes that lead to disease development. A number of genome-wide miRNA studies in IPF have been published, while DNA methylation and histone modification studies on the genomic scale are just emerging in IPF. ECM: Extracellular matrix; IPF: Idiopathic pulmonary fibrosis; Me: Methyl.

Published in final edited form as:
Am J Med Sci. 2011 June ; 341(6): 439–443. doi:10.1097/MAJ.0b013e31821a9d7a.

GENETICS IN PULMONARY FIBROSIS – FAMILIAL CASES PROVIDE CLUES TO THE PATHOGENESIS OF IPF

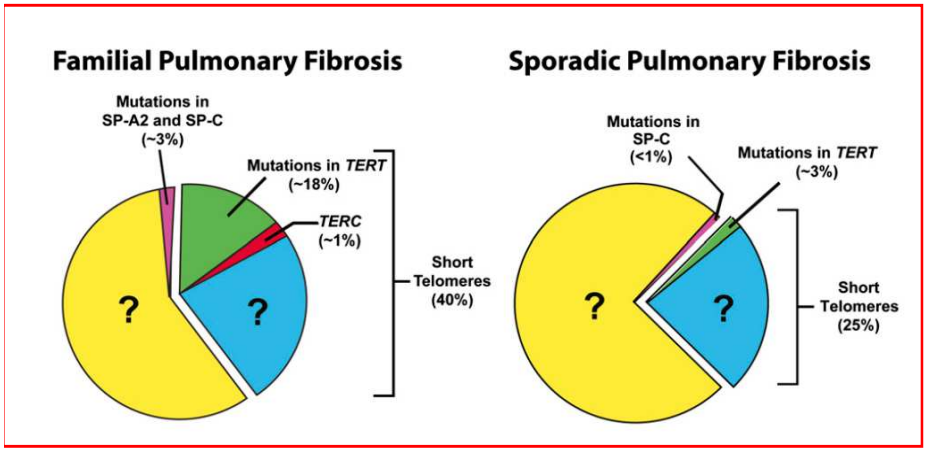
William E. Lawson, MD[1,2], **James E. Loyd, MD**[1], and **Amber L. Degryse, MD**[1]
[1]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN

Idiopathic Pulmonary Fibrosis

Update on Genetic Discoveries

Christine Kim Garcia[1]

Proc Am Thorac Soc Vol 8. pp 158–162, 2011



Adult-onset pulmonary fibrosis caused by mutations in telomerase

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Short telomeres are a risk factor for idiopathic pulmonary fibrosis

Jonathan K. Alder*, Julian J.-L. Chen†‡, Lisa Lancaster§, Sonye Danoff¶, Shu-chih Su‖, Joy D. Cogan**, Irma Vulto‡‡, Mingyi Xie†, Xiaodong Qi†, Rubin M. Tuder††, John A. Phillips, III**, Peter M. Lansdorp‡‡§§, James E. Loyd§, and Mary Y. Armanios*¶¶

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J Med Genet. 2008 Oct;45(10):654-6.

IPF

Telomere dysfunction

Endoplasmic reticulum stress (unfolded proteins)

Epithelial stem cell exhaustion

The genetic basis of idiopathic pulmonary fibrosis

Jonathan A. Kropski1, Timothy S. Blackwell, and James E. Loyd.

ERJ Express. Published on April 2, 2015 as doi: 10.1183/09031936.00163814

TABLE 2 Rare genetic variants linked to familial interstitial pneumonia (FIP)

Gene	Reported % of FIP	Reference
TERT	8–15%	[20, 21]
RTEL1	5%	[28]
hTR	<1%	[20, 21]
DKC1	<1%	[23, 24]
TINF2	<1%	[25–27]
SFTPC	2–25%	[13–16, 87, 88]
SFTPA2	<1%	[17]
ABCA3	<1%	[18, 19]
Unknown	75–85%	

TABLE 1 Summary of common genetic variants linked to idiopathic pulmonary fibrosis (IPF)

Locus	Gene	SNP	IPF risk	IPF survival	Reference
2q14	*IL1RN*	rs408392	Yes		[29–31]
		rs419598	Yes		
		rs2637988	Yes		
3q26	*hTR*	rs6793295	Yes		[32]
4q13	*IL8*	rs4073	Yes		[33]
		rs2227307	Yes		
4q22	*FAM13A*	rs2609255	Yes		[32]
4q35	*TLR3*	rs3775291		Harmful	[34]
5p15	*TERT*	rs2736100	Yes		[32, 35]
6p21	*CDKN1A*	rs2395655	Yes	Harmful	[36]
6p21	*HLA-DRB1*		Yes		[37]
6q24	*DSP*	rs2076295	Yes		[32]
7q22	Intergenic	rs47274443	Yes		[32]
10q24	*OBFC1*	rs11191865	Yes		[32]
11p15	*MUC5B*	rs35705950	Yes	Protective	[32, 38–43]
	MUC2	rs7934606	Yes		[32]
	TOLLIP	rs111521887	Yes		[40]
	TOLLIP	rs5743894	Yes		[40]
	TOLLIP	rs2743890	Yes	Protective	[40]
13q34	*ATP11A*	rs1278769	Yes		[32]
14q21	*MDGA2*	rs7144383	Yes		[40]
15q14–15	Intergenic	rs2034650	Yes		[32]
17q13	*TP53*	rs12951053	No	Harmful	[36]
	TP53	rs12602273	No	Harmful	
17q21	*MAPT*	rs1981997	Yes		[32]
17q21	*SPPL2C*	rs17690703	Yes		[40]
19q13	*DPP9*	rs12610495	Yes		[32]
19q13	*TGFB1*	rs1800470	No	Harmful	[44, 45]

nature genetics

Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis

Tasha E Fingerlin[1], Elissa Murphy[2,23], Weiming Zhang[1,23], Anna L Peljto[1], Kevin K Brown[2,3], Mark P Steele[4], James E Loyd[4], Gregory P Cosgrove[2,3], David Lynch[3], Steve Groshong[3], Harold R Collard[5], Paul J Wolters[5], Williamson Z Bradford[6], Karl Kossen[6], Scott D Seiwert[6], Roland M du Bois[7,8], Christine Kim Garcia[9], Megan S Devine[9], Gunnar Gudmundsson[10–13], Helgi J Isaksson[10–13], Naftali Kaminski[14], Yingze Zhang[14], Kevin F Gibson[14], Lisa H Lancaster[4], Joy D Cogan[4], Wendi R Mason[4], Toby M Maher[7,8], Philip L Molyneaux[7,8], Athol U Wells[7,8], Miriam F Moffatt[7,8], Moises Selman[15], Annie Pardo[16], Dong Soon Kim[17], James D Crapo[2,3], Barry J Make[2,3], Elizabeth A Regan[3], Dinesha S Walek[18], Jerry J Daniel[18], Yoichiro Kamatani[19], Diana Zelenika[20], Keith Smith[2], David McKean[2], Brent S Pedersen[2], Janet Talbert[3], Raven N Kidd[21], Cheryl R Markin[4], Kenneth B Beckman[18], Mark Lathrop[19,20], Marvin I Schwarz[2,3] & David A Schwartz[2,3,22]

We performed a genome-wide association study of non-Hispanic, white individuals with fibrotic idiopathic interstitial pneumonias (IIPs; $n = 1,616$) and controls ($n = 4,683$), with follow-up replication analyses in 876 cases and 1,890 controls. We confirmed association with *TERT* at 5p15, *MUC5B* at 11p15 and the 3q26 region near *TERC*, and we identified seven newly associated loci ($P_{meta} = 2.4 \times 10^{-8}$ to 1.1×10^{-19}), including *FAM13A* (4q22), *DSP* (6p24), *OBFC1* (10q24), *ATP11A* (13q34), *DPP9* (19p13) and chromosomal regions 7q22 and 15q14-15. Our results suggest that genes involved in host defense, cell-cell adhesion and DNA repair contribute to risk of fibrotic IIPs.

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Abstract Send to:

Nat Genet. 2015 Apr 13. doi: 10.1038/ng.3278. [Epub ahead of print]

Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening.

Stuart BD[1], Choi J[2], Zaidi S[2], Xing C[3], Holohan B[4], Chen R[5], Choi M[3], Dharwadkar P[5], Torres F[5], Girod CE[5], Weissler J[5], Fitzgerald J[5], Kershaw C[5], Klesney-Tait J[6], Mageto Y[7], Shay JW[4], Ji W[2], Bilguvar K[8], Mane S[8], Lifton RP[9], Garcia CK[10].

Author information

Abstract

Idiopathic pulmonary fibrosis (IPF) is an age-related disease featuring progressive lung scarring. To elucidate the molecular basis of IPF, we performed exome sequencing of familial kindreds with pulmonary fibrosis. Gene burden analysis comparing 78 European cases and 2,816 controls implicated PARN, an exoribonuclease with no previous connection to telomere biology or disease, with five new heterozygous damaging mutations in unrelated cases and none in controls ($P = 1.3 \times 10^{-8}$); mutations were shared by all affected relatives (odds in favor of linkage = 4,096:1). RTEL1, an established locus for dyskeratosis congenita, harbored significantly more new damaging and missense variants at conserved residues in cases than in controls ($P = 1.6 \times 10^{-6}$). PARN and RTEL1 mutation carriers had shortened leukocyte telomere lengths, and we observed epigenetic inheritance of short telomeres in family members. Together, these genes explain ~7% of familial pulmonary fibrosis and strengthen the link between lung fibrosis and telomere dysfunction.

PMID: 25848748 [PubMed - as supplied by publisher]

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Related citations in PubMed

Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. [PLoS One. 2010]

Rare Variants in RTEL1 Are Associated with Familial Inters [Am J Respir Crit Care Med. 2015]

Germline mutations of regulator of telomere elongation helicase 1, RTEL1. [Hum Genet. 2013]

Review Telomeres in lung diseases. [Prog Mol Biol Transl Sci. 2014]

Review Telomerase and idiopathic pulmonary fibrosis. [Mutat Res. 2012]

PARN and RTEL1 mutation carriers had shortened leukocyte telomere lengths, and we observed epigenetic inheritance of short telomeres in family members. Together, these genes explain ~7% of familial pulmonary fibrosis and strengthen the link between lung fibrosis and telomere dysfunction.

Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

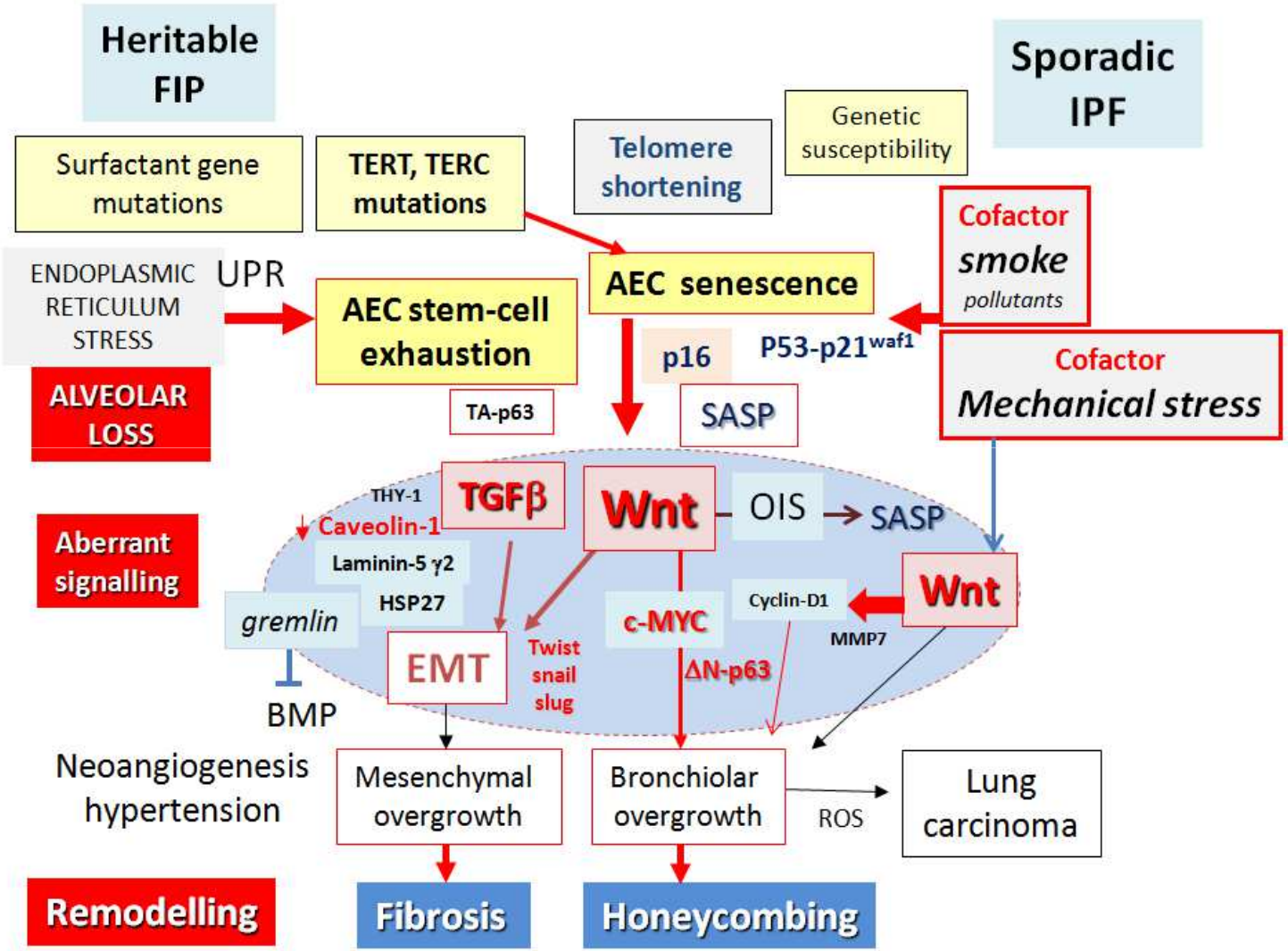
VERONA, TERNI; AND FORLÌ, ITALY

Cell Senescence
Immunosenescence
SASP
Stem cell exhaustion
Aberrant signaling
WNT pathway
Mechanical stress
Oxidative stress

Different anatomic and physiological changes occur in the lung of aging people that can affect pulmonary functions, and different pulmonary diseases, including deadly diseases such as chronic obstructive pulmonary disease (COPD)/emphysema and idiopathic pulmonary fibrosis (IPF), can be related to an acceleration of the aging process. The individual genetic background, as well as exposure to a variety of toxic substances (cigarette smoke *in primis*) can contribute significantly to accelerating pulmonary senescence. Premature aging can impair lung function by different ways: by interfering specifically with tissue repair mechanisms after damage, thus perturbing the correct crosstalk between mesenchymal and epithelial components; by inducing systemic and/or local alteration of the immune system, thus impairing the complex mechanisms of lung defense against infections; and by stimulating a local and/or systemic inflammatory condition (inflammaging). According to recently proposed pathogenic models in COPD and IPF, premature cellular senescence likely affects distinct progenitors cells (mesenchymal stem cells in COPD, alveolar epithelial precursors in IPF), leading to stem cell exhaustion. In this review, the large amount of data supporting this pathogenic view are discussed, with emphasis on the possible molecular and cellular mechanisms leading to the severe parenchymal remodeling that characterizes, in different ways, these deadly diseases. (Translational Research 2013;162:156–173)

Abbreviations: AECII = type-II alveolar epithelial cells; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; ER = endoplasmic reticulum; EMT = epithelial mesenchymal transition; FF = fibroblast foci; FIP = familial interstitial pneumonia; Hsp27 = heat shock protein 27; IPF = idiopathic pulmonary fibrosis; LAM5γ2 = laminin-5-γ2 chain; SASP = senescence-associated secretory phenotype; TGF = transforming growth factor; UIP = usual interstitial pneumonia; UPR = unfolded protein response

Chilosi M, Carloni A, Rossi A, Poletti V. **Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD emphysema.** **Transl Res 162: 156-73, 2013**



Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

VERONA, TERNI; AND FORLÌ, ITALY

IPF

Epithelial Stem cell exhaustion

Replicative senescence and Telomere attrition	**Aging**
Endoplasmic reticulum stress	**Surfactant**
Oxidative stress	**Smoke**
Mechanical stress	**Anatomy**

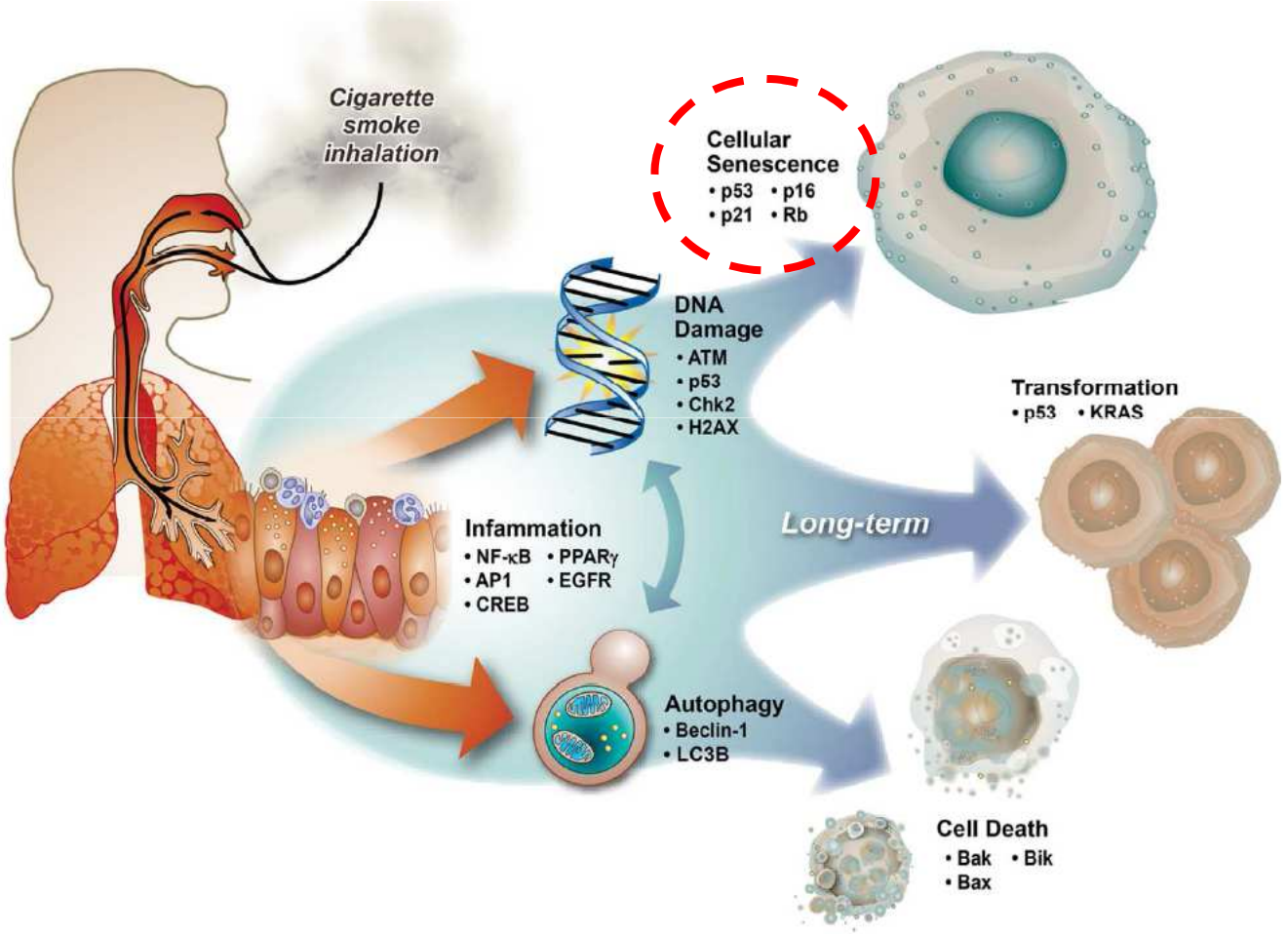
Parenchymal senescence

Am J Respir Cell Mol Biol. 2013 Oct 10. [Epub ahead of print]

Molecular Processes That Drive Cigarette Smoke-Induced Epithelial Cell Fate of the Lung.

Nyunoya T, Mebratu Y, Contreras A, Delgado M, Chand HS, Tesfaigzi Y.

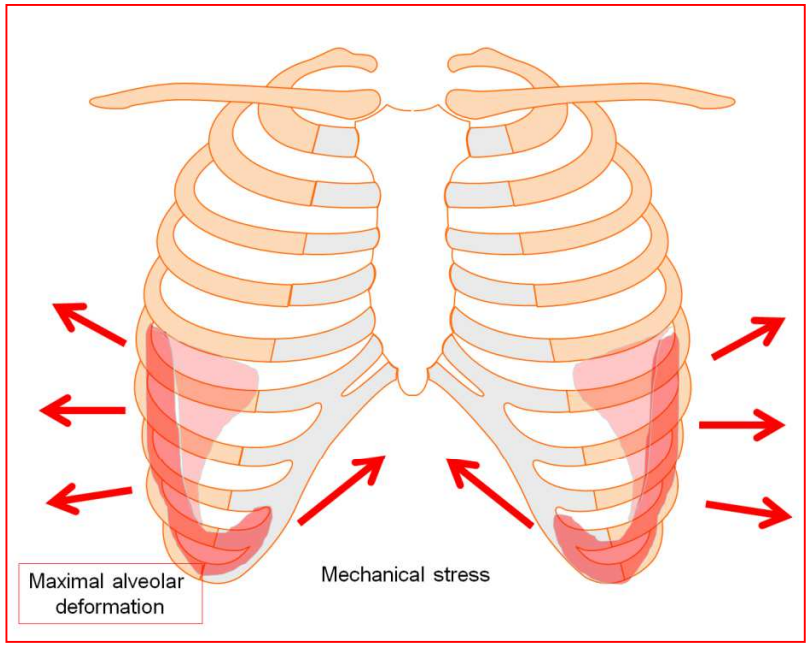
LRRI, Albuquerque, New Mexico, United States.

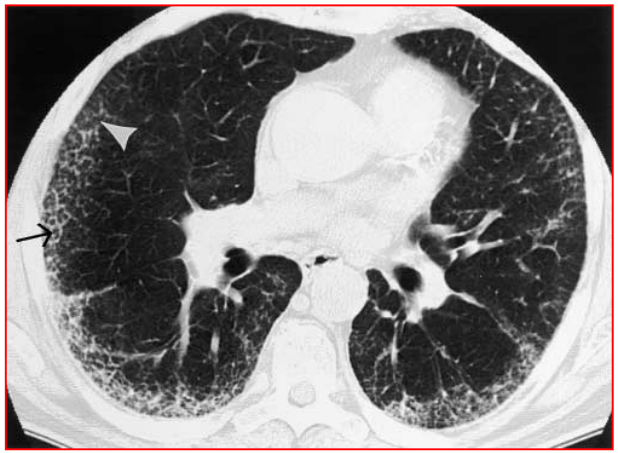


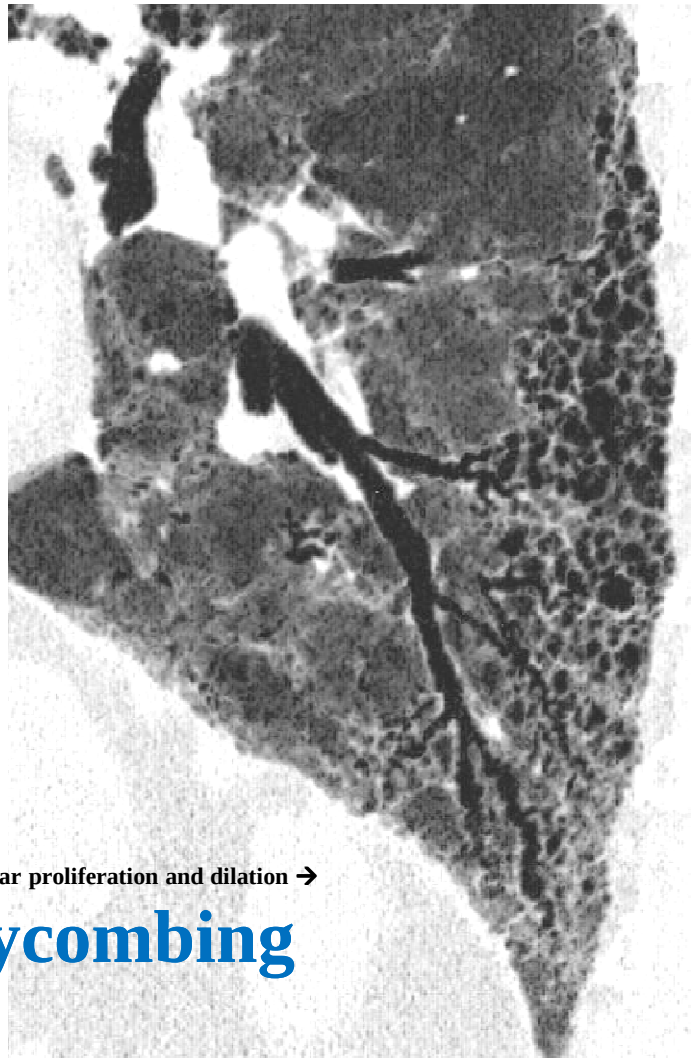
Molecular Processes that Drive Cigarette Smoke-Induced Epithelial Cell Fate of the Lung. Cigarette smoke exposure induces inflammation, DNA damage, and autophagy that cause lung epithelial cells to undergo cell death, cellular senescence, and/or transformation.

IPF

Anatomical location lower lobes, posterior, peripheral







Abnormal bronchiolar proliferation and dilation →

Honeycombing

Journal of Theoretical Biology 332 (2013) 136–140

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Heterogeneous distribution of mechanical stress in human lung: A mathematical approach to evaluate abnormal remodeling in IPF☆

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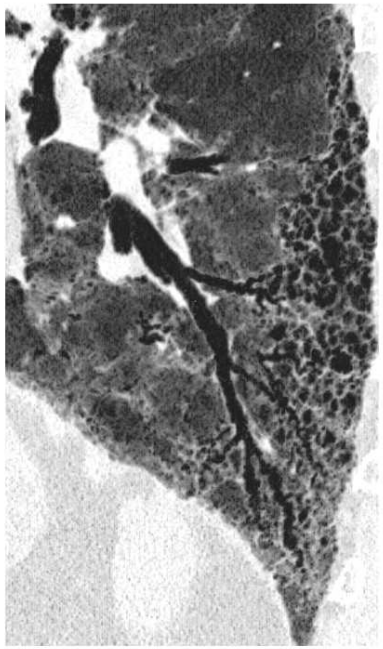
[c] Department of Mathematics and Computer Science, University of Cagliari, Viale Merello 92, 10123 Cagliari, Italy
[d] Department of Mathematical Sciences, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy
[e] Department of Pathology and Diagnostics, University of Verona, Verona, Italy

Maximal alveolar deformation

$$\begin{cases} \mathrm{M}\dfrac{d^2\mathbf{X}}{dt^2} = \mathbf{F}_x + \mathbf{f}_x \\ \mathrm{M}\dfrac{d^2\mathbf{Y}}{dt^2} = \mathbf{F}_y + \mathbf{f}_y \end{cases}$$



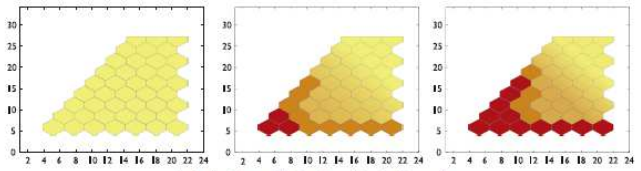
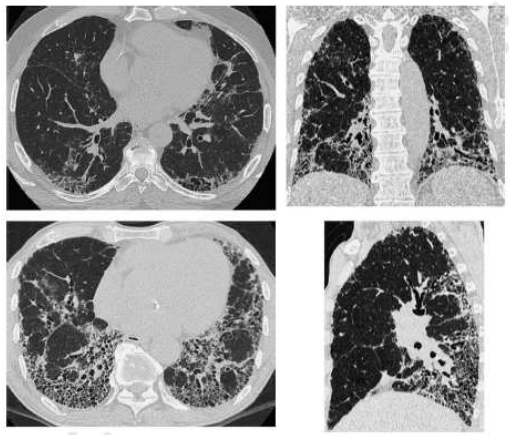


Fig. 3. Simulations of the Lung Parenchima for different times.



PULMONARY PERSPECTIVE

Revealing the Pathogenic and Aging-related Mechanisms of the Enigmatic Idiopathic Pulmonary Fibrosis

An Integral Model

Am J Respir Crit Care Med Vol 189, 10, 1161–1172, 2014

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Abstract

A growing body of evidence indicates that aberrant activation of alveolar epithelial cells and fibroblasts in an aging lung plays a critical role in the pathogenesis of idiopathic pulmonary fibrosis (IPF). However, the biopathological processes linking aging with IPF and the mechanisms responsible for the abnormal activation of epithelial cells and fibroblasts have not been elucidated. Many of the hallmarks of aging (e.g., genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, and cellular senescence) have been proposed as essential mechanisms for the development of IPF; however, these disturbances are not restricted to IPF and also occur in other aging-related lung disorders, primarily chronic obstructive pulmonary disease (COPD). Therefore, an unanswered question is why a current/former smoker of about 60 years of age with shorter telomeres, alveolar epithelial senescence, excessive oxidative stress, and mitochondrial dysfunction develops IPF and not COPD; in other words, what makes old lungs specifically susceptible to develop IPF? In this Perspective, we propose an integral model in which the combination of some gene variants and/or gene expression in the aging lung results in the loss of epithelial integrity and consequently in the failure of the alveoli to correctly respond to injury and to face the stress associated with mechanical stretch. Afterward, a distinctive epigenetic "reprogramming" that affects both epithelial cells and fibroblasts provokes, among others, the recapitulation of developmental pathways and the aberrant activation and miscommunication between both cell types, resulting in the exaggerated production and accumulation of extracellular matrix and the subsequent destruction of the lung architecture.

Keywords: pulmonary fibrosis; epithelial cells; aging; genetic susceptibility; chronic obstructive pulmonary disease

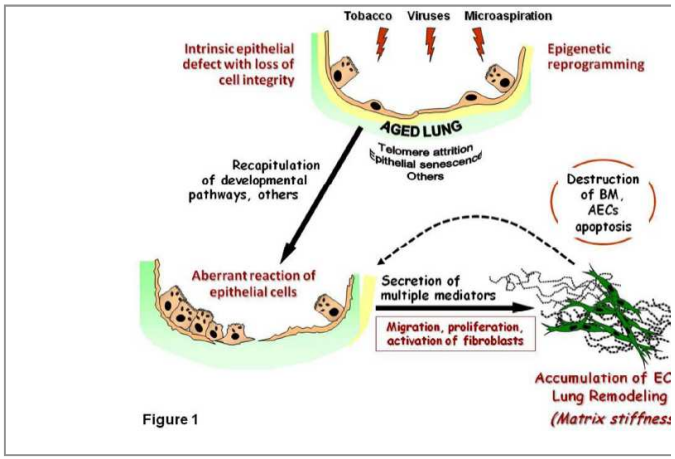
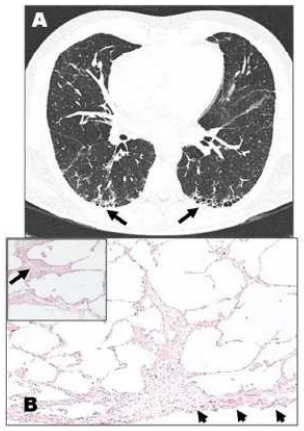
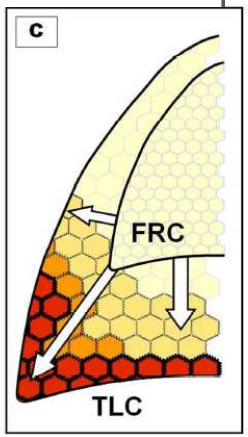
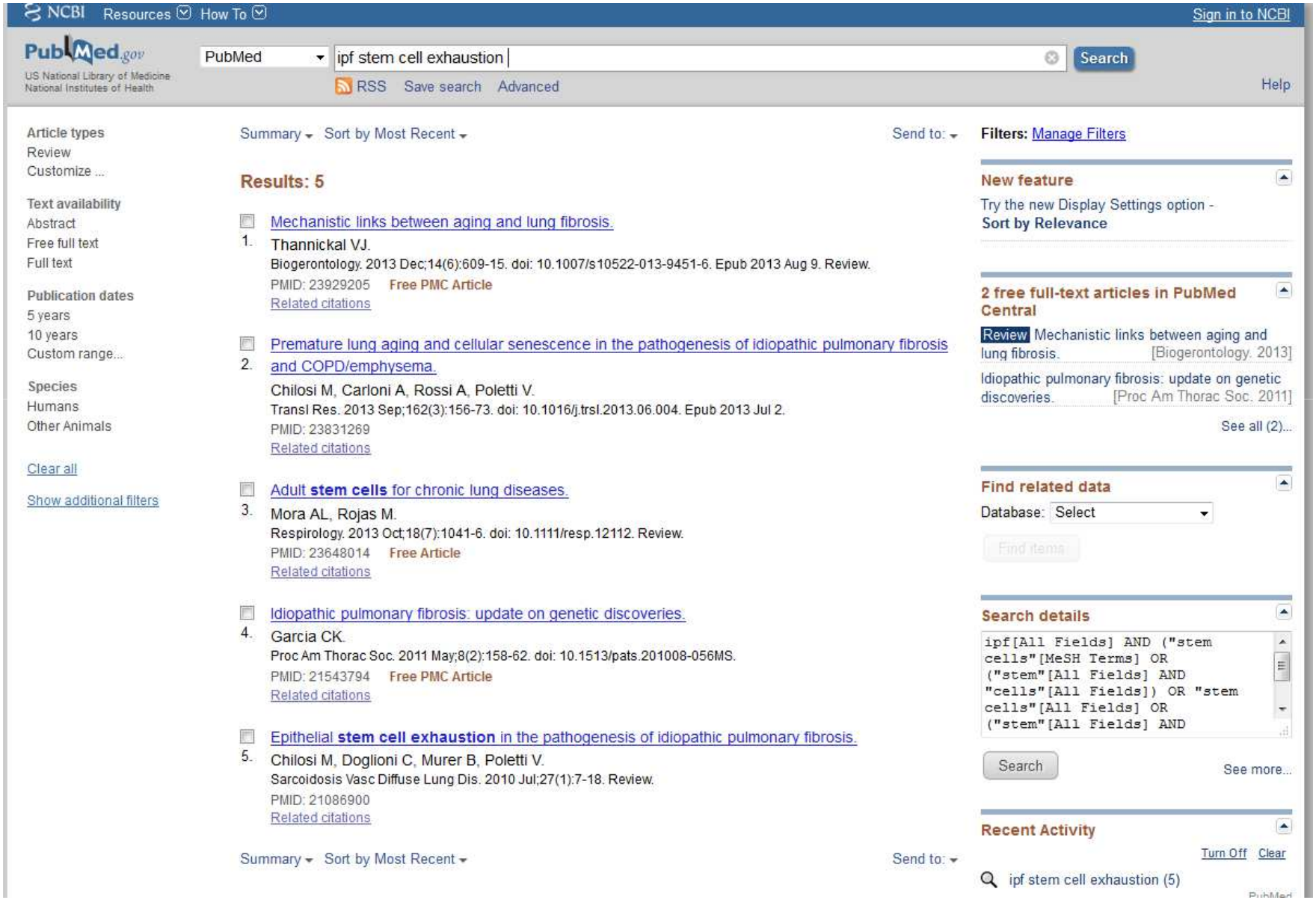


Figure 1





Stem cell exhaustion in IPF



Telomere dysfunction causes alveolar stem cell failure

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Contributed by Brigid L. M. Hogan, March 11, 2015 (sent for review February 3, 2015)

Telomere syndromes have their most common manifestation in lung disease that is recognized as idiopathic pulmonary fibrosis and emphysema. In both conditions, there is loss of alveolar integrity, but the underlying mechanisms are not known. We tested the capacity of alveolar epithelial and stromal cells from mice with short telomeres to support alveolar organoid colony formation and found that type 2 alveolar epithelial cells (AEC2s), the stem cell-containing population, were limiting. When telomere dysfunction was induced in adult AEC2s by conditional deletion of the shelterin component telomeric repeat-binding factor 2, cells survived but remained dormant and showed all the hallmarks of cellular senescence. Telomere dysfunction in AEC2s triggered an immune response, and this was associated with AEC2-derived up-regulation of cytokine signaling pathways that are known to provoke inflammation in the lung. Mice uniformly died after challenge with bleomycin, underscoring an essential role for telomere function in AEC2s for alveolar repair. Our data show that alveoloar progenitor senescence is sufficient to recapitulate the regenerative defects, inflammatory responses, and susceptibility to injury that are characteristic of telomere-mediated lung disease. They suggest alveolar stem cell failure is a driver of telomere-mediated lung disease and that efforts to reverse it may be clinically beneficial.

telomerase | idiopathic pulmonary fibrosis | emphysema | senescence

with AEC2s' regenerative capacity (14–16), led us to hypothesize that telomere dysfunction is sufficient to provoke AEC2 failure and that this event drives lung disease pathogenesis.

One hurdle to modeling the consequences of telomere dysfunction in a cell type-specific manner is that laboratory mice have very long telomeres (17). In the absence of telomerase, telomere dysfunction can be generated only after several generations of breeding, precluding cell type-specific studies (18). To overcome this limitation, we designed two experimental systems. First we examined the role of telomere shortening in purified AEC2s in a stem cell assay ex vivo. For an in vivo system, we generated a model in which telomere dysfunction can be induced by deleting telomeric repeat-binding factor 2 (*Trf2*) (19, 20) exclusively in adult AEC2s. Trf2 functions to suppress the DNA damage response, and its loss leads to telomere dysfunction by uncapping, thus allowing cell type-specific studies within a single generation (19, 20). The latter surrogate model allowed us to test the consequences of acquired DNA damage and telomere dysfunction in the adult lung. We show here, in both late-generation telomerase-null mice and in a conditional mutant model, that telomere dysfunction restricted to AEC2s impairs stem cell function by inducing senescence. This program recapitulates the inflammatory responses and susceptibility

GENETICS

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Mechanistic Links between Aging and Lung Fibrosis

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Abstract

Our understanding of the biology of aging has advanced significantly in recent years. This has resulted in the recent formulation of the "hallmarks of aging" that include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease that results from the accumulation of scar tissue in the lungs of affected individuals. IPF is a disease of aging that most commonly affects human subjects older than sixty years of age. While progress has been made in elucidating key pathological processes in IPF, the relationship of these processes to those that occur during aging are not well defined. In this review, we explore existing and emerging paradigms in the pathogenesis of IPF in light of the recently defined hallmarks of aging.

Introduction: Idiopathic Pulmonary Fibrosis is a Disease of Aging

Cellular Senescence

While there is strong evidence that senescent cells accumulate in tissues with aging (Krishnamurthy et al. 2004), the mechanisms by which they contribute to aging and age-related diseases deserves further study. Fibrosis is generally considered as a fibro-"proliferative", but benign (non-cancerous) disease process. Consistent with this concept, the emergence of senescent fibrogenic cells in the context of wound healing has been proposed to mediate anti-fibrotic effects (Krizhanovsky et al. 2008; Jun and Lau 2010). Thus, similar to its role in tumor-suppression, cellular senescence may function as a mechanism for fibrosis-suppression (Rodier and Campisi 2011). Such "antagonistically pleiotropic" roles of senescence must be reconciled in specific age-related diseases, including IPF, before effective therapeutics targeting senescence pathways can be designed.

Stem Cell Exhaustion

Stem cell exhaustion has been implicated in a number of age-related diseases, including IPF (Chilosi et al. 2010; Chilosi et al. 2013). The principal cells implicated in "stem cell exhaustion" associated with IPF are alveolar type II epithelial cells (Chilosi et al. 2013); however, a hyperplastic response around fibroblastic foci with abnormal bronchiolarization is often seen, an observation that has not been adequately explained. Whether this hyper-proliferative response reflects differences in the susceptibility of distinct groups of airway epithelial stem cells is currently not known. Additionally, a better understanding of stem cell niches that also under aging is required before the potential beneficial effects of stem cell-based therapies for chronic lung diseases can be realized (Mora and Rojas 2013).

PULMONARY PERSPECTIVE

Blue Journal Conference
Aging and Susceptibility to Lung Disease

Am J Respir Crit Care Med Vol 191, Iss 3, pp 261–269, Feb 1, 2015

Victor J. Thannickal[1], Mahadev Murthy[2], William E. Balch[3], Navdeep S. Chandel[4], Silke Meiners[5], Oliver Eickelberg[5], Moisés Selman[6], Annie Pardo[7], Eric S. White[8], Bruce D. Levy[9], Paula J. Busse[10], Rubin M. Tuder[11], Veena B. Antony[1], Jacob I. Sznajder[4], and G. R. Scott Budinger[4]

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Abstract

The aging of the population in the United States and throughout the developed world has increased morbidity and mortality attributable to lung disease, while the morbidity and mortality from other prevalent diseases has declined or remained stable. Recognizing the importance of aging in the development of lung disease, the American Thoracic Society (ATS) highlighted this topic as a core theme for the 2014 annual meeting. The relationship between aging and lung disease was discussed in several oral symposiums and poster sessions at the annual ATS meeting. In this article, we used the input gathered at the conference to develop a broad framework and perspective to stimulate basic, clinical, and translational research to understand how the aging process contributes to the onset and/or progression of lung diseases. A consistent theme that emerged from the conference was the need to apply novel, systems-based approaches to integrate a growing body of genomic, epigenomic, transcriptomic, and proteomic data and elucidate the relationship between biologic hallmarks of aging, altered lung function, and increased susceptibility to lung diseases in the older population. The challenge remains to causally link the molecular and cellular changes of aging with age-related changes in lung physiology and disease susceptibility. The purpose of this review is to stimulate further research to identify new strategies to prevent or treat age-related lung disease.

Cellular Phenotypes of Aging

Environmental factors and changes in gene expression alter the proteome and metabolome over the life span to induce profound changes in cellular phenotypes that are strongly associated with lung aging. These cellular phenotypes include cellular senescence, stem cell dysfunction, immune dysregulation, and ECM alterations among others. The molecular pathways that drive many of these phenotypes have been described in detail; however, we are only beginning to understand how these processes contribute to age-related lung disease in the context of intracellular and intercellular functional and signaling networks.

Cellular Senescence and Aging

Cellular senescence is broadly defined as a state of stable growth arrest in combination with distinctive phenotypic changes that include profound alterations in chromatin and in the secretome (74, 75). A number of stimuli, both intrinsic and extrinsic, can mediate senescence via well-described signaling networks that converge on tumor suppressor pathways to induce stable cell cycle arrest (75). There is an emerging view that cellular senescence may mediate beneficial or detrimental effects depending on its contextual roles in embryogenesis, tissue repair, tumor suppression, aging, and age-related diseases (74, 75). There is evidence for senescence of aging phenotypes and the susceptibility of tissues and organs to disease is increasingly recognized and has been the subject of several reviews (13, 19). It is hypothesized that during aging, the maintenance and/or restorative function of the stem cell pools progressively declines, perhaps via the accumulation of epigenetic marks (13). This concept of stem cell exhaustion has been suggested to play a role in age-related diseases including emphysema and IPF; however, the evidence is not definitive (80, 82). Several groups of investigators have worked to identify stem cell populations in the lung and determine their role in tissue homeostasis and function during lung aging and disease. Although the low turnover rate of cells within the mouse lung makes these studies challenging, these investigators have identified a hierarchically arranged system of partially differentiated self-renewing cells scattered throughout the airways and the distal lung epithelium (83) including basal cells in the trachea and bronchi (84) and type 2 cells in the alveolar compartment (85, 86). In addition, investigators have identified a population of lung-resident mesenchymal stem cells (MSCs) (87, 88), which may modulate epithelial stem cell behavior via interactions in stem cell niches (89) and serve as stromal cell progenitors for tissue repair. At present, the precise identity and/or location of MSCs and other mesenchymal progenitors are unclear, even in the mouse lung, and little is known about the location,

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2. Multifactorial/complex pathogenesis: genetic predisposition, cell senescence, stem cell exhaustion

- **pediatric ILD** *(Surfactant-PB or PC-deficiency, ABCA3 mutation, NKX2-1 mutations)*

- **familial IPF** *(TERT, TERC, SP-A2, SP-C, ABCA3, pro-MUC5B rs35705950 polymorphism)*
- Dyskeratosis congenita with pulmonary involvement (*telomeropathy*)

- **Idiopatic pulmonary fibrosis** - IPF/CPFE

  - genetic features: rare: *surfactant SPA2 and SPC, ABCA3 mutations,*

  frequent*: pro-MUC5B rs35705950 polymorphism,*

  - molecular features: telomere shortening, WNT-pathway activation , EMT, etc.)

6

Mutations in Surfactant Protein C and Interstitial Lung Disease

Ralph J. Panos and James P. Bridges

Abstract Less than 5% of all cases of idiopathic interstitial lung disease (ILD) are due to familial pulmonary fibrosis. The clinical manifestations of familial pulmonary fibrosis are indistinguishable from the presenting symptoms in sporadic idiopathic pulmonary fibrosis. Mutations in *SFTPC*, the gene encoding surfactant protein C (SP-C), have been identified in kindreds with familial ILD as well as individuals with sporadic IPF. SP-C is a surfactant-associated protein that is essential for the reduction in surface tension at the air–liquid interface within the alveolus and the prevention of end-expiratory alveolar collapse. Because of its hydrophobic properties, SP-C is synthesized as a proprotein that is processed within the secretory pathway of alveolar type II cells as it is conducted to the lamellar body, the intracellular storage site of surfactant. The carboxy terminus of the proprotein appears to function as an intramolecular chaperone that guides posttranslational processing of the SP-C protein and the majority of mutations associated with ILD occur within this domain. Over 50 distinct *SFTPC* mutations have been identified and individuals with SP-C mutations range in age from infants to adults. The clinical manifestations extend from fatal respiratory failure to no clinically apparent respiratory symptoms. The pattern of inheritance appears to be autosomal dominant with variable penetrance. In infants and children, the most common histopathological pattern is nonspecific interstitial pneumonitis with features of pulmonary alveolar proteinosis. In contrast, usual interstitial pneumonitis is the most frequent pattern in adults. These mutations may cause lung fibrosis through protein misprocessing within the endoplasmic reticulum activating the unfolded protein response, proteasome dysfunction, and alveolar epithelial cell death. Alveolar type II cells expressing SP-C mutant proteins may be more susceptible to environmental factors that may trigger epithelial cell injury, death, and the development of parenchymal fibrosis. Understanding the pathogenetic mechanisms by which mutations in SP-C cause pulmonary fibrosis

Table 6.2 Published *SFTPC* mutations associated with IIP.

Mutation	Domain	Inheritance	Diagnosis	References
c.435+1 G>A (SP-C$^{\Delta exon4}$)	C-terminal peptide	Familial	Child: NSIP; adult: DIP	*(38)*
c.435+1 G>T (SP-C$^{\Delta exon4}$)	C-terminal peptide	Sporadic	Unknown	*(39)*
L188Q	C-terminal peptide	Familial	Children: NSIP; adults: UIP	*(44, 100)*
I73T	C-terminal peptide	Familial and sporadic	Children: DIP, NSIP, PAP, CPI; adult: UIP	*(33, 34, 37, 39, 40)*
P30L	Mature peptide	Unknown	Unknown	*(39)*
G100V	C-terminal peptide	Familial	Unknown	*(39)*
Y104H	C-terminal peptide	Familial by history	Unknown	*(39)*
P115L	C-terminal peptide	Familial	Unknown	*(39)*
T187N	C-terminal peptide	Familial by history	Unknown	*(39)*
140delA (deletion of adenosine in codon 140) c.420delA	C-terminal peptide	Sporadic	Unknown	*(39)*
del codons 91–93	C-terminal peptide	Sporadic	Child: fibrosis, alveolar proteinosis	*(36)*
E66K	C-terminal peptide	Sporadic	Child: NSIP, PAP	*(43)*
H64P	C-terminal peptide	Unknown	Unknown	*(35)*
C189G	C-terminal peptide	Unknown	Unknown	*(35)*
R167Q	C-terminal peptide	Unknown	Child: PAP	*(45)*
392delT	C-terminal peptide	Unknown	Child: NSIP	*(42)*
A116D	C-terminal peptide	Familial	Child: NSIP	*(41)*

Case Report

Pulmonary Pathology in Thyroid Transcription Factor-1 Deficiency Syndrome

Csaba Galambos[1], Hara Levy[2], Carolyn L. Cannon[2], Sara O. Vargas[1], Lynne M. Reid[1], Robert Cleveland[3], Robert Lindeman[2], Daphne E. deMello[4], Susan E. Wert[5], Jeffrey A. Whitsett[5], Antonio R. Perez-Atayde[1], and Harry Kozakewich[1]

[1]Department of Pathology, [2]Department of Medicine, and [3]Department of Radiology, Children's Hospital Boston, Boston, Massachusetts; [4]Department of Pathology, Phoenix Children's Hospital, Phoenix, Arizona; and [5]Division of Pulmonary Biology, Perinatal Institute, Children's Hospital Research Foundation, Cincinnati, Ohio

Thyroid transcription factor-1 (TTF-1) deficiency syndrome is characterized by neurologic, thyroidal, and pulmonary dysfunction. Children usually have mild-to-severe respiratory symptoms and occasionally die of respiratory failure. Herein, we describe an infant with a constitutional 14q12–21.3 haploid deletion encompassing the TTF-1 gene locus who had cerebral dysgenesis, thyroidal dysfunction, and respiratory insufficiency. The clinical course was notable for mild hyaline membrane disease, continuous ventilatory support, and symmetrically distributed pulmonary cysts by imaging. He developed pneumonia and respiratory failure and died at 8 months. Pathologically, the lungs had grossly visible emphysematous changes with "cysts" up to 2 mm in diameter. The airway generations and radial alveolar count were diminished. In addition to acute bacterial pneumonia, there was focally alveolar septal fibrosis, pneumocyte hypertrophy, and clusters of airspace macrophages. Ultrastructurally, type II pneumocytes had numerous lamellar bodies, and alveolar spaces contained fragments of type II pneumocytes and extruded lamellar bodies. Although immunoreactivity for surfactant protein SP-A and ABCA3 was diminished, that for SP-B and proSP-C was robust, although irregularly distributed, corresponding to the distribution of type II pneumocytes. Immunoreactivity for TTF-1 protein was readily detected. In summation, we document abnormal airway and alveolar morphogenesis and altered expression of surfactant-associated proteins, which may explain the respiratory difficulties encountered in TTF-1 haploinsufficiency. These findings are consistent with experimental evidence documenting the important role of TTF-1 in pulmonary morphogenesis and surfactant metabolism.

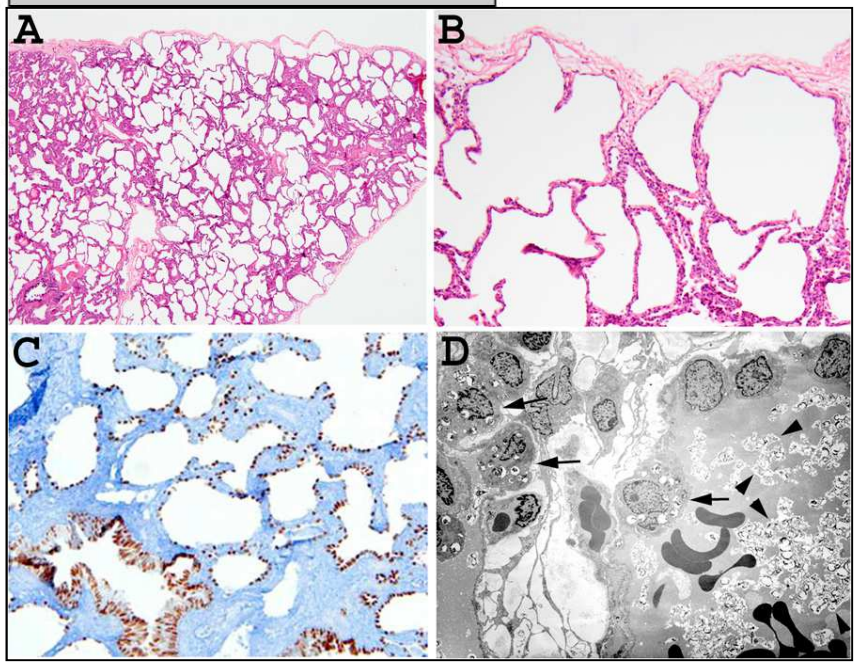
AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Awareness of TTF-1 deficiency syndrome and its pulmonary manifestations is limited. Studies describing pulmonary imaging and pathologic features are scarce.

What This Study Adds to the Field

We provide detailed pulmonary histopathologic, ultrastructural and immunohistochemical findings in an infant with this syndrome and describe abnormal airway and alveolar morphogenesis as well as abnormalities in surfactant protein expression in TTF-1 haploinsufficiency, which may account for the respiratory problems in this syndrome.



Modern Pathology (2007) 20, 1009–1018

www.modernpathology.org

Ultrastructural and molecular analysis in fatal neonatal interstitial pneumonia caused by a novel *ABCA3* mutation

Elisabeth Bruder[1], Jörg Hofmeister[2], Charalampos Aslanidis[3], Jürg Hammer[4], Lukas Bubendorf[1], Gerd Schmitz[3], Alex Rufle[1] and Christoph Bührer[2]

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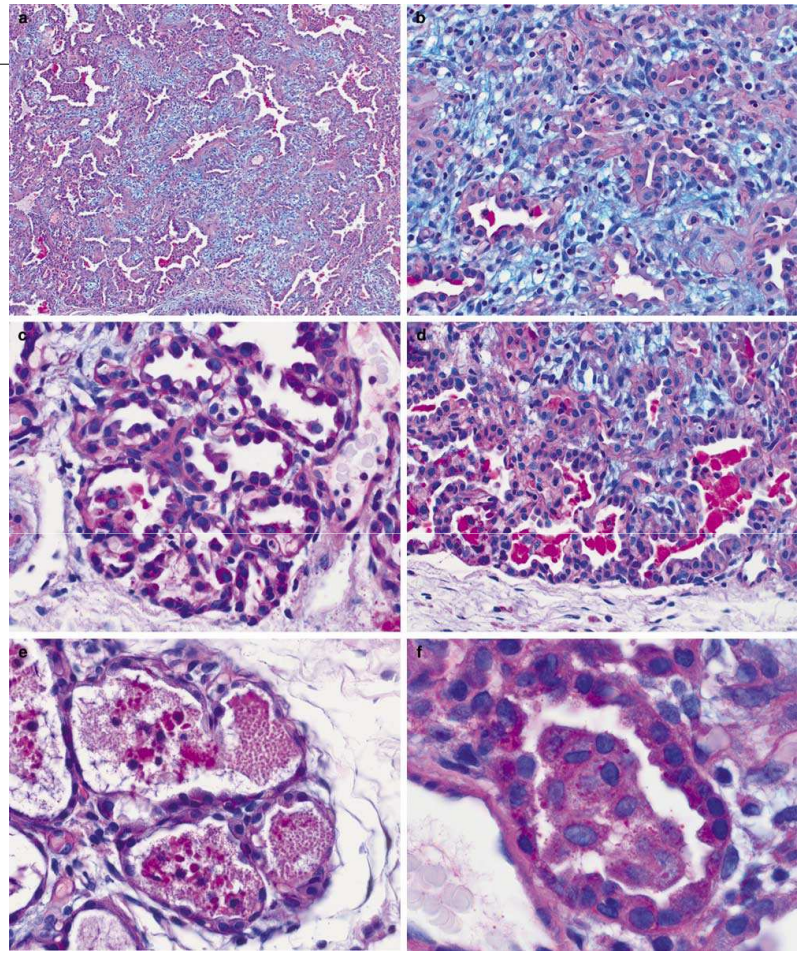
Pulmonary surfactant is essential to maintain alveolar patency, and invariably fatal neonatal lung disease has been recognized to involve mutations in the genes encoding surfactant protein-B or ATP-binding cassette transporter family member ABCA3. The lipid transporter ABCA3 targets surfactant phospholipids to lamellar bodies that are lysosomal-derived organelles of alveolar type II cells. *ABCA3*−/− mice have grossly reduced surfactant phosphatidyl glycerol levels and die of respiratory failure soon after birth. We studied lung biopsy samples of two siblings with a novel homozygous *ABCA3* mutation at nucleotide position 578 (c.578C>G), leading to a Pro193Arg amino-acid exchange, who died at 55 and 105 days of age. Light microscopy revealed thickened alveolar septa with abundant myxoid interstitial matrix, marked hyperplasia of type II pneumocytes, desquamation of alveolar macrophages and focal alveolar proteinosis. Surfactant protein-B was detected by immunohistochemistry after antigen retrieval. Transmission electron microscopy showed rare cytoplasmic inclusions with concentric membranes and eccentrically placed electron-dense aggregates. These 'fried-egg'-appearing lamellar bodies differed both from normal lamellar bodies and the larger, poorly formed composite bodies with multiple vesicular inclusions observed in surfactant protein-B deficiency. In conclusion, our findings underscore that the implications of interstitial lung disease in infant lungs differ from those in adults. In infants with a desquamative interstitial pneumonitis pattern, surfactant or *ABCA3* mutations should be evaluated. Importantly, these findings support the notion that electron microscopy is useful in distinguishing between surfactant protein-B and ABCA3 deficiency, and has an important role in evaluating biopsies or autopsies of term infants with unexplained severe respiratory failure and interstitial lung disease.
Modern Pathology (2007) **20,** 1009–1018; doi:10.1038/modpathol.3800928; published online 27 July 2007



ORIGINAL ARTICLE

ABCA3 Gene Mutations in Newborns with Fatal Surfactant Deficiency

Sergey Shulenin, Ph.D., Lawrence M. Nogee, M.D., Tarmo Annilo, Ph.D., Susan E. Wert, Ph.D., Jeffrey A. Whitsett, M.D., and Michael Dean, Ph.D.

ABSTRACT

BACKGROUND

Pulmonary surfactant forms a lipid-rich monolayer that coats the airways of the lung and is essential for proper inflation and function of the lung. Surfactant is produced by alveolar type II cells, stored intracellularly in organelles known as lamellar bodies, and secreted by exocytosis. The gene for ATP-binding cassette transporter A3 (ABCA3) is expressed in alveolar type II cells, and the protein is localized to lamellar bodies, suggesting that it has an important role in surfactant metabolism.

METHODS

We sequenced each of the coding exons of the *ABCA3* gene in blood DNA from 21 racially and ethnically diverse infants with severe neonatal surfactant deficiency for which the etiologic process was unknown. Lung tissue from four patients was examined by high-resolution light and electron microscopy.

RESULTS

Nonsense and frameshift mutations, as well as mutations in highly conserved residues and in splice sites of the *ABCA3* gene were identified in 16 of the 21 patients (76 percent). In five consanguineous families with mutations, each pair of siblings was homozygous for the same mutation and each mutation was found in only one family. Markedly abnormal lamellar bodies were observed by ultrastructural examination of lung tissue from four patients with different *ABCA3* mutations, including nonsense, splice-site, and missense mutations.

CONCLUSIONS

Mutation of the *ABCA3* gene causes fatal surfactant deficiency in newborns. ABCA3 is critical for the proper formation of lamellar bodies and surfactant function and may also be important for lung function in other pulmonary diseases. Since it is closely related to ABCA1 and ABCA4, proteins that transport phospholipids in macrophages and photoreceptor cells, it may have a role in surfactant phospholipid metabolism.

From the Human Genetics Section, Laboratory of Genomic Diversity, National Cancer Institute — Frederick, Frederick, Md. (S.S., T.A., M.D.); the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore (L.M.N.); and Cincinnati Children's Hospital Medical Center and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati (S.E.W., J.A.W.). Address reprint requests to Dr. Dean at Bldg. 560, Rm. 21-18, NCI — Frederick, Frederick, MD 21702, or at dean@ncifcrf.gov.

N Engl J Med 2004;350:1296-303.

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ABCA3 Is Critical for Lamellar Body Biogenesis *in Vivo*[*]

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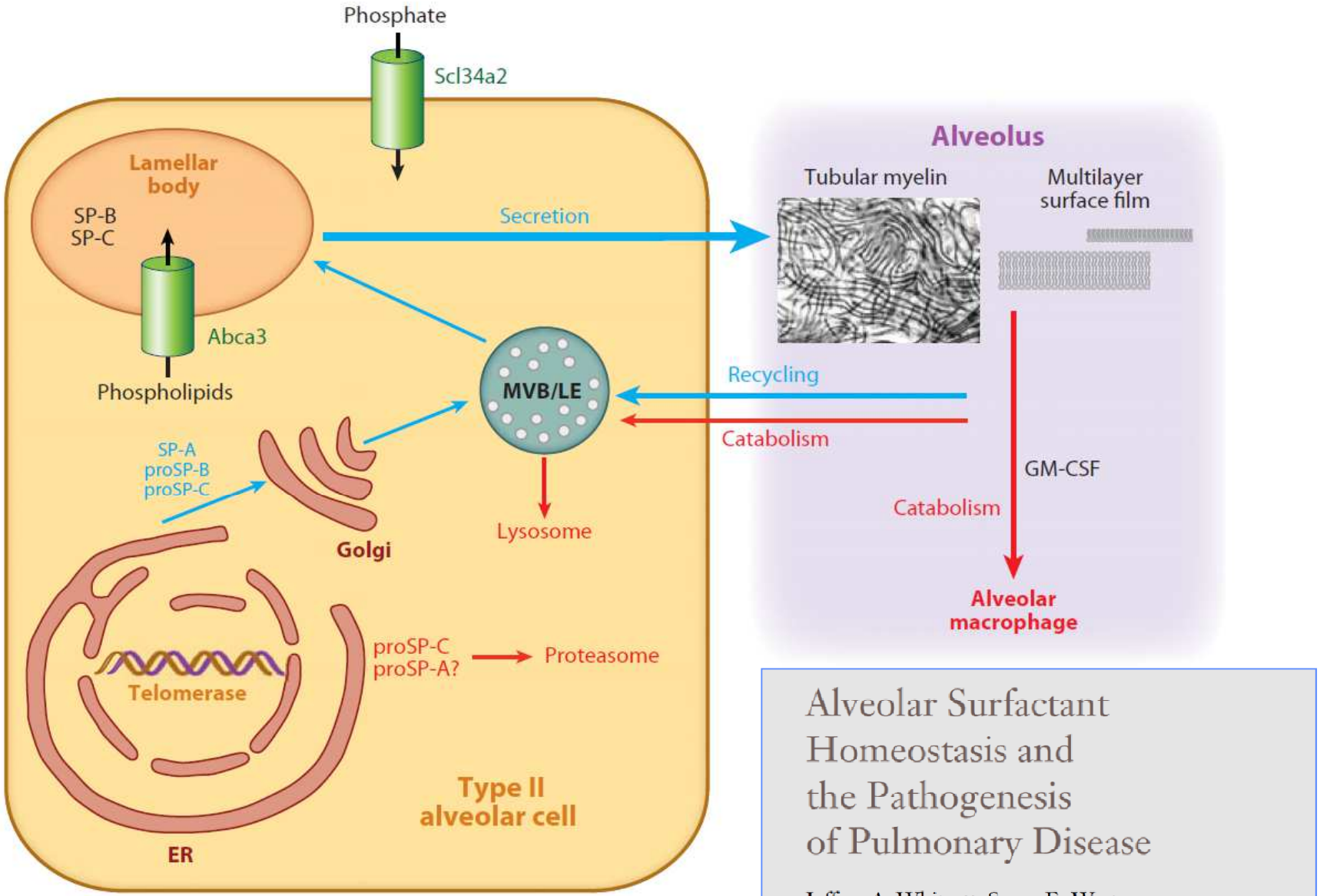
Mutations in ATP-binding cassette transporter A3 (human ABCA3) protein are associated with fatal respiratory distress syndrome in newborns. We therefore characterized mice with targeted disruption of the *ABCA3* gene. Homozygous $Abca3^{-/-}$ knock-out mice died soon after birth, whereas most of the wild type, $Abca3^{+/+}$, and heterozygous, $Abca3^{+/-}$, neonates survived. The lungs from E18.5 and E19.5 $Abca3^{-/-}$ mice were less mature than wild type. Alveolar type 2 cells from $Abca3^{-/-}$ embryos contained no lamellar bodies, and expression of mature SP-B protein was disrupted when compared with the normal lung surfactant system of wild type embryos. Small structural and functional differences in the surfactant system were seen in adult $Abca3^{+/-}$ compared with $Abca3^{+/+}$ mice. The heterozygotes had fewer lamellar bodies, and the incorporation of radiolabeled substrates into newly synthesized disaturated phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, and phosphatidylserine in both lamellar bodies and surfactant was lower than in $Abca3^{+/+}$ mouse lungs. In addition, since the fraction of near term $Abca3^{-/-}$ embryos was significantly lower than expected from Mendelian inheritance ABCA3 probably plays roles in development unrelated to surfactant. Collectively, these findings strongly suggest that ABCA3 is necessary for lamellar body biogenesis, surfactant protein-B processing, and lung development late in gestation.

lated (4–6). The final steps in post-translational modification of both SP-B and SP-C occur in lamellar bodies (7–11). One of the striking abnormalities observed in hereditary SP-B deficiency, which is characterized by deficiencies of surfactant quantity and function, is derangement of lamellar body morphology (12), abnormalities that are replicated in the SP-B knock-out mouse (13, 14).

Fatal deficiencies of lung surfactant in the neonate and interstitial lung disease have recently been associated with mutations in the ATP-binding cassette protein A3 gene (ABCA3) (15, 16). ABCA3 is required for normal lamellar body formation in AT2 cells (17). Similarly, the lamellar bodies in electron micrographs from lung tissue of infants with surfactant deficiency and *ABCA3* mutations have dense inclusions and are structurally immature (15, 18, 19). ABCA3 expressed exogenously in cultured cells, in the absence of surfactant proteins, facilitates the transfer of phosphatidylcholine and cholesterol into the lysosomes, the likely progenitor of lamellar bodies, whereas the surfactant in infants with ABCA3 mutations has decreased phosphatidylcholine content (17, 20). The surfactant phosphatidylcholine (PC) and phosphatidylglycerol (PG) content is decreased in $Abca3^{-/-}$ mice (21, 22). Decreased expression of ABCA3 in both isolated AT2 cells and in lungs alters the expression, localization, and processing of SP-B protein (16, 17, 19). Together, these findings are suggestive that ABCA3 is



Alveolar Surfactant Homeostasis and the Pathogenesis of Pulmonary Disease

Jeffrey A. Whitsett, Susan E. Wert, and Timothy E. Weaver

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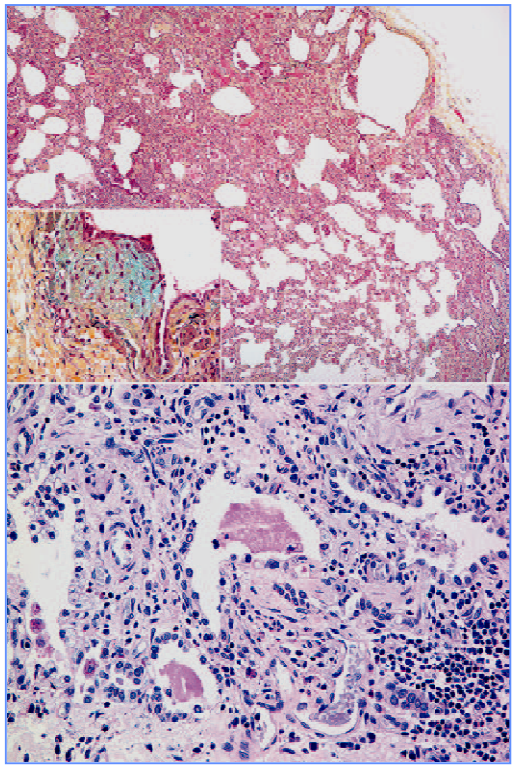
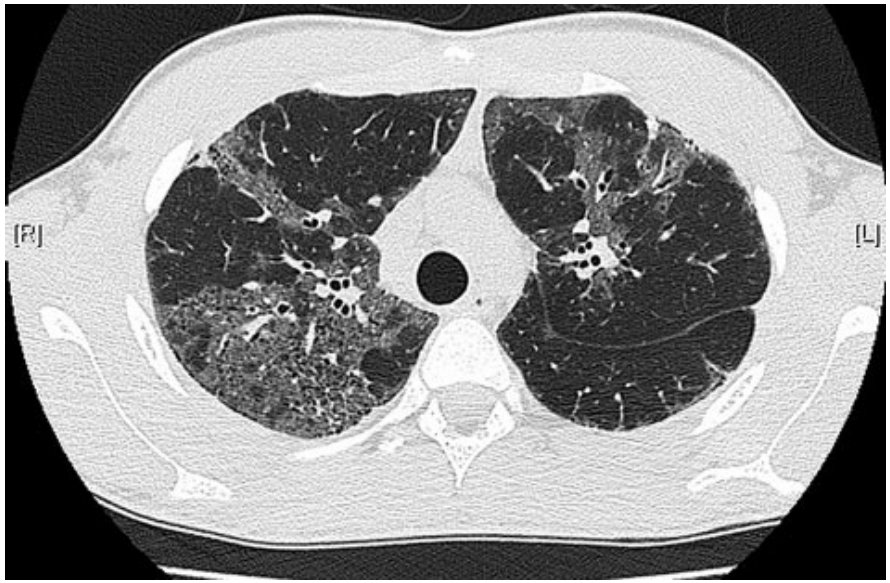
Annu. Rev. Med. 2010. 61:105–19

Usual Interstitial Pneumonia in an Adolescent With *ABCA3* Mutations*

Lisa R. Young, MD; Lawrence M. Nogee, MD, FCCP; Bruce Barnett, MD; Ralph J. Panos, MD; Thomas V. Colby, MD, FCCP; and Gail H. Deutsch, MD





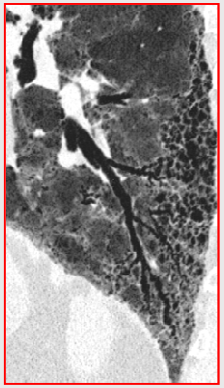
Many diverse and frequently idiopathic disorders cause interstitial lung disease (ILD) in children. Although the histologic patterns of ILD in children and adults share similar features, important differences exist in etiology, clinical manifestations, and outcome. Usual interstitial pneumonia (UIP) is the most frequent histologic pattern in adult ILD; however, the characteristic histologic features of UIP have yet to be demonstrated in a child. We report a 15-year-old boy with the UIP pattern of pulmonary fibrosis who had mutations in the adenosine triphosphate-binding-cassette-A3 gene. Discovery of how genetic mutations of proteins involved in surfactant biosynthesis lead to progressive fibrosis will have implications for the understanding of the pathogenesis and clinical manifestations of ILD in both adults and children. *(CHEST 2008; 134:192–195)*

Cell senescence

- is a permanent state of cell cycle arrest unresponsive to growth factors that can be triggered by different mechanisms including:

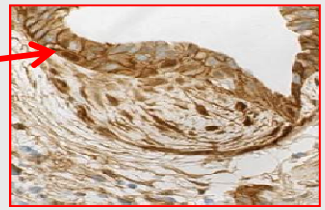
- *replicative telomere erosion,*
- *cellular stresses,*
- *DNA damage,*
- *oncogene activation (OIS)*

Etio-pathogenic model for IPF:
matching clinical, pathological and imaging features

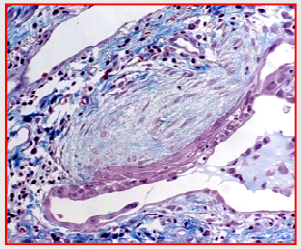


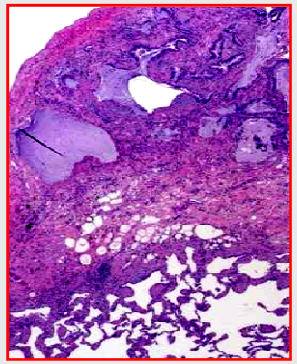
- **Age**
- **Smoke**
- **Lower-posterior lobes**

- **Familial vs sporadic**
- **Exacerbations**
- **Molecular features** *(wnt, caveolin, etc.)*



- **Remodelling**
  - ***fibroblast foci***
  - ***honeycombing***

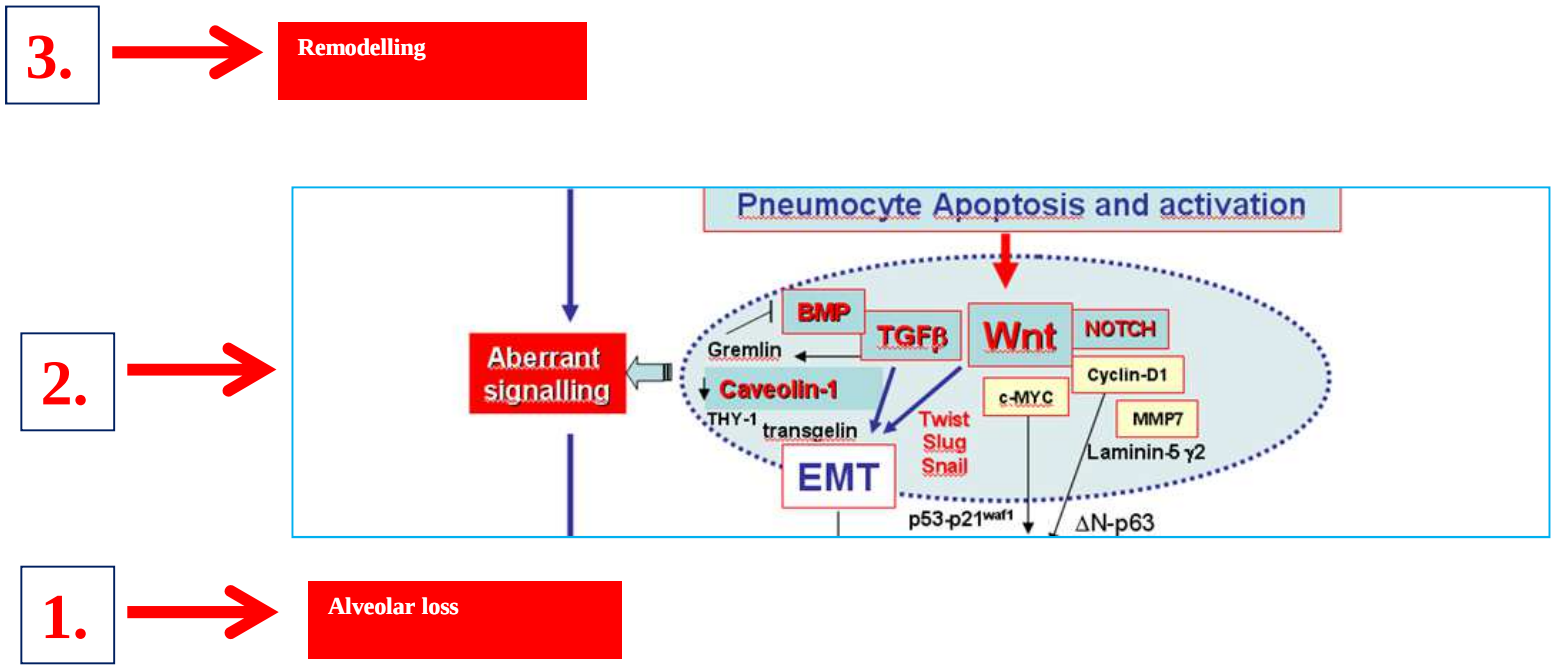




Sarcoidosis Vasc Diffuse Lung Dis. 2010

Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis

M. Chilosi[1], C. Doglioni[2], B. Murer[3], V. Poletti[4]




OIS: a dangerous mechanism
PLAST
plasty
KOMWAG
SKLO
Prague, June 2014

OIS
Oncogene Induced Senescence

• Oncogene-induced senescence (OIS) is a defense mechanism and a major obstacle to cancer development and progression.

• As senescent cells are incapable of further proliferation, OIS has to be overcome for cancers to grow and progress (e.g. mutations in p53, p16 genes).

nature Vol 436|4 August 2005|doi:10.1038/nature03890

LETTERS

BRAF^{E600}-associated senescence-like cell cycle arrest of human naevi

Chrysiis Michaloglou[1]*, Liesbeth C. W. Vredeveld[1]*, Maria S. Soengas[3]*, Christophe Denoyelle[3], Thomas Kuilman[1], Chantal M. A. M. van der Horst[4], Donné M. Majoor[2], Jerry W. Shay[5], Wolter J. Mooi[6] & Daniel S. Peeper[1]

Most normal mammalian cells have a finite lifespan[1], thought to constitute a protective mechanism against unlimited proliferation[2–4]. This phenomenon, called senescence, is driven by telomere attrition, which triggers the induction of tumour suppressors including p16^{INK4a} (ref. 5). In cultured cells, senescence can be elicited prematurely by oncogenes[6]; however, whether such oncogene-induced senescence represents a physiological process has long been debated. Human naevi (moles) are benign tumours of melanocytes that frequently harbour oncogenic mutations (predominantly V600E, where valine is substituted for glutamic acid) in BRAF[7], a protein kinase and downstream effector of Ras. Nonetheless, naevi typically remain in a growth-arrested state for decades and only rarely progress into malignancy (melanoma)[8–10]. This raises the question of whether naevi undergo BRAF^{V600E}-induced senescence. Here we show that sustained BRAF^{V600E} expression in human melanocytes induces cell cycle arrest, which is accompanied by the induction of both p16^{INK4a} and senescence-associated acidic β-galactosidase (SA-β-Gal) activity, a commonly used senescence marker. Validating these results *in vivo*, congenital naevi are invariably positive for SA-β-Gal, demonstrating the presence of this classical senescence-associated marker in a largely growth-arrested, neoplastic human lesion. In growth-arrested melanocytes, both *in vitro* and *in situ*, we observed a marked mosaic induction of p16^{INK4a}, suggesting that factors other than p16^{INK4a} contribute to protection against BRAF^{V600E}-driven proliferation. Naevi do not appear to suffer from telomere attrition, arguing in favour of an active oncogene-driven senescence process, rather than a loss of replicative potential. Thus, both *in vitro* and *in vivo*, BRAF^{V600E}-expressing melanocytes display classical hallmarks of senescence, suggesting that oncogene-induced senescence represents a genuine protective physiological process.

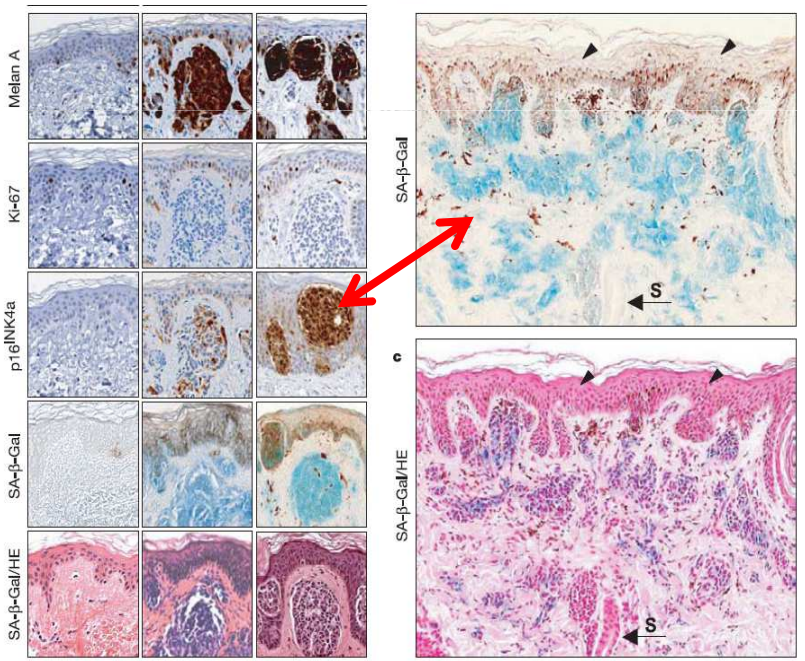
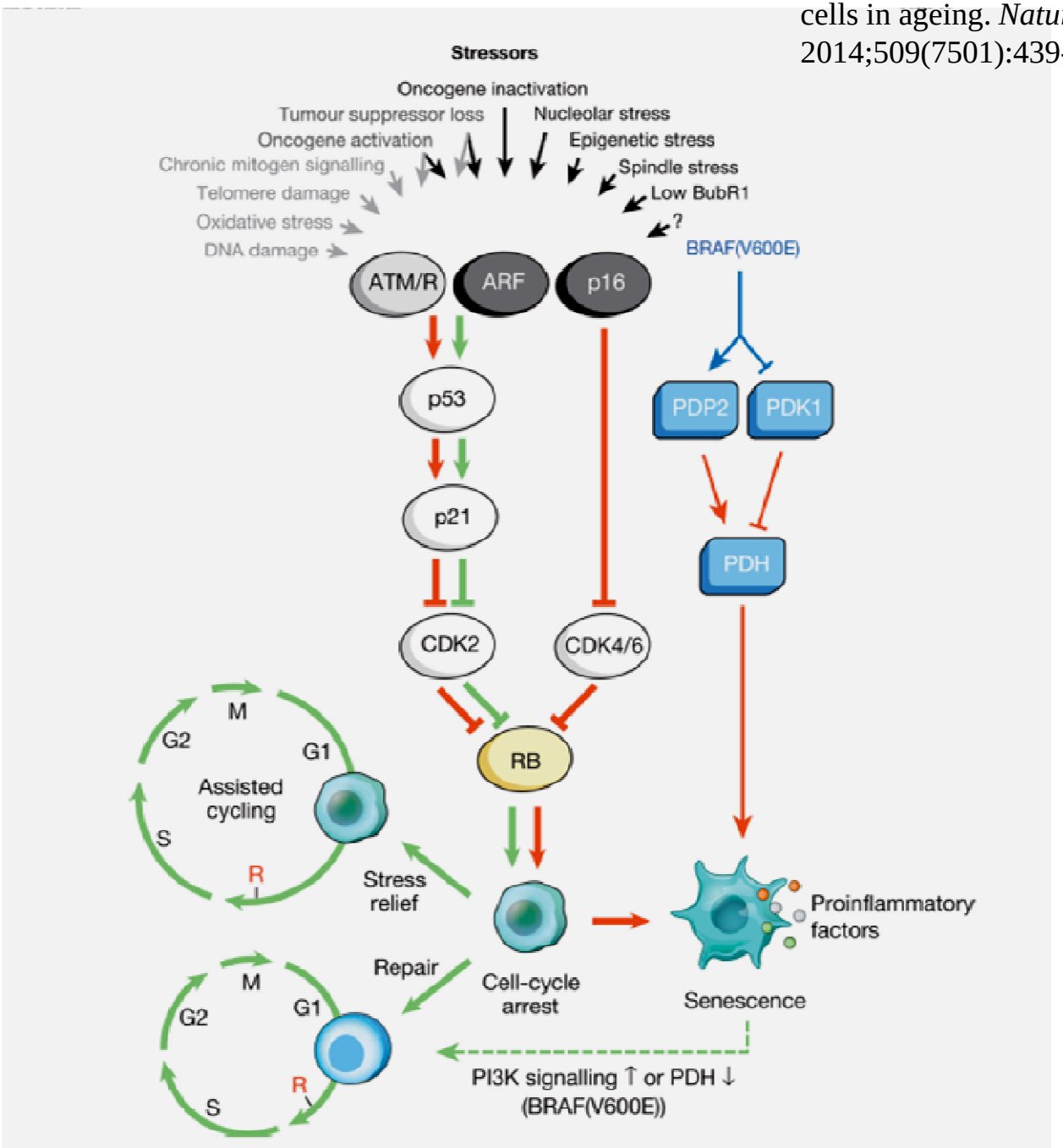
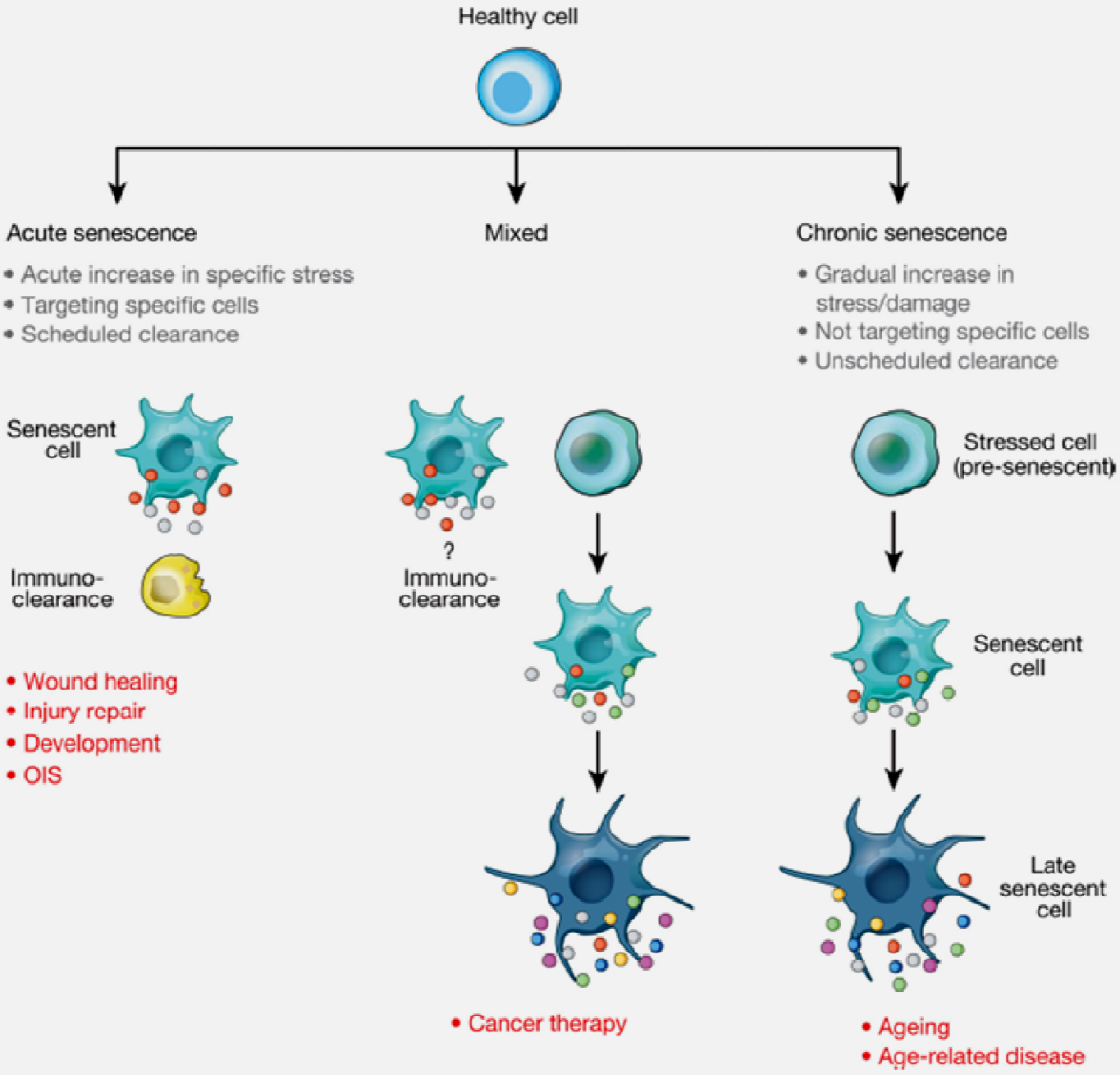


Figure 3 | Human melanocytic naevi display the hallmarks of senescent cells. Paraffin-embedded sections of human naevi and normal skin were subjected to immunohistochemistry with the indicated antibodies. **a**, Melan A (brown) identifies melanocytes, MIB1 (brown) recognizes the proliferation marker Ki-67 and p16^{INK4a} antibody (brown) detects p16^{INK4a}. **a–c**, Frozen sections of human naevi were subjected to SA-β-Gal staining. The blue staining corresponds exactly to the sites of naevus cell nests. All cells of the epidermis (mostly keratinocytes, arrowheads) and sweat gland (S), as well as dermal cells between the naevus cell nests, are completely negative for SA-β-Gal (**b** and **c**). Note that the brown staining in these samples comes from pigment released by the naevus cells. Where indicated, haematoxylin and eosin (HE) was used as a counter stain on the consecutive (SA-β-Gal-stained) section to visualize the melanocyte lesions, within the context of the surrounding tissue.

Van Deursen JM. The role of senescent cells in ageing. *Nature* 2014;509(7501):439-446




Healthy cell
Acute senescence
• Acute increase in specific stress
• Targeting specific cells
• Scheduled clearance
Mixed
Chronic senescence
• Gradual increase in stress/damage
• Not targeting specific cells
• Unscheduled clearance
Senescent cell
Immuno-clearance
• Wound healing
• Injury repair
• Development
• OIS
?
Immuno-clearance
• Cancer therapy
Stressed cell (pre-senescent)
Senescent cell
Late senescent cell
• Ageing
• Age-related disease

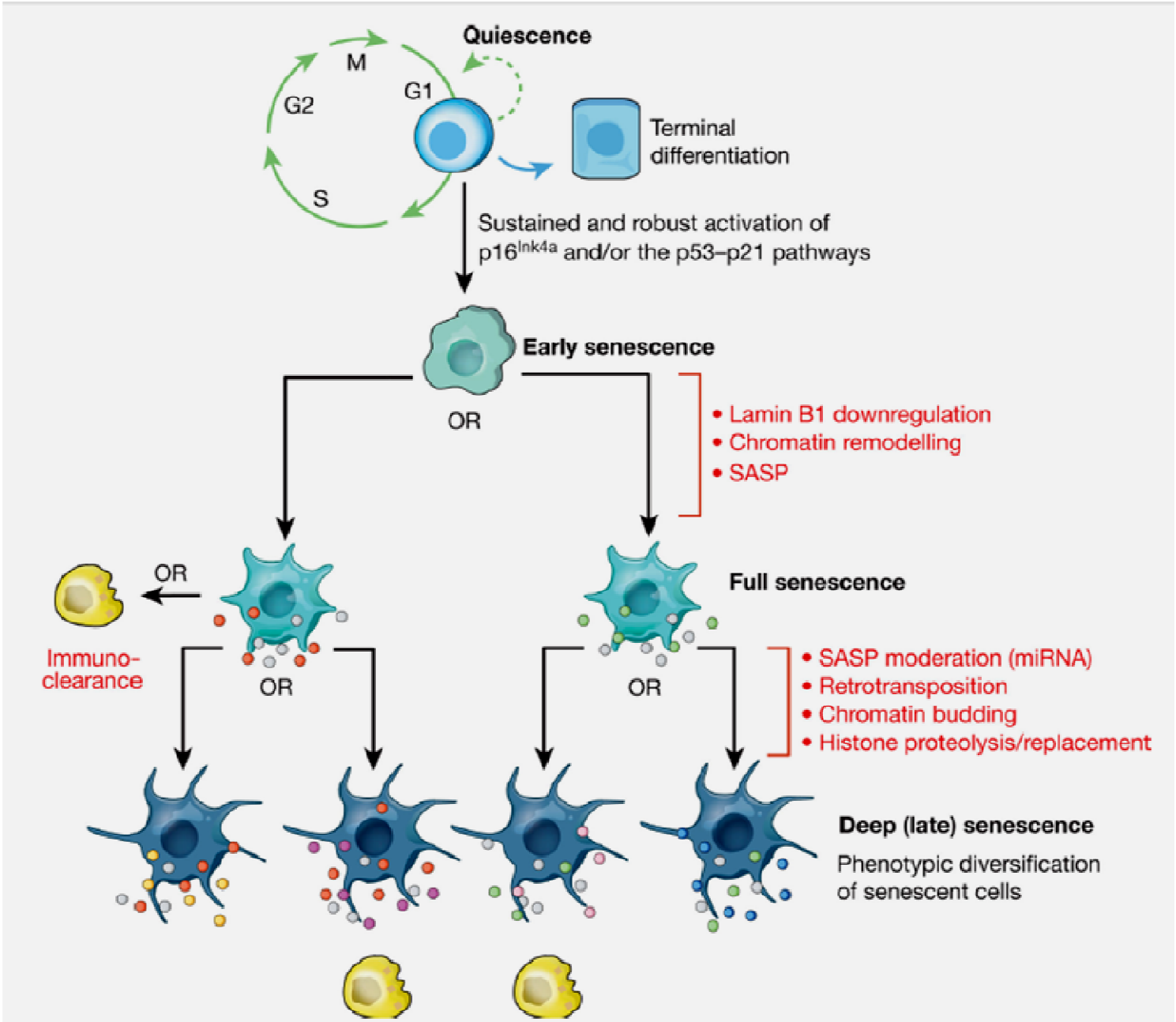


Figure 2. Hypothetical multi-step senescence model

Mounting evidence suggests that cellular senescence is a dynamic process driven by

The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression

SASP

Jean-Philippe Coppé,[1] Pierre-Yves Desprez,[2,3] Ana Krtolica,[1] and Judith Campisi[1,2]

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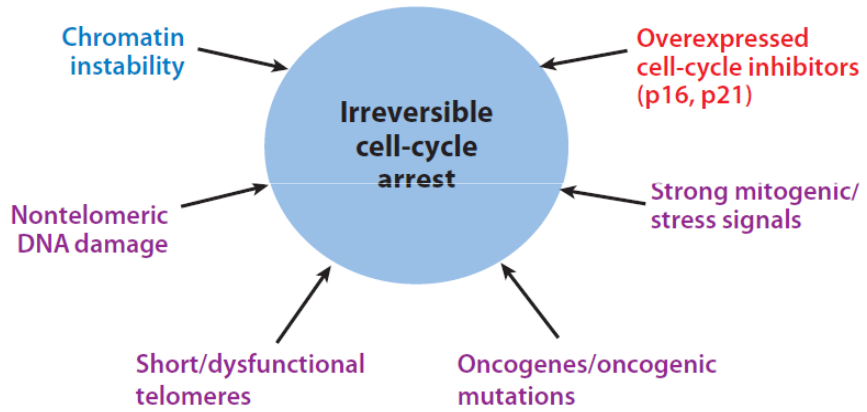
Abstract

Cellular senescence is a tumor-suppressive mechanism that permanently arrests cells at risk for malignant transformation. However, accumulating evidence shows that senescent cells can have deleterious effects on the tissue microenvironment. The most significant of these effects is the acquisition of a senescence-associated secretory phenotype (SASP) that turns senescent fibroblasts into proinflammatory cells that have the ability to promote tumor progression.

The secretory phenotype of senescent cells



DNA damage = SASP
No DNA damage = No SASP

Table 1 The senescence-associated secretory phenotype (SASP). Factors significantly altered between presenescent and senescent states are listed

SASP factors[a]	Secretory profile of senescent cells[b]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
Soluble factors		
Interleukins (IL)		
IL-6	↑	↑
IL-7	↑	↑
IL-1a, -1b	↑	↑
IL-13	↑	↑
IL-15	↑	↑
Chemokines (CXCL, CCL)		
IL-8	↑	↑
GRO-a,-b,-g[c]	↑	↑
MCP-2	↑	↑
MCP-4	↑	×
MIP-1a	↑	↑
MIP-3a	↑	×
HCC-4	↑	×
Eotaxin	×	↑
Eotaxin-3	↑	↑
TECK	×	↑
ENA-78	×	↑
I-309	×	↑
I-TAC	×	↓
Other inflammatory factors		
GM-CSF	↑	↑
G-CSF	×	↑
IFN-γ	×	↑
BLC	×	↑
MIF	↑	↓
Growth factors and regulators		
Amphiregulin	↑	×
Epiregulin	↑	×
Heregulin	↑	×
EGF	↑ or ×	↑
bFGF	↑	↑
HGF	↑	×
KGF (FGF7)	↑	↑
VEGF	↑	×
Angiogenin	↑	×
SCF	↑	×
SDF-1	↑ or ×	↑
PIGF	↑	×
NGF	×	↓

(Continued)

Telomere dysfunction causes alveolar stem cell failure

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[a]Department of Oncology, [b]Sidney Kimmel Comprehensive Cancer Center, and [g]McKusick–Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205; Departments of [c]Medicine and [f]Cell Biology, Duke University School of Medicine, Durham, NC 27710; [d]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205; and [e]Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Denver, Aurora, CO 80045

Significance

Idiopathic pulmonary fibrosis and emphysema are leading causes of mortality, but there are no effective therapies. Mutations in telomerase are the most common identifiable risk factor for idiopathic pulmonary fibrosis. They also predispose to severe emphysema in smokers, occurring at a frequency similar to α-1 antitrypsin deficiency. The work shown here points to alveolar stem cell senescence as a driver of these pathologies. Epithelial stem cell failure was associated with secondary inflammatory recruitment and exquisite susceptibility to injury from "second hits." The findings suggest that efforts to reverse the stem cell failure state directly, rather than its secondary consequences, may be an effective therapy approach in telomere-mediated lung disease.

GENETICS

Leukemia & Lymphoma, November 2014; 55(11): 2620–2626

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2014.887713

informa
healthcare

ORIGINAL ARTICLE: RESEARCH

Oncogene-induced senescence distinguishes indolent from aggressive forms of pulmonary and non-pulmonary Langerhans cell histiocytosis

Marco Chilosi[1], Fabio Facchetti[2], Anna Caliò[1], Alberto Zamò[1], Matteo Brunelli[1], Guido Martignoni[1], Andrea Rossi[3], Licia Montagna[1], Paola Piccoli[1], Alessandra Dubini[4], Andrea Tironi[2], Sara Tomassetti[5], Venerino Poletti[5] & Claudio Doglioni[6]

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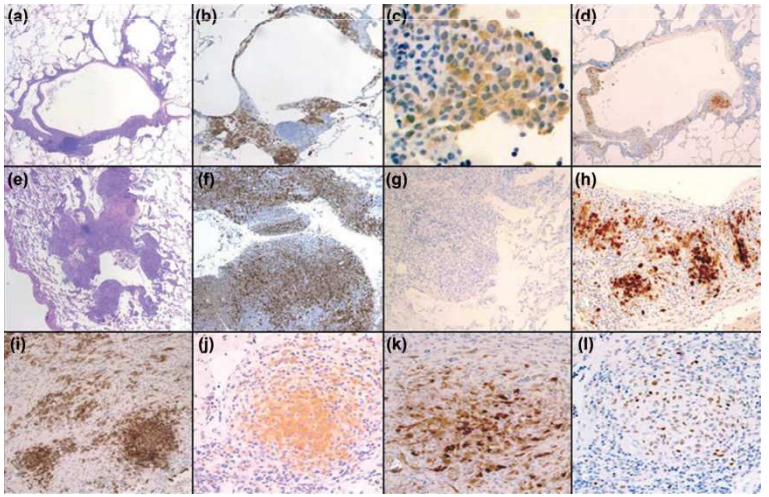
Abstract

The clonal/neoplastic nature of Langerhans cell histiocytosis (LCH) has recently been demonstrated by a high prevalence of *BRAF* mutations, including pulmonary LCH (PLCH). We hypothesized that *BRAF*-induced senescence, as demonstrated in nevi and melanoma, is involved in the pathogenesis of LCH and PLCH. In a series of pulmonary (19 cases) and non-pulmonary LCH (19 cases), including five aggressive cases, we investigated occurrence of the *BRAF* V600E mutation by molecular analysis and/or immunohistochemistry using a validated antibody (VE1). The expression of cell-senescence markers $p16^{INK4a}$ and $p21^{CIP1/WAF1}$ was also immunohistochemically investigated. We demonstrated that 6/19 cases of LCH and 12/19 cases of PLCH were VE1 positive, matching with molecular analysis, and in all cases both $p16^{INK4a}$ and $p21^{CIP1/WAF1}$ were expressed, irrespective of *BRAF* mutation status. Interestingly, all the aggressive cases did not express $p16^{INK4a}$, thus suggesting that loss of senescence control could be related to clinical aggressiveness of LCH, as in melanoma.



12/19 pulmonary LCH → BRAF+
19/19 → p16+, p21+

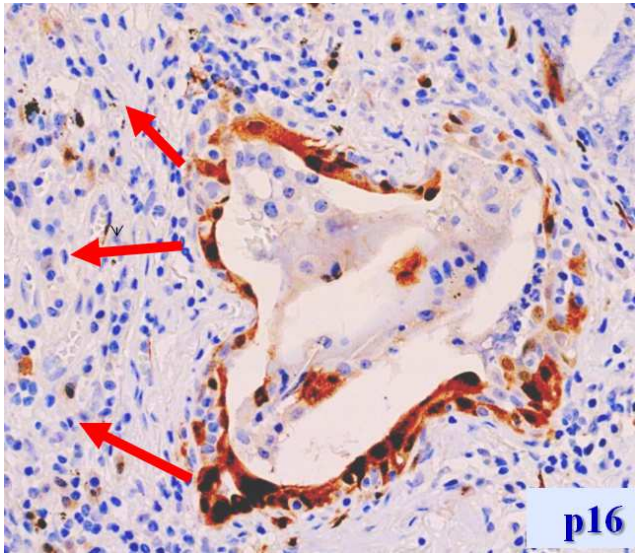
- **beta-catenin is an oncogene**
- **can trigger cell senescence by OIS,**
- **can amplify in a vicious circle aberrant signaling and SASP**

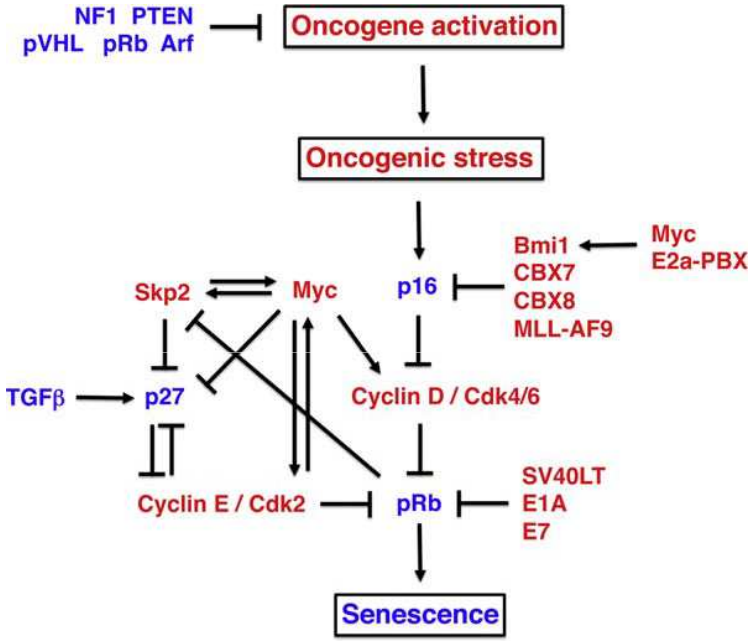
MOLECULAR AND CELLULAR BIOLOGY, Mar. 2008, p. 1713–1723 Vol. 28, No. 5
0270-7306/08/$08.00+0 doi:10.1128/MCB.01360-07

β-Catenin Expression Results in p53-Independent DNA Damage and Oncogene-Induced Senescence in Prelymphomagenic Thymocytes In Vivo▽†

Mai Xu,[1] Qing Yu,[1] Ramesh Subrahmanyam,[2] Michael J. Difilippantonio,[3] Thomas Ried,[3] and Jyoti Misra Sen[1]*

Lymphocyte Development Unit, Laboratory of Immunology,[1] and Laboratory of Cellular and Molecular Biology,[2] National Institute on Aging, Baltimore, Maryland 21224, and Section of Cancer Genomics, Genetics Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892[3]





SASP

Oncogene (2012), 1–9

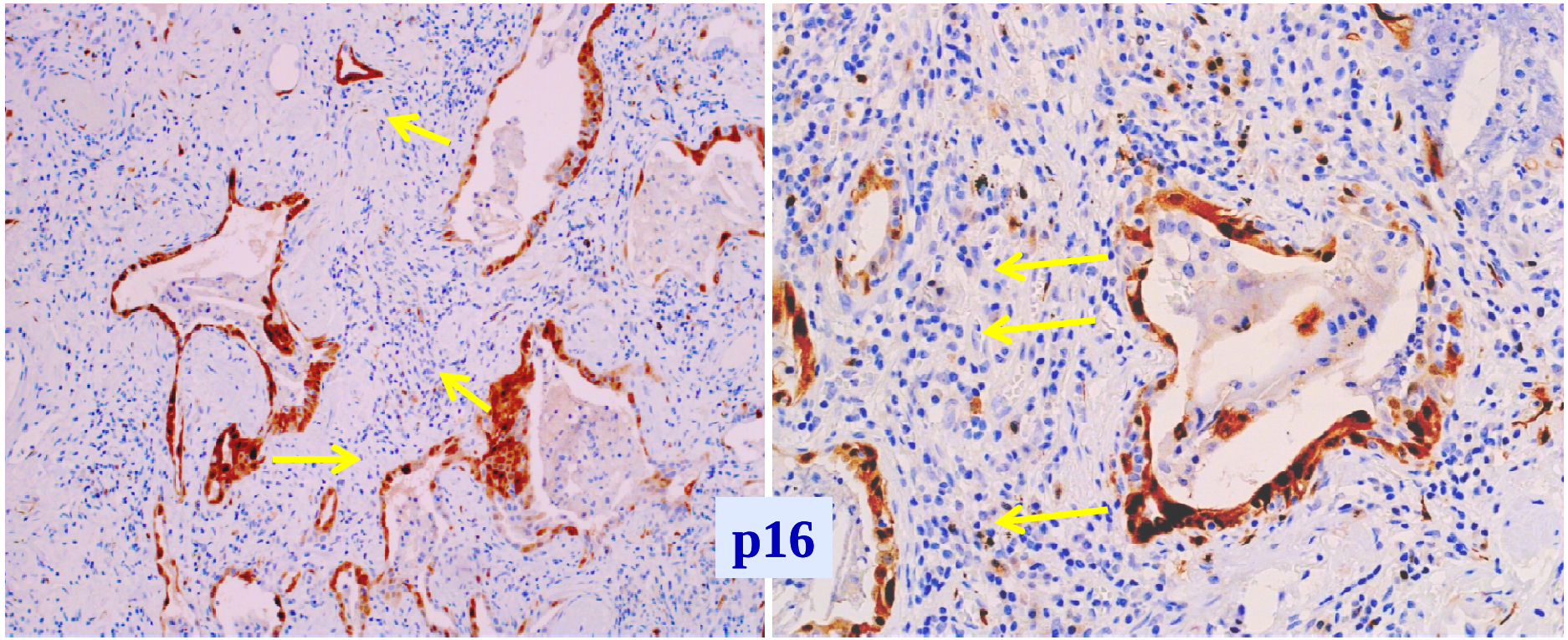
www.nature.com/onc

ORIGINAL ARTICLE

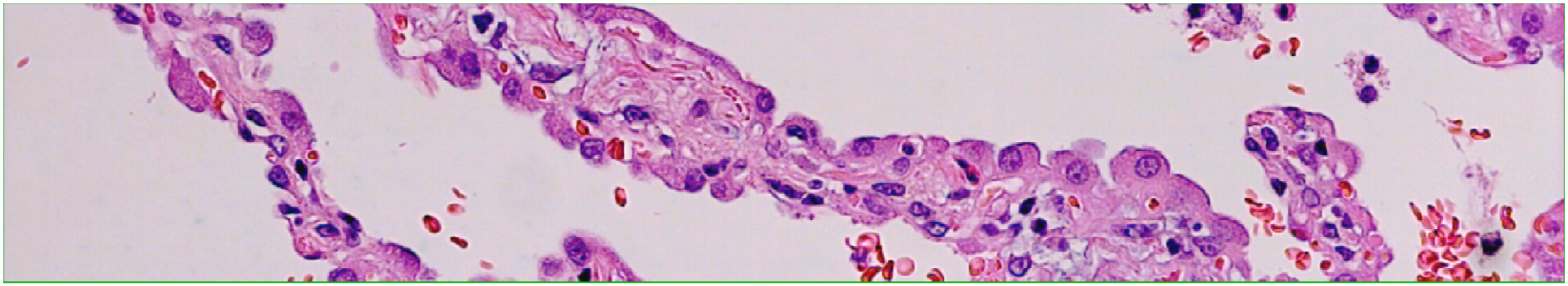
Molecular basis for the tissue specificity of β-catenin oncogenesis

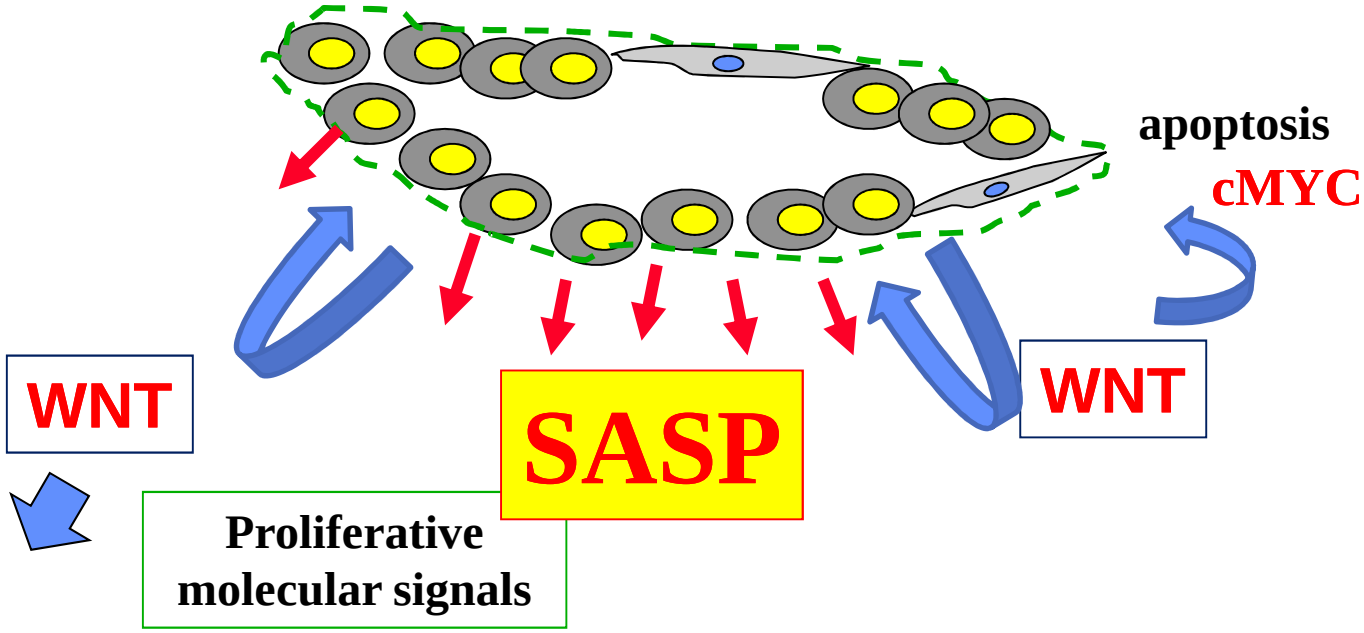
A Sharma and JM Sen

Inflammation in IPF

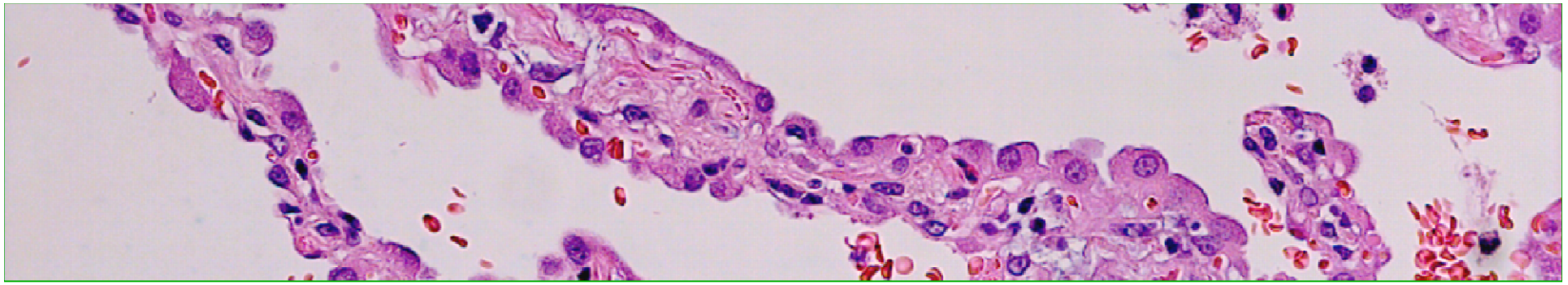


SASP





- *Progressive alveolar loss*
- *PN-II attempted regeneration*
- *Frustrated renewal*



- Progressive alveolar loss
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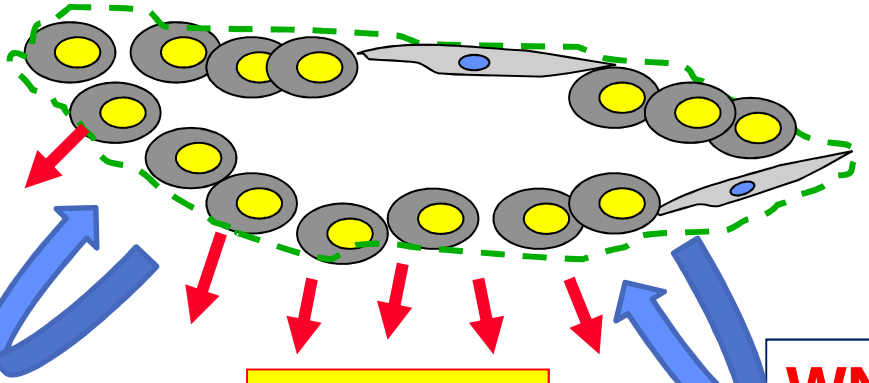


apoptosis

cMYC

WNT

SASP

WNT

Proliferative molecular signals

Bronchiolar proliferation Honeycombing

Gremlin

BMP

OIS

Beta-Catenin

myofibroblast proliferation

WNT

Vascular changes

neoangiogenesis

INTERSTITIAL FIBROSIS Honeycombing

EMT

PAH

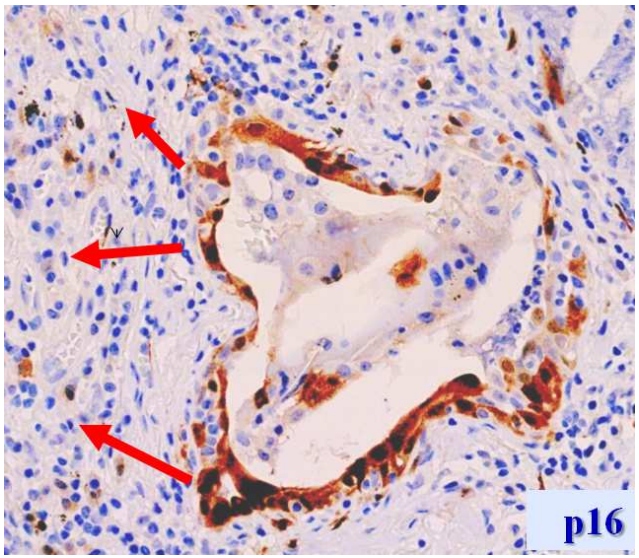
- **beta-catenin is an <u>oncogene</u>**
- **can trigger cell senescence by OIS,**
- **can amplify in a vicious circle aberrant signaling and SASP**

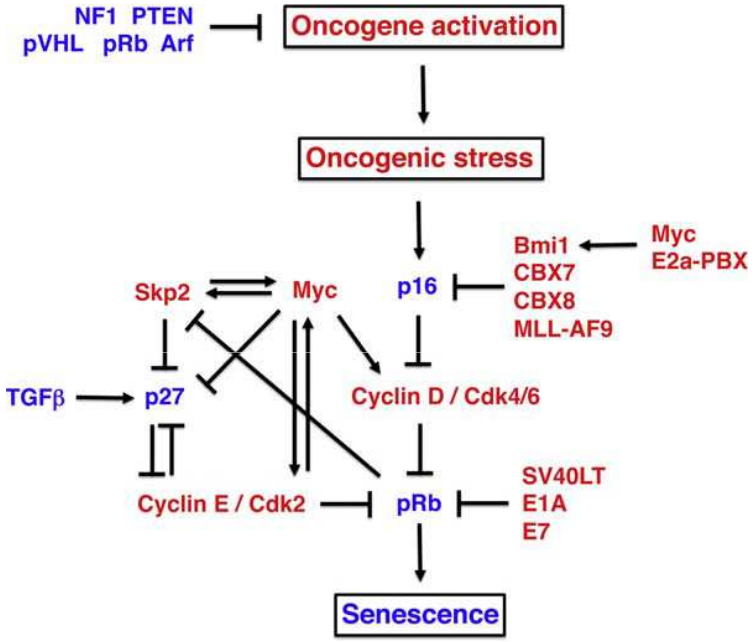
MOLECULAR AND CELLULAR BIOLOGY, Mar. 2008, p. 1713–1723 Vol. 28, No. 5
0270-7306/08/$08.00+0 doi:10.1128/MCB.01360-07

β-Catenin Expression Results in p53-Independent DNA Damage and Oncogene-Induced Senescence in Prelymphomagenic Thymocytes In Vivo▽†

Mai Xu,[1] Qing Yu,[1] Ramesh Subrahmanyam,[2] Michael J. Difilippantonio,[3] Thomas Ried,[3] and Jyoti Misra Sen[1]*

Lymphocyte Development Unit, Laboratory of Immunology,[1] and Laboratory of Cellular and Molecular Biology,[2] National Institute on Aging, Baltimore, Maryland 21224, and Section of Cancer Genomics, Genetics Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892[3]





SASP

Oncogene (2012), 1–9

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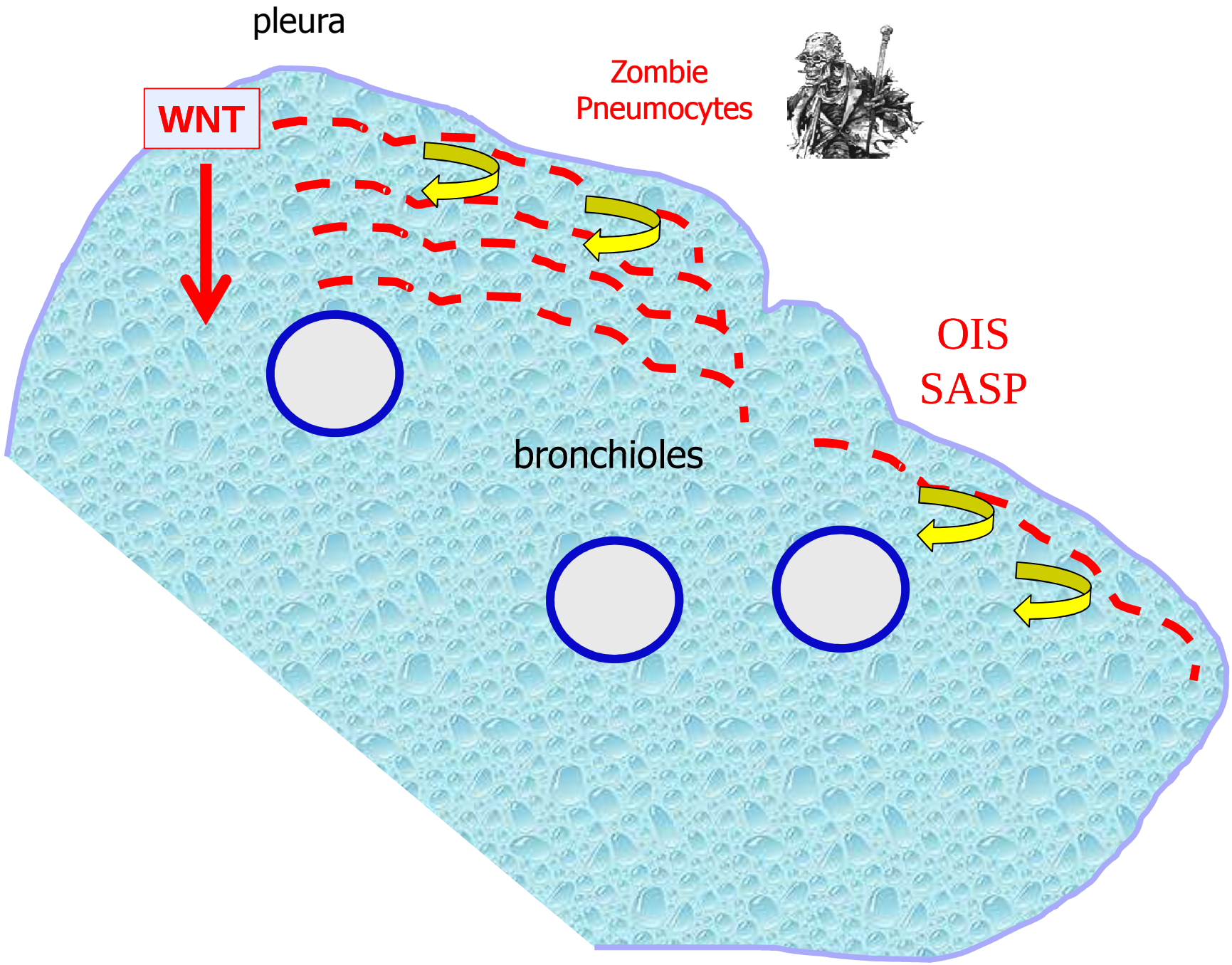
ORIGINAL ARTICLE

Molecular basis for the tissue specificity of β-catenin oncogenesis

A Sharma and JM Sen


pleura
WNT
Zombie
Pneumocytes
OIS
SASP
bronchioles

pleura

Zombie
Pneumocytes

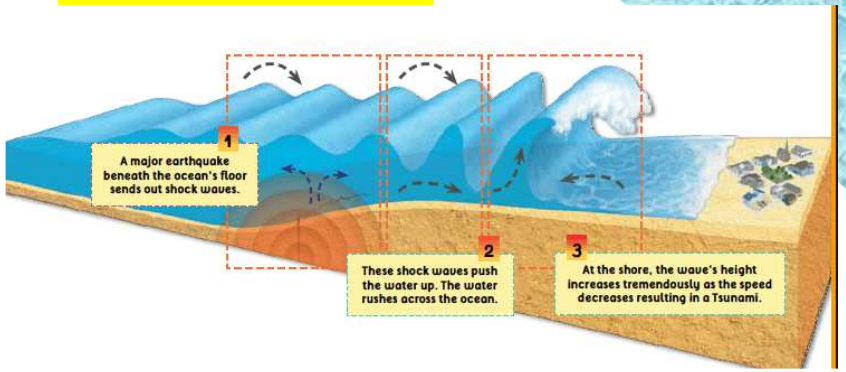
WNT

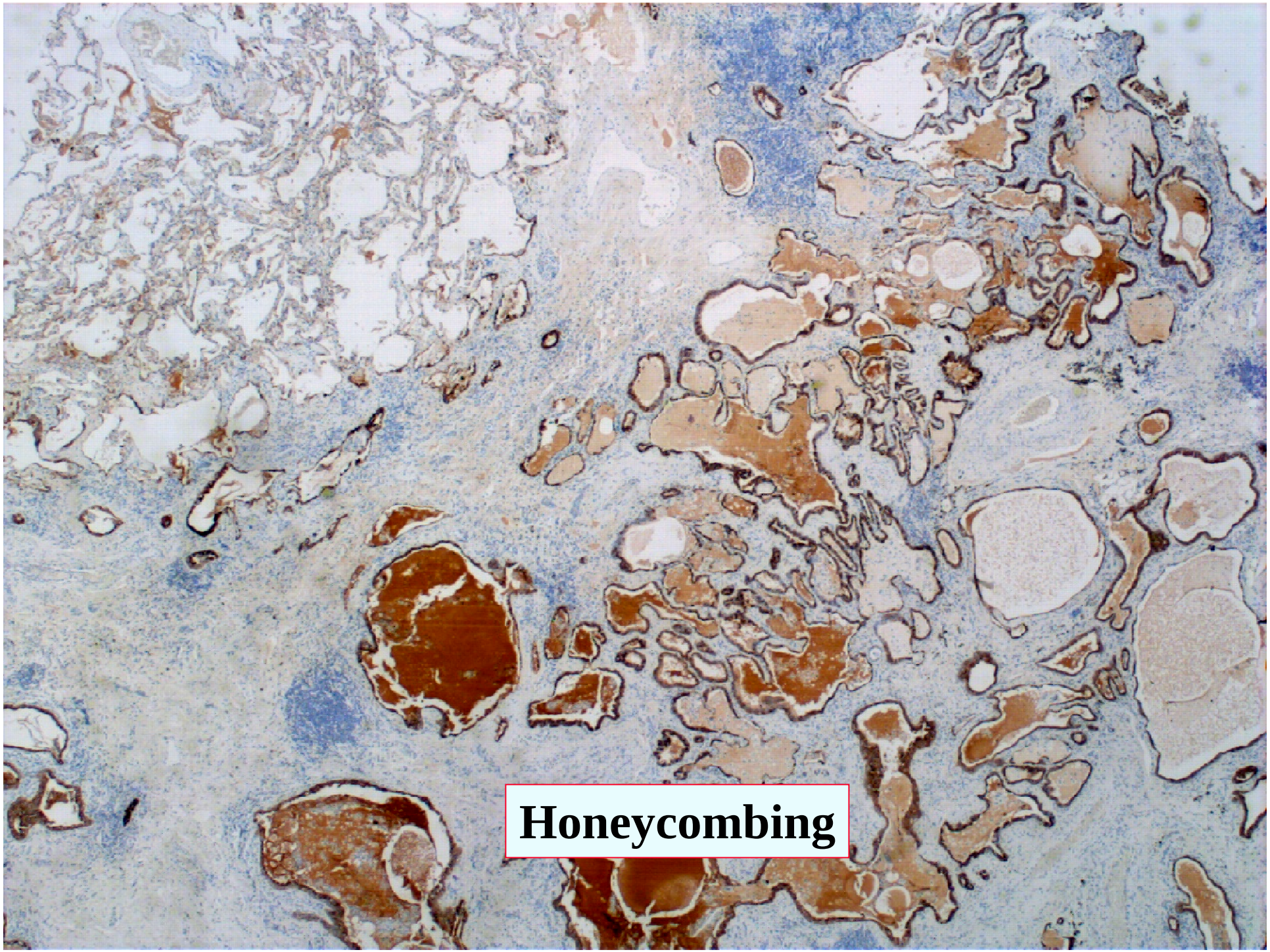
OIS
SASP

Micro-Honeycombing

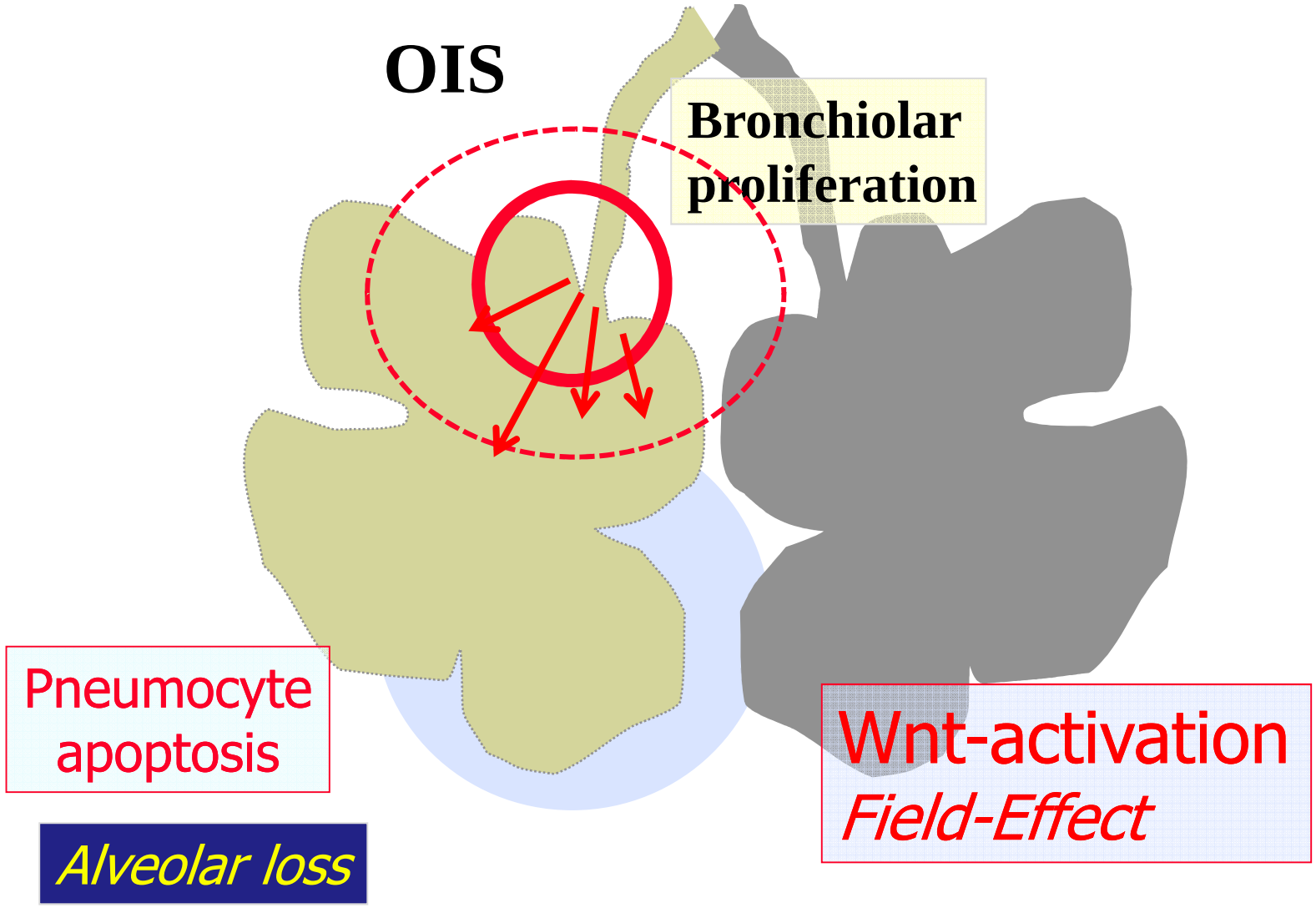
bronchioles

WNT-Tsunami



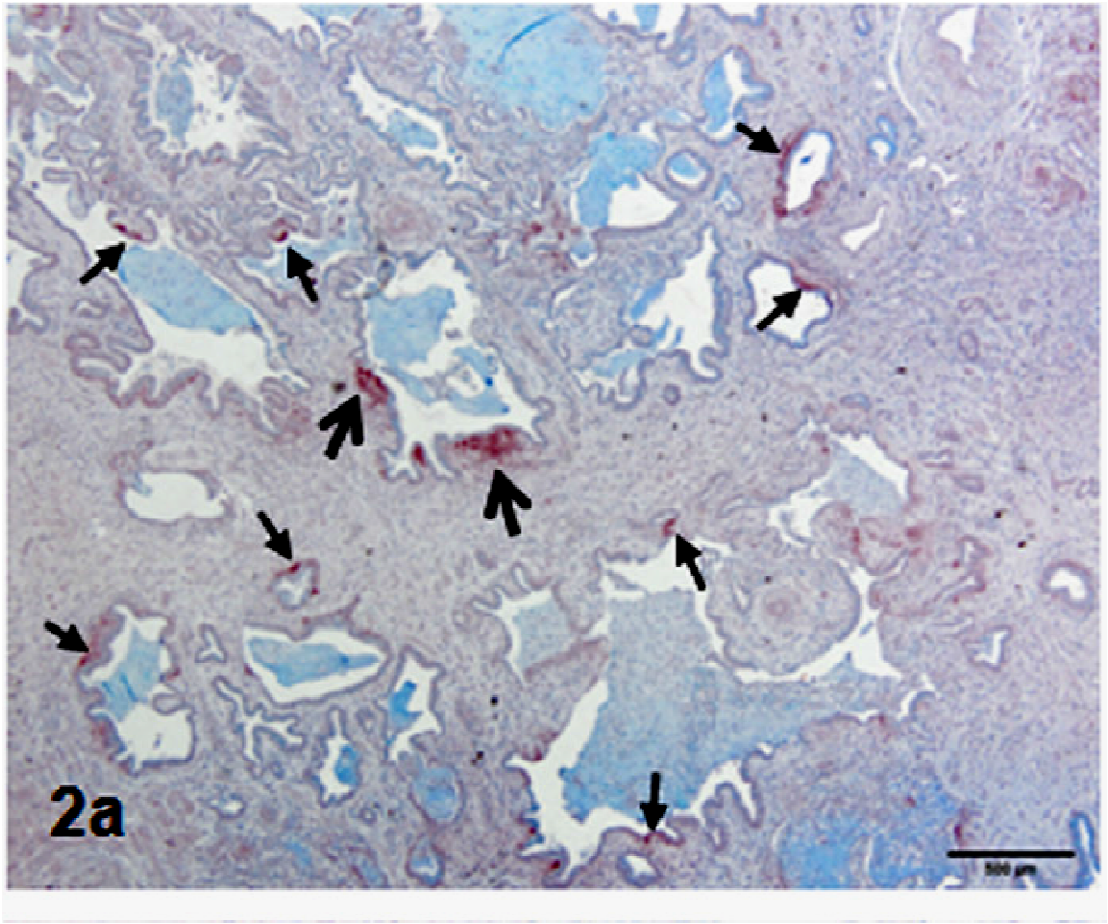

Honeycombing

Injury at bronchiolo-alveolar junctions

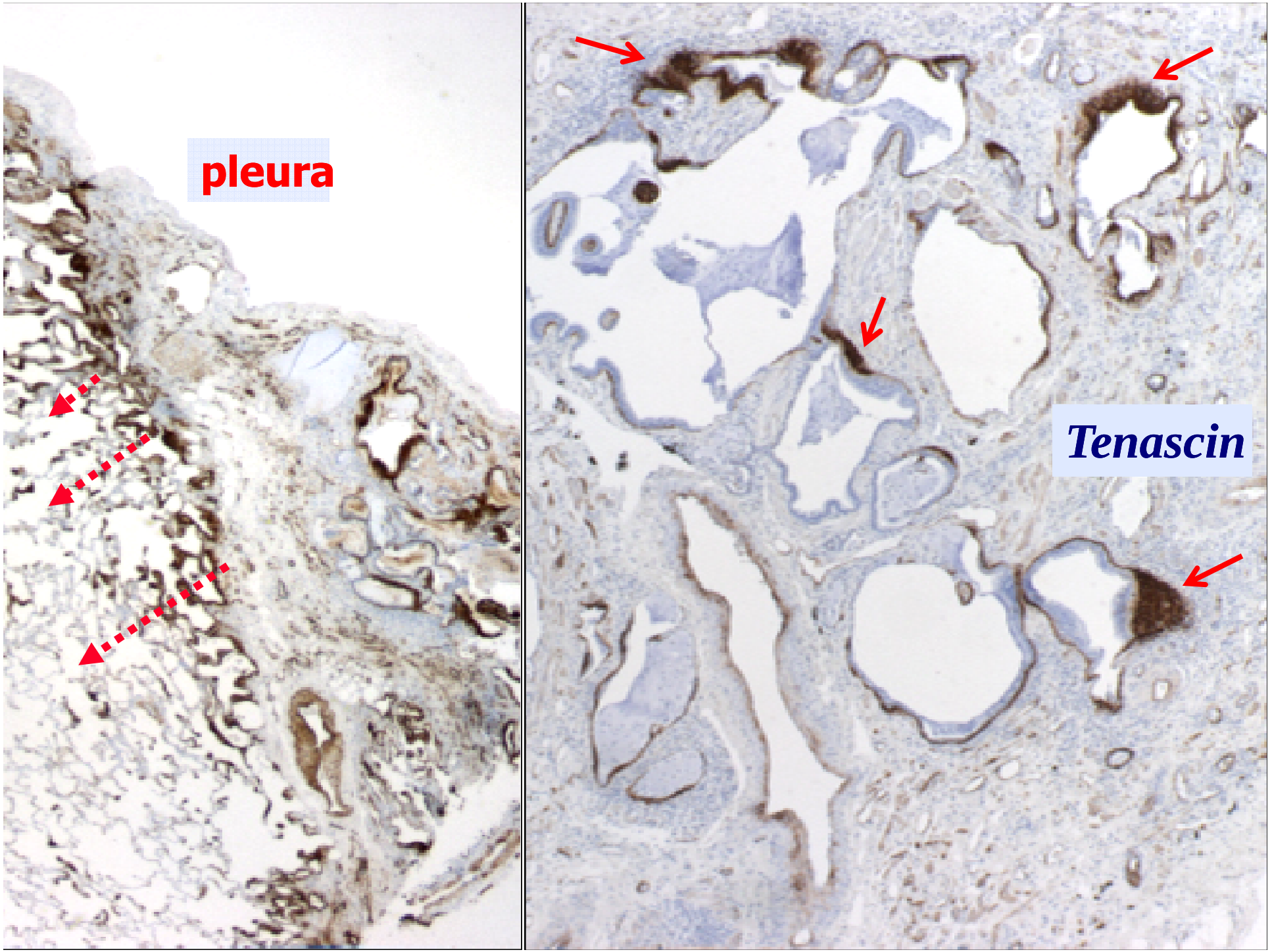


WNT7B in fibroblastic foci of idiopathic pulmonary fibrosis

Travis Meuten[1], Ariel Hickey[1], Katherine Franklin[1], Brian Grossi[1], Jeremy Tobias[2], Donna R Newman[1], Samuel H Jennings[1], Maria Correa[2] and Philip L Sannes[1*]

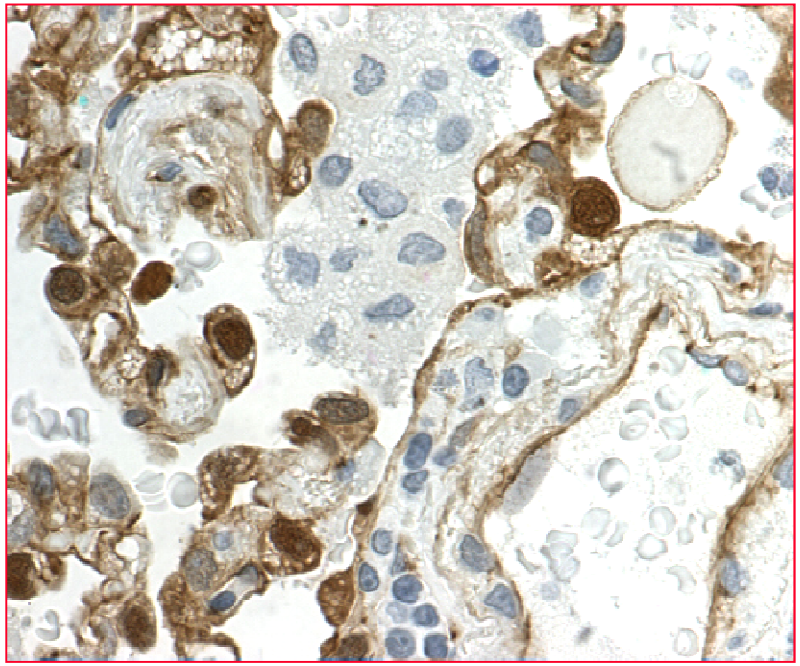


Meuten et al. Respiratory Research 2012, 13:62


pleura
Tenascin

b-catenin nuclear accumulation in type-II pneumocytes

WNT-pathway



β-catenin → • Cyclin-D1 • MMP7 • *c-myc* → Proliferation Apoptosis → **EMT**

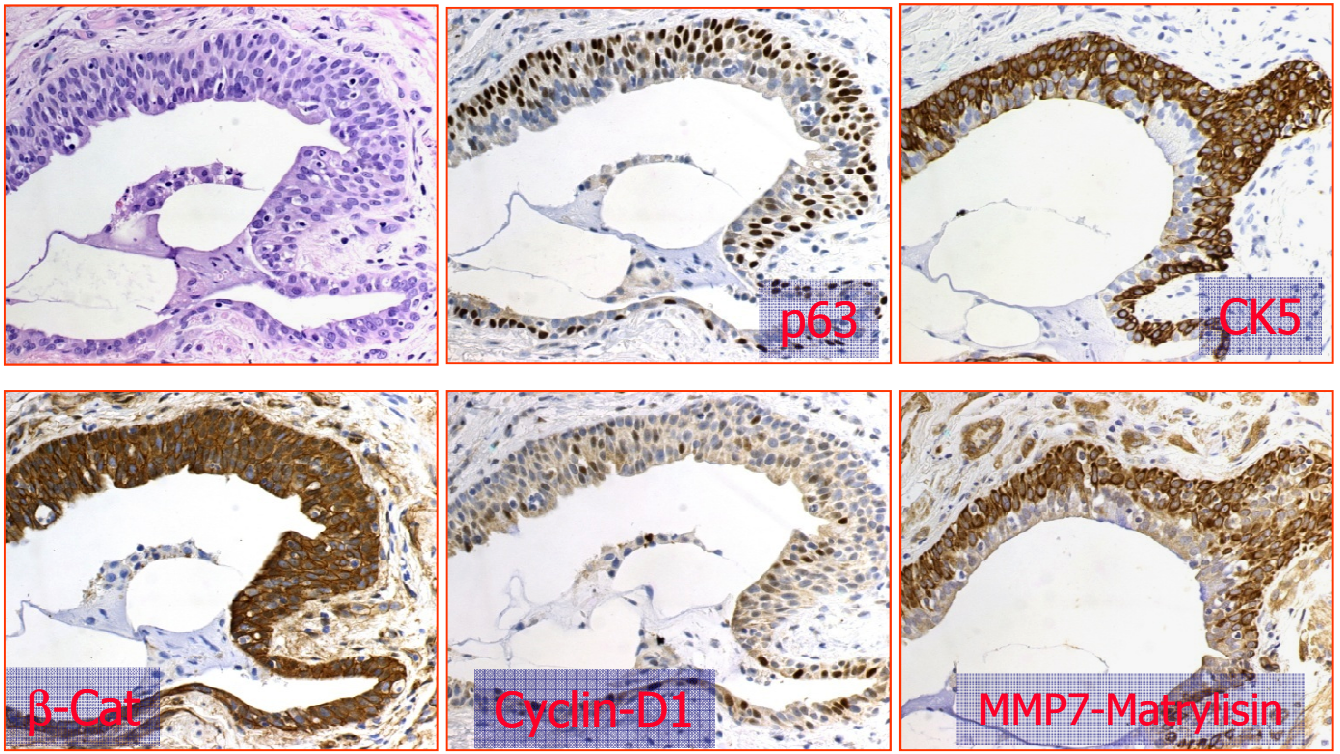
J Biol Chem. 2003 Oct 10;278(41):40231-8.

β-Catenin is required for specification of proximal/distal cell fate during lung morphogenesis. ***Mucenski ML, Wert SE, Nation JM, Loudy DE, Huelsken J, Birchmeier W, Morrisey EE, Whitsett JA.*** Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229-3039, USA.

Am J Pathol 2003 May;162(5):1495-502

Aberrant Wnt/beta-Catenin Pathway Activation in Idiopathic Pulmonary Fibrosis.

Chilosi M, Poletti V, Zamo A, Lestani M, Montagna L, Piccoli P, Pedron S, Bertaso M, Scarpa A, Murer B, Cancellieri A, Maestro R, Semenzato G, Doglioni C.
Department of Pathology, University of Verona, Verona.



Renewal strategies in bronchiolar and alveolar epithelia are different

Rigged game

TAp63

C-Myc

telomerase

AECII

β-catenin

Surfactant SPA

AEC-I

ΔN-p63

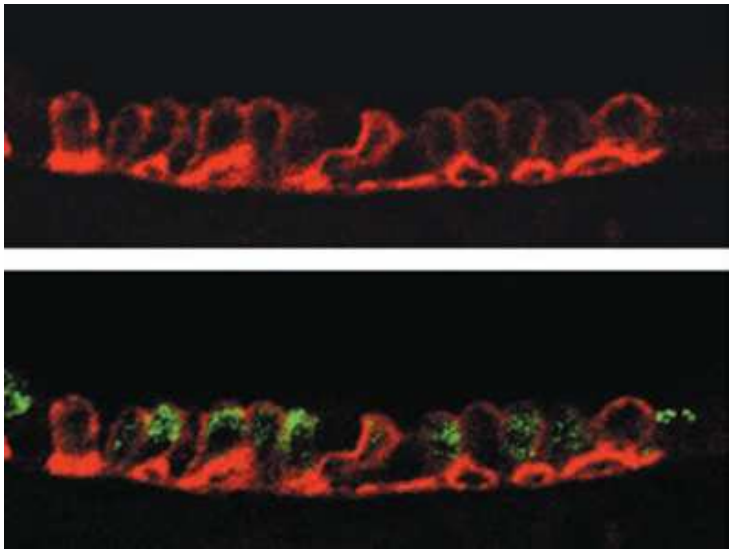
CK5

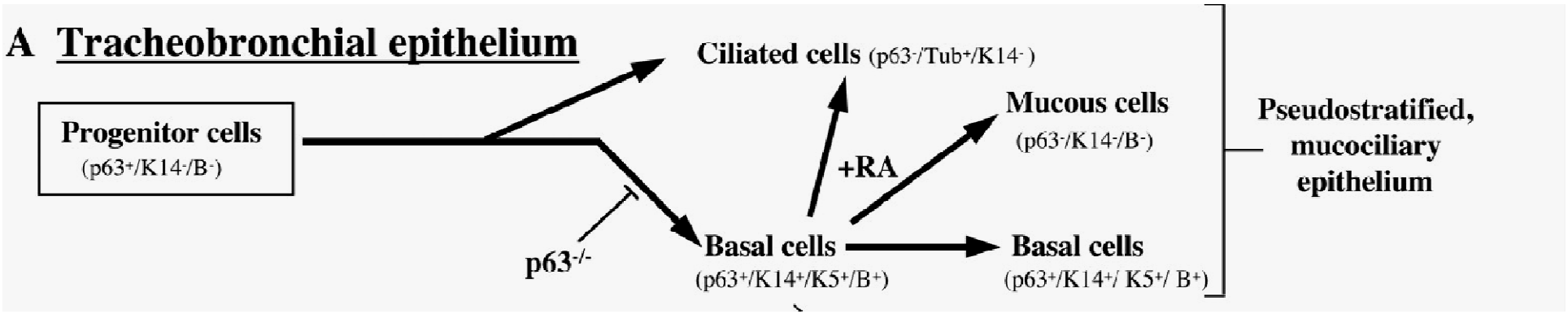
American Journal of Pathology, Vol. 164, No. 2, February 2004

Basal Cells Are a Multipotent Progenitor Capable of Renewing the Bronchial Epithelium

Kyung U. Hong,* Susan D. Reynolds,*†
Simon Watkins,‡ Elaine Fuchs,§ and
Barry R. Stripp*†‡

From the Department of Environmental Medicine, University of Rochester, Rochester, New York; the Departments of Environmental and Occupational Health,† and Cell Biology and Physiology,‡ University of Pittsburgh, Pittsburgh, Pennsylvania; and the Laboratory of Mammalian Cell Biology and Development,§ Rockefeller University, New York, New York*





Cell

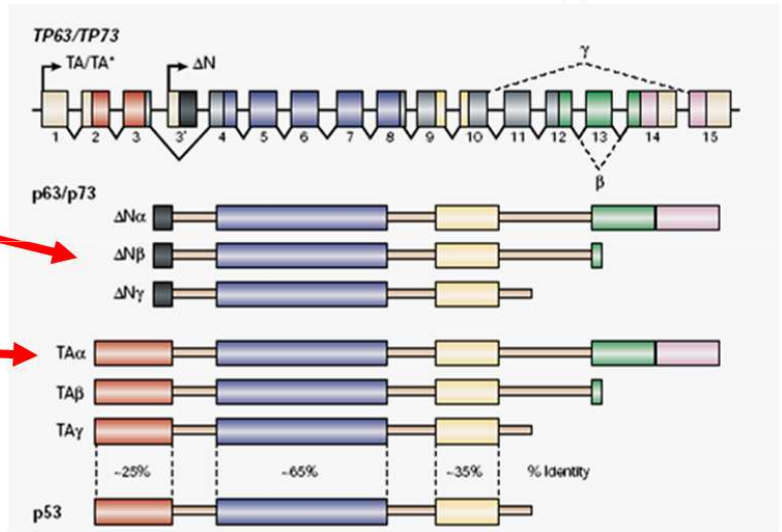
p63 Is Essential for the Proliferative Potential of Stem Cells in Stratified Epithelia

Makoto Senoo,[1,3] Filipa Pinto,[1,3] Christopher P. Crum,[2] and Frank McKeon[1,*]
[1]Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA
[2]Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA
[3]These authors contributed equally to this work.
*Correspondence: fmckeon@hms.harvard.edu
DOI 10.1016/j.cell.2007.02.045

Nat Rev Mol Cell Biol. 2000 Dec;1(3):199-207.

Oncogene

Tumor-suppressor gene

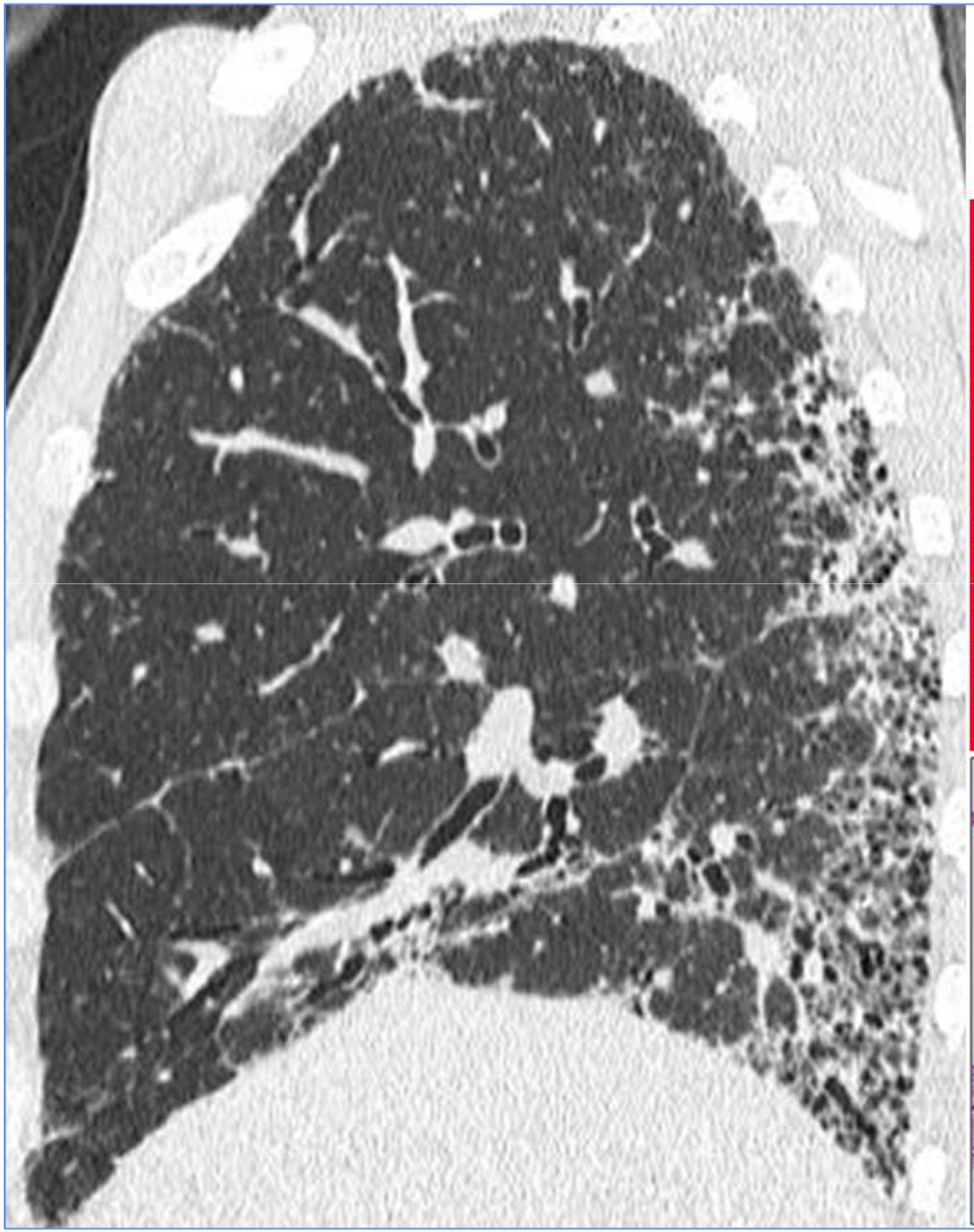


Two separate promoters give rise to the transactivating and ΔN classes of products

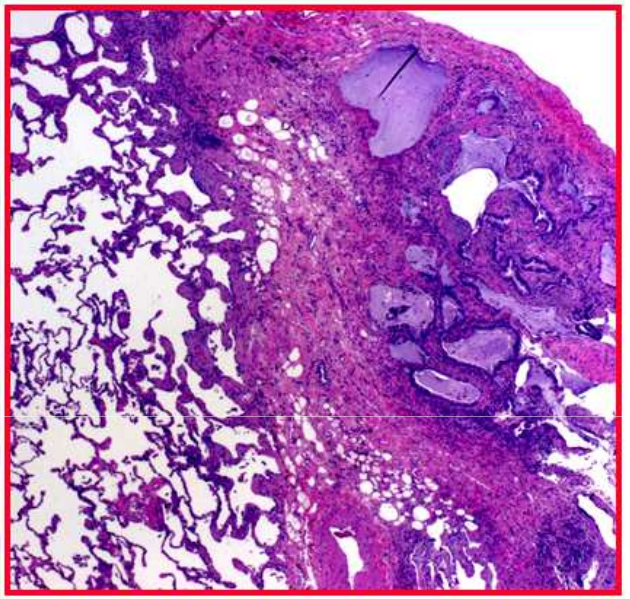
Sarcoidosis Vasc Diffuse Lung Dis. 2001 Mar;18(1):23-6.

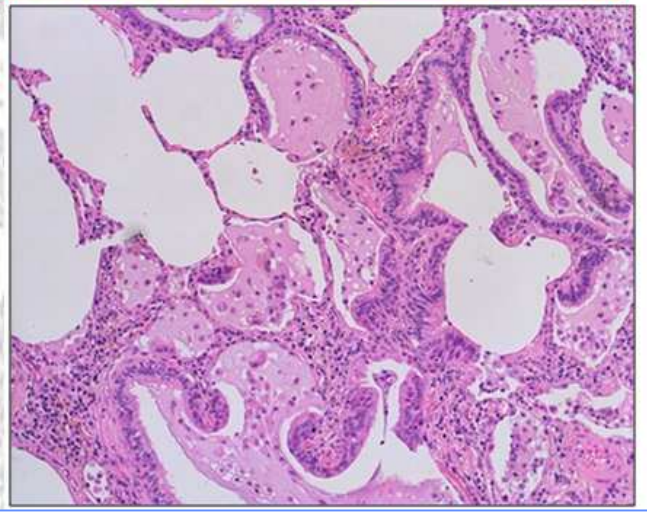
Constitutive p63 expression in airway basal cells. A molecular target in diffuse lung diseases.

Chilosi M, Doglioni C.
Department of Pathology, University of Verona, Italy. m.chilosi@univr.it

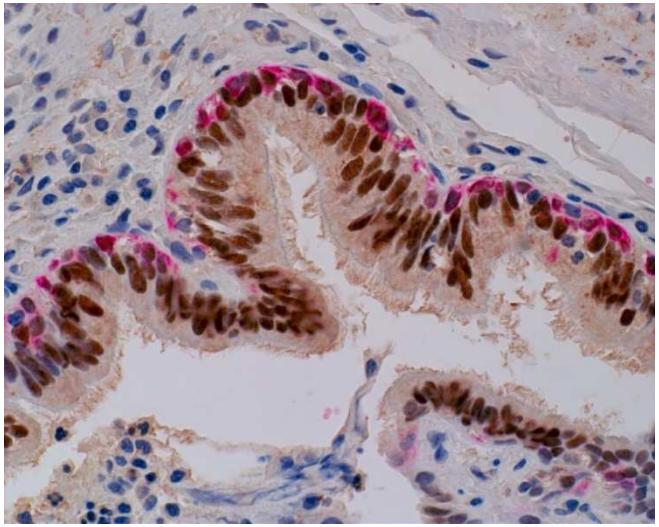


Honeycomb changes are typically formed by varicoid bronchiolar structures



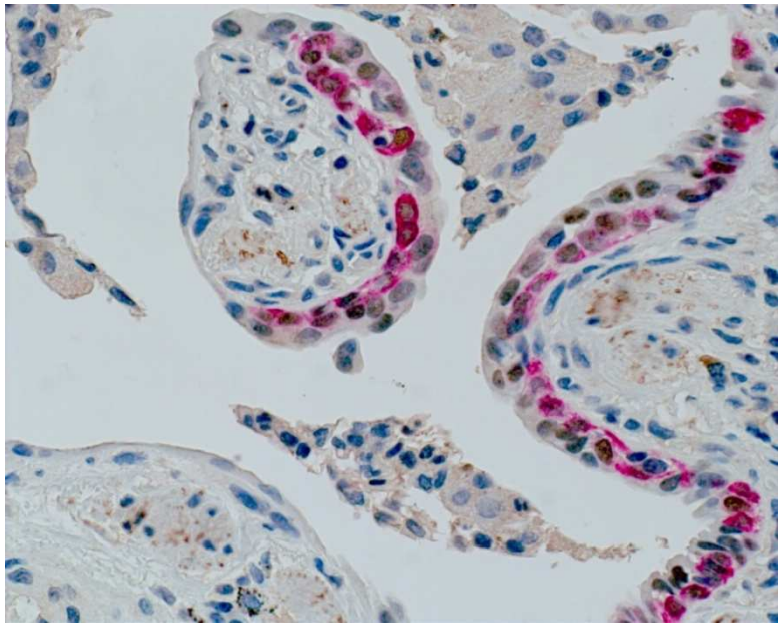


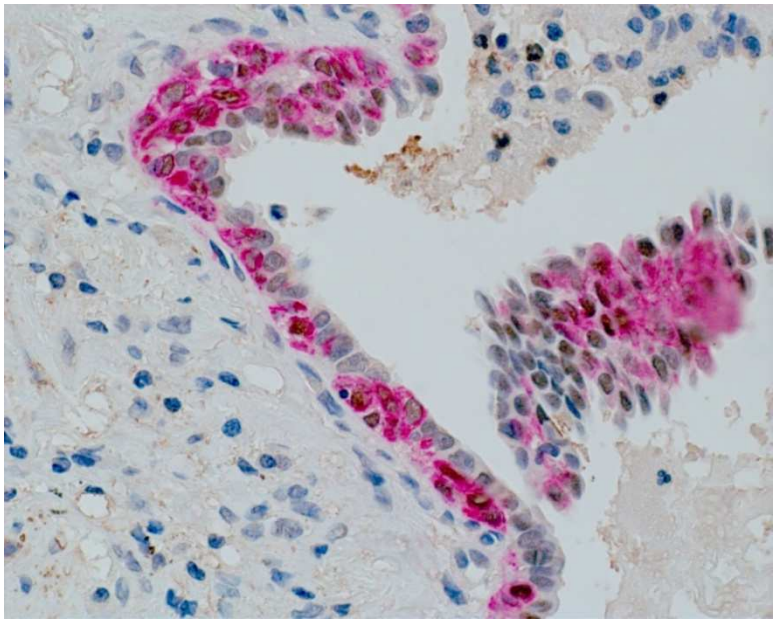
CK5/sox2



Normal bronchiole

Micro-honeycombing In IPF





β-Catenin–SOX2 signaling regulates the fate of developing airway epithelium

Shuichi Hashimoto[1,2], Huaiyong Chen[1,2], Jianwen Que[2], Brian L. Brockway[1,2], Jeffrey A. Drake[1,2], Joshua C. Snyder[1,2], Scott H. Randell[3] and Barry R. Stripp[1,2,*]

[1]Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Duke University Medical Center, 106 Research Drive, 2075 MSRBII, DUMC Box 103000, Durham, NC, 27710, USA
[2]Department of Cell Biology, Duke University Medical Center, Box 3709, Durham, NC, 27710, USA
[3]Departments of Cell and Molecular Physiology and Medicine, The University of North Carolina at Chapel Hill, 111 Mason Farm Road, 5200 Medical Biomolecular Research Building, CB 7545 Chapel Hill, NC, 27599-7545, USA

*Author for correspondence (barry.stripp@duke.edu)

Accepted 11 September 2011
Journal of Cell Science 125, 932–942

doi: 10.1242/jcs.092734

Summary

Wnt–β-catenin signaling regulates cell fate during organ development and postnatal tissue maintenance, but its contribution to specification of distinct lung epithelial lineages is still unclear. To address this question, we used a Cre recombinase (Cre)-LoxP approach to activate canonical Wnt signaling ectopically in developing lung endoderm. We found that persistent activation of canonical Wnt signaling within distal lung endoderm was permissive for normal development of alveolar epithelium, yet led to the loss of developing bronchiolar epithelium and ectasis of distal conducting airways. Activation of canonical Wnt led to ectopic expression of a lymphoid-enhancing factor and a T-cell factor (LEF and TCF, respectively) and absence of SRY (sex-determining region Y)-box 2 (SOX2) and tumor protein p63 (p63) expression in proximal derivatives. Conditional loss of SOX2 in airways phenocopied epithelial differentiation defects observed with ectopic activation of canonical Wnt. Our data suggest that Wnt negatively regulates a SOX2-dependent signaling program required for developmental progression of the bronchiolar lineage.

Key words: Wnt, SOX2, Lung development, Endoderm, Bronchiolar epithelium

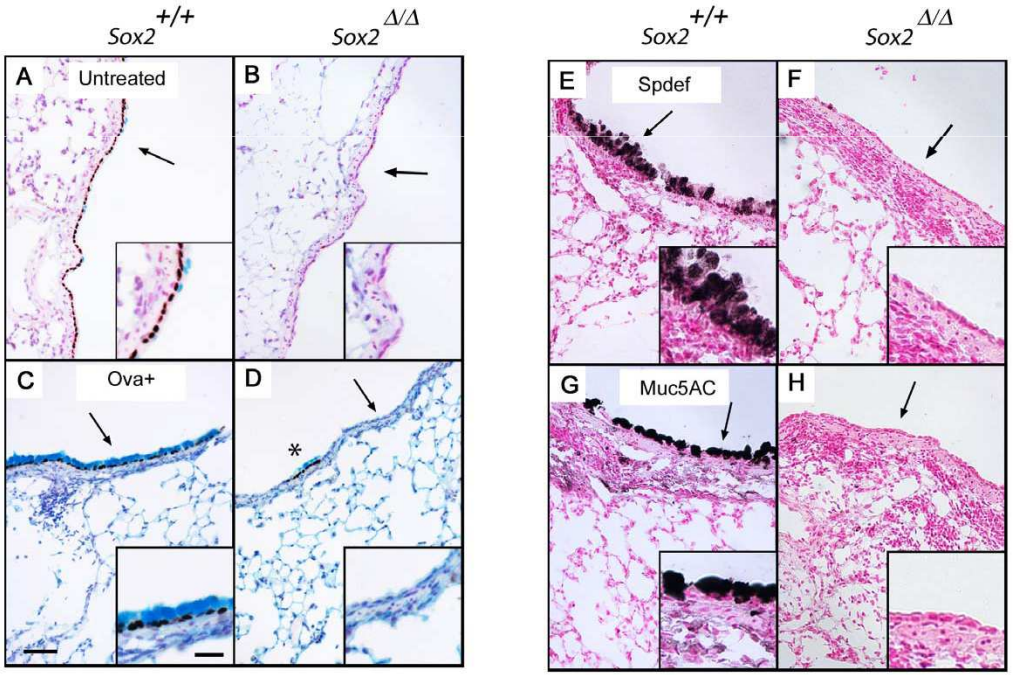
OPEN ACCESS Freely available online

PLoS one

Sox2 Is Required for Maintenance and Differentiation of Bronchiolar Clara, Ciliated, and Goblet Cells

David H. Tompkins, Valérie Besnard, Alexander W. Lange, Susan E. Wert, Angela R. Keiser, April N. Smith, Richard Lang, Jeffrey A. Whitsett*

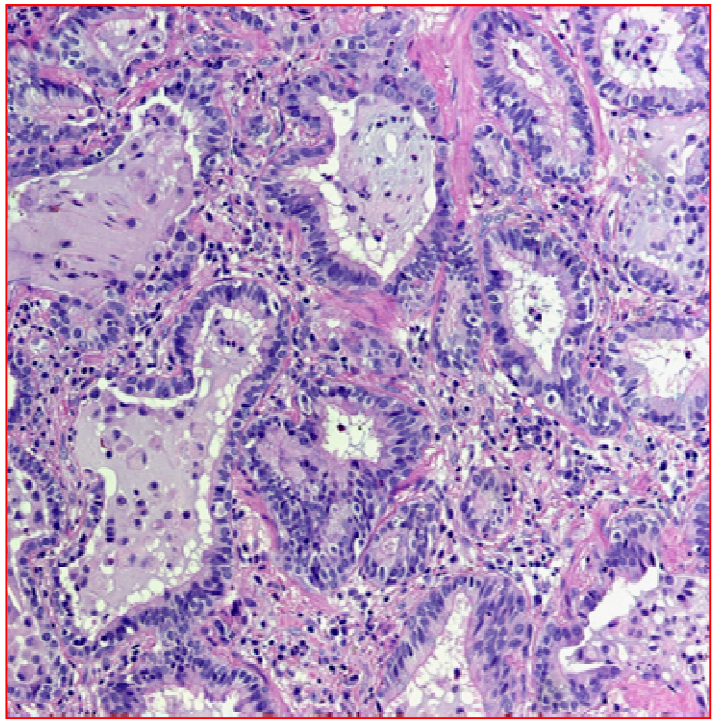
Division of Pulmonary Biology in the Perinatal Institute and Division of Pediatric Ophthalmology, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America



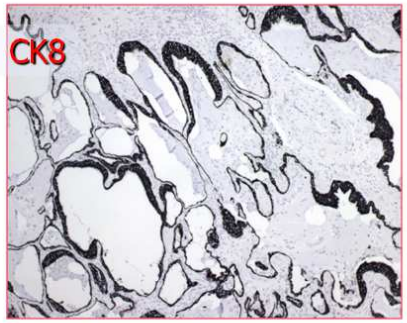
Lab Invest. 2002 Oct;82(10):1335-45.

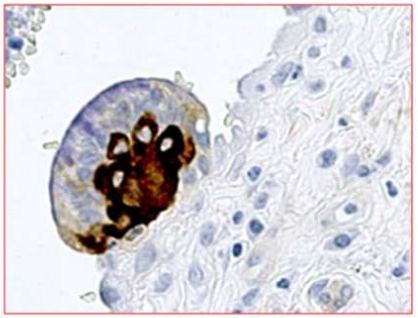
Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63.

Chilosi M, Poletti V, Murer B, Lestani M, Cancellieri A, Montagna L, Piccoli P, Cangi G, Semenzato G, Doglioni C.

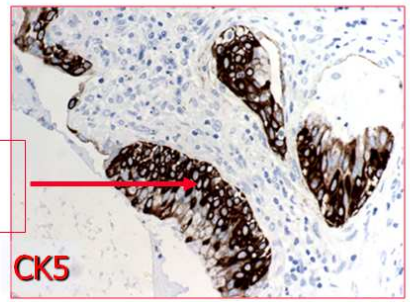


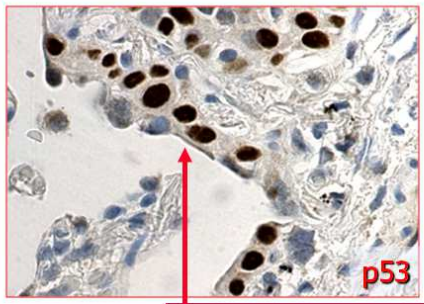
Abnormal epithelial (bronchiolar) proliferation





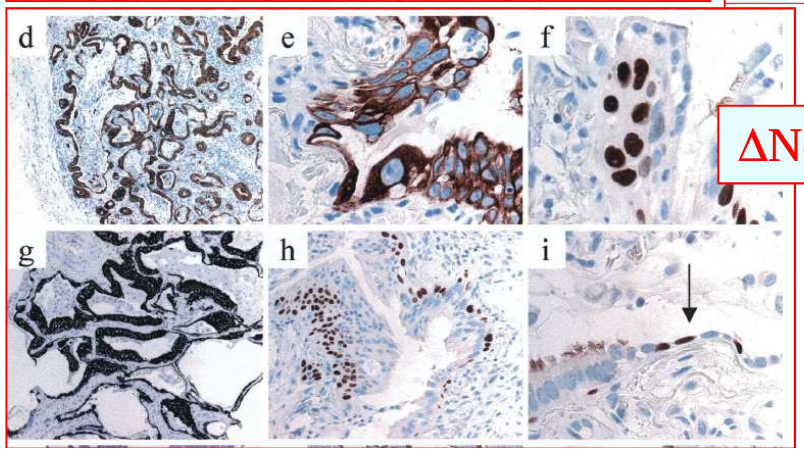
Hsp27
polypoid
bronchiolar
fragments





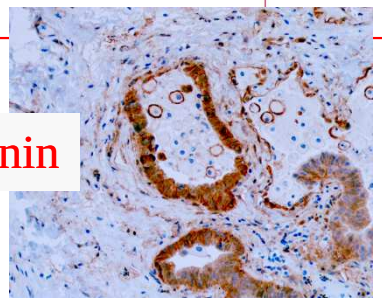
Squamous
metaplasia

Basal cell hyperplasia and
atypia



ΔN-p63

β-catenin



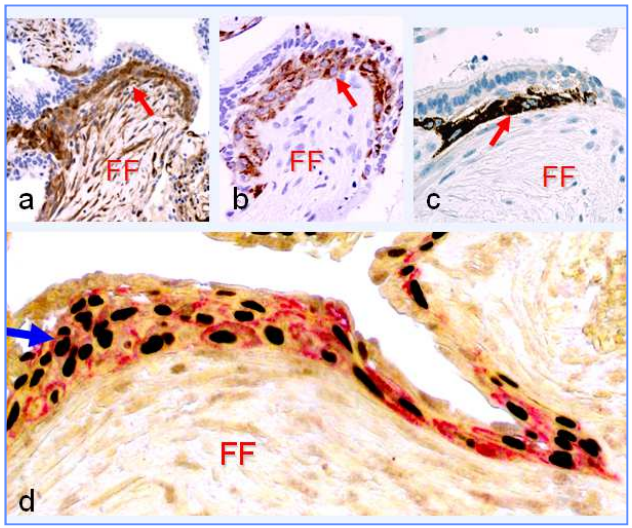
Bronchiolar dysplasia in IPF: molecular features

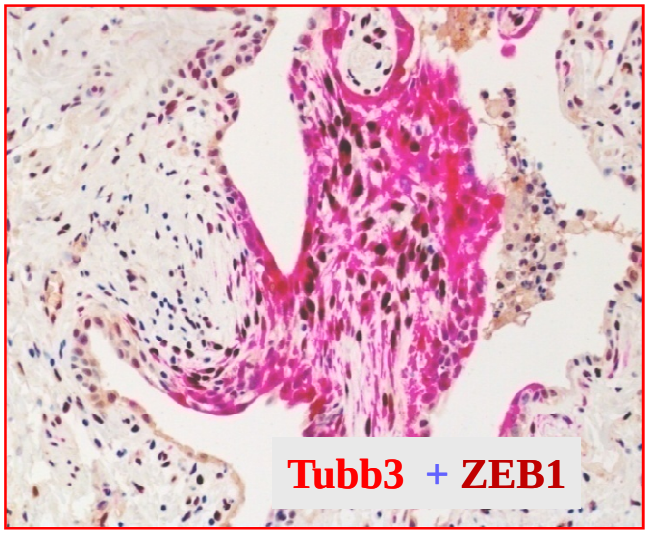
hyper-expression

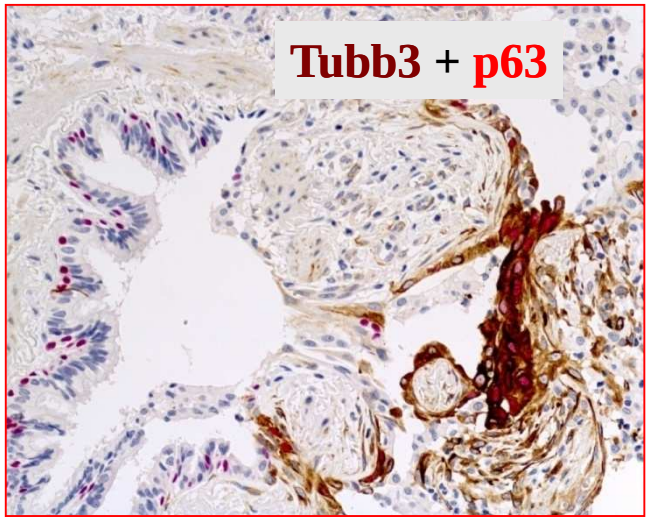
- **N-beta-Catenin**
- **Laminin-5g2**
- **Hsp27**
- **Tubb3**
- **P63**
- **ZEB1**
- **MUC5B**
- **S100A4**
- **Fascin**
- **C-Myc**
- **MMP7**
- **K14**

impaired-expression

- **SOX2**
- **MUC5AC**







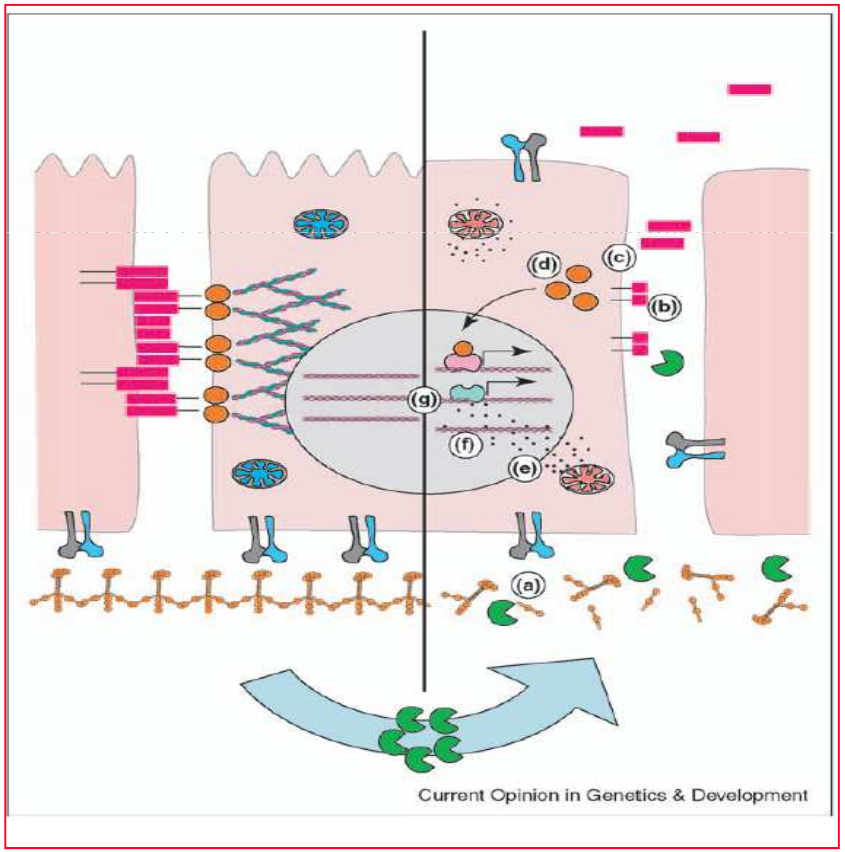
Chilosi et al, in preparation

ELSEVIER

Matrix metalloproteinase-induced genomic instability

Derek C Radisky[1] and Mina J Bissell[2]

Increased expression of matrix metalloproteinases (MMPs) is associated with nearly every tumor type. Although many studies have shown that MMPs can promote malignancy, recent evidence has revealed that MMPs can play a causative role also in the earliest stages of cancer development. A complex story is now emerging in which MMPs not only compromise cell–cell and cell–substratum adhesion processes that impact genomic surveillance mechanisms but also act directly on molecules at the cell surface to stimulate physiological processes that cause genetic alterations. Delineating the mechanisms involved in these processes and identifying how they are coordinated *in vivo* could aid identification of the crucial contribution of MMPs to tumorigenesis.

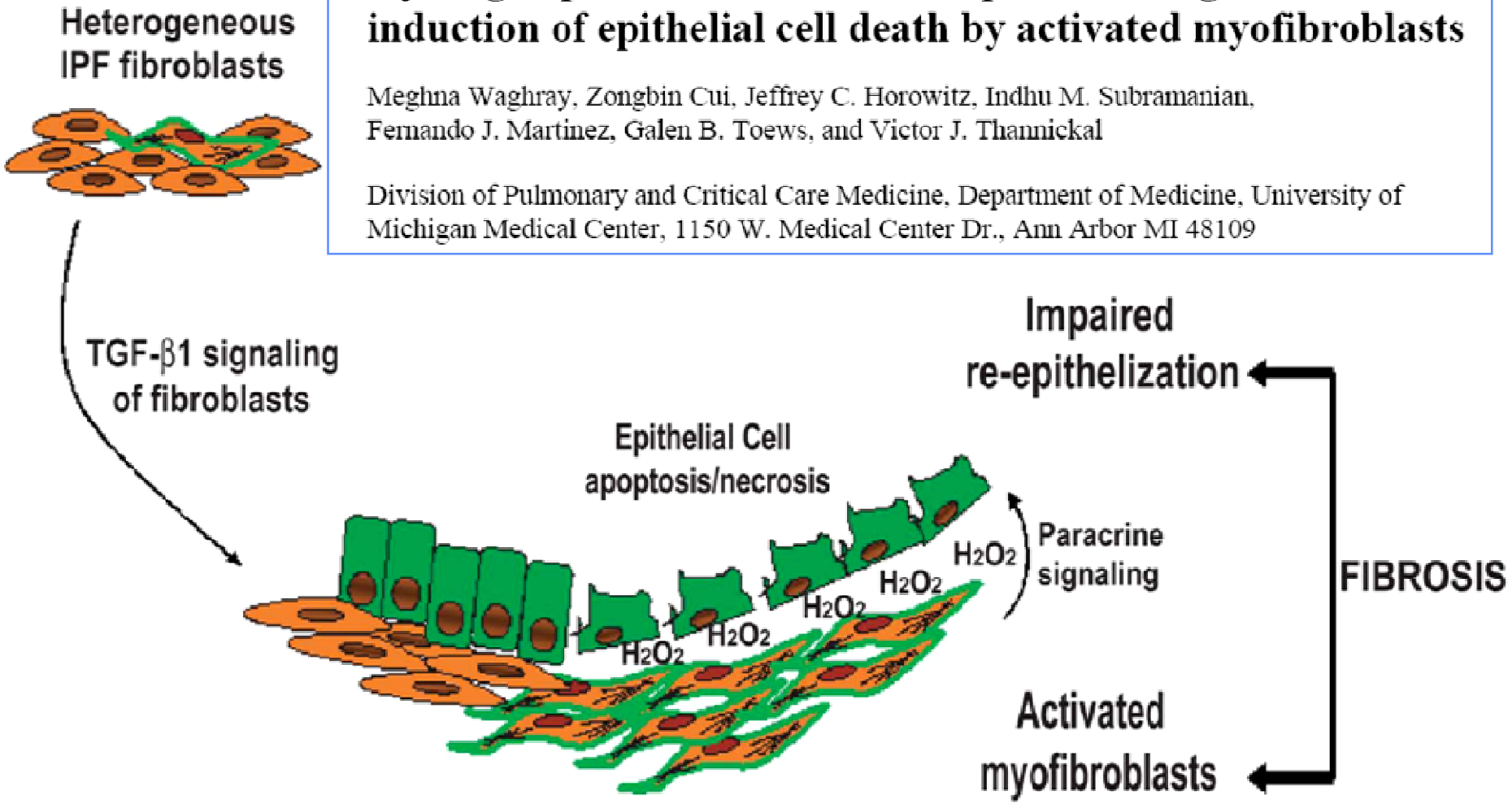


The FASEB Journal express article10.1096/fj.04-2882fje. Published online February 16, 2005.

Hydrogen peroxide is a diffusible paracrine signal for the induction of epithelial cell death by activated myofibroblasts

Meghna Waghray, Zongbin Cui, Jeffrey C. Horowitz, Indhu M. Subramanian, Fernando J. Martinez, Galen B. Toews, and Victor J. Thannickal

Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Michigan Medical Center, 1150 W. Medical Center Dr., Ann Arbor MI 48109



Oncogenetic Model: fibroblast foci in IPF/UIP

Respiratory Research

BioMed Central

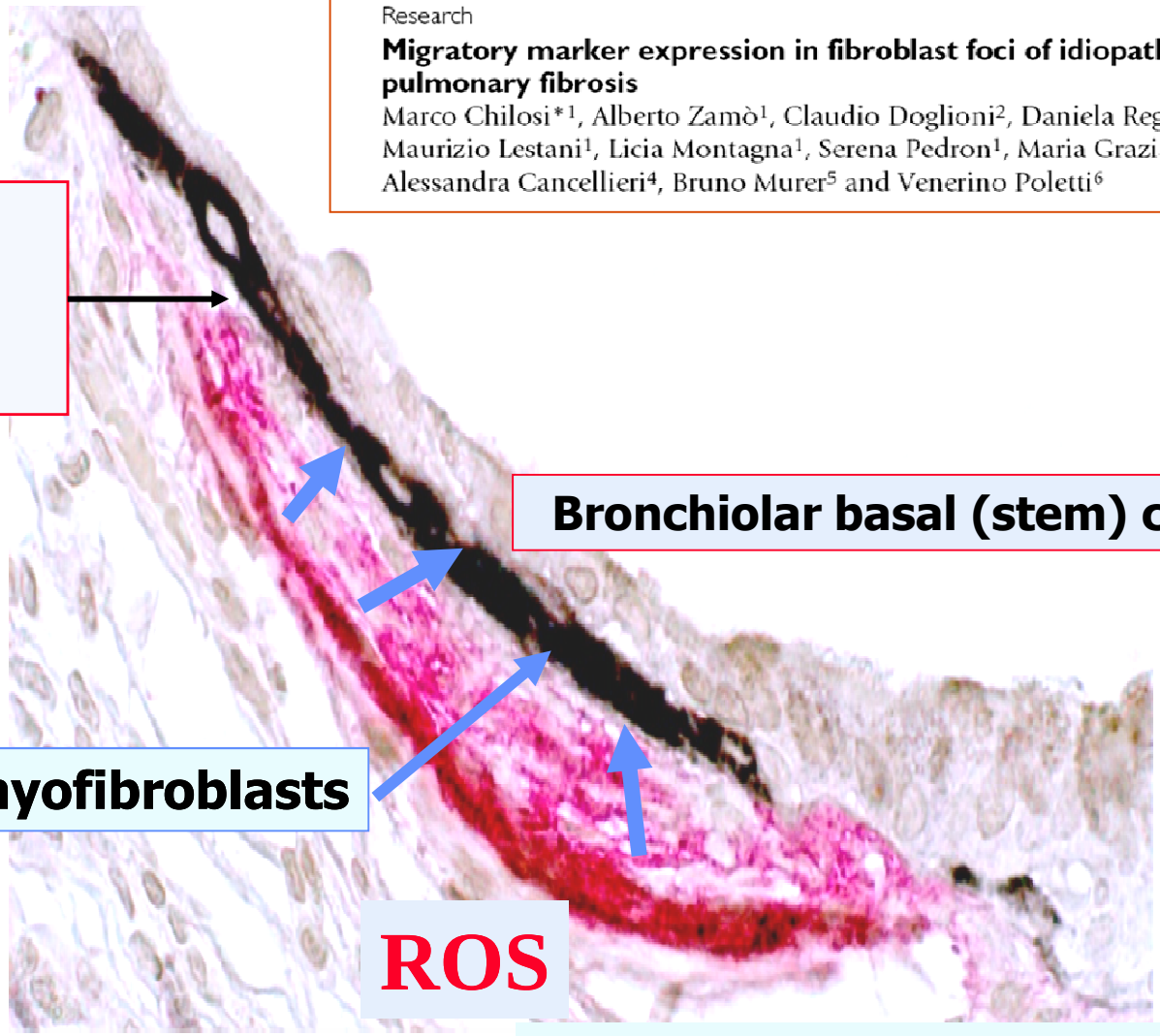
Research

Open Access

Migratory marker expression in fibroblast foci of idiopathic pulmonary fibrosis

Marco Chilosi*[1], Alberto Zamò[1], Claudio Doglioni[2], Daniela Reghellin[1], Maurizio Lestani[1], Licia Montagna[1], Serena Pedron[1], Maria Grazia Ennas[3], Alessandra Cancellieri[4], Bruno Murer[5] and Venerino Poletti[6]

Laminin-5 gamma-2 chain



Bronchiolar basal (stem) cells

myofibroblasts

ROS

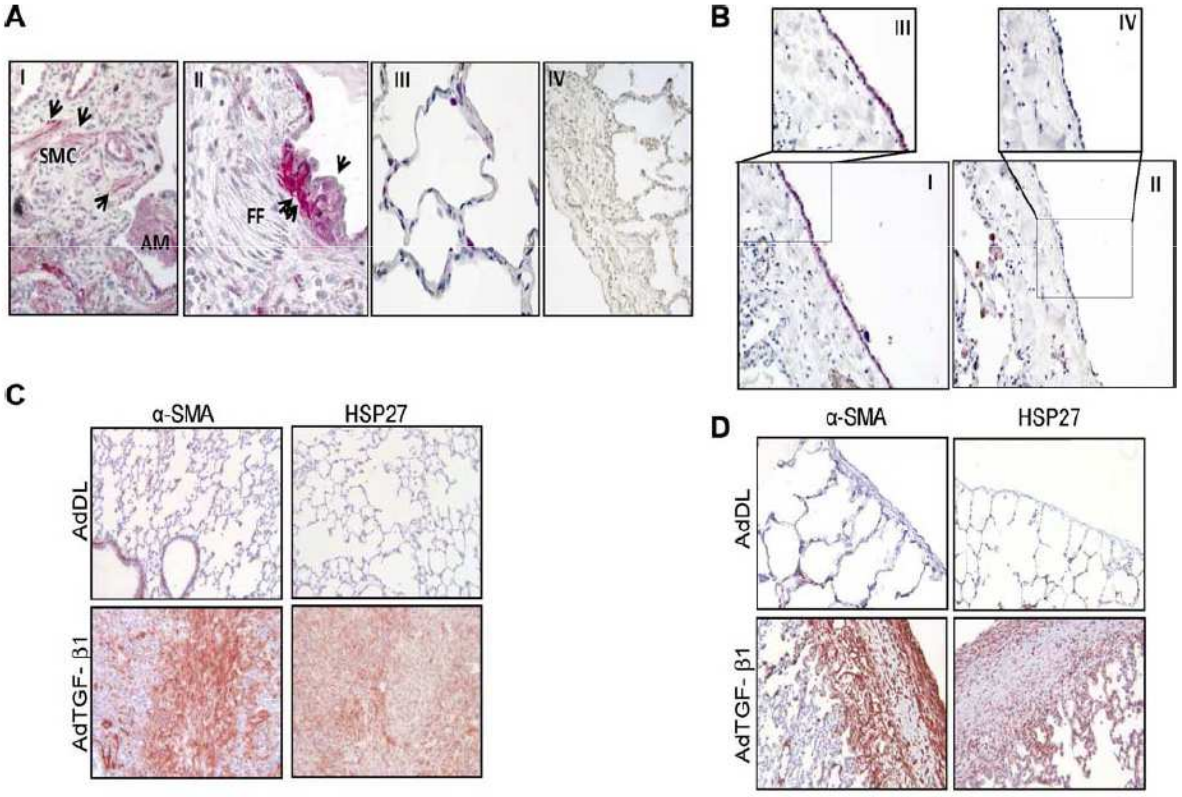
Reactive Oxigen Species

The FASEB Journal article fj.12-220053. Published online January 3, 2013.

The FASEB Journal • Research Communication

Inhibition of HSP27 blocks fibrosis development and EMT features by promoting Snail degradation

Guillaume Wettstein,[*,†] Pierre-Simon Bellaye,[*,†] Martin Kolb,[‡,§] Arlette Hammann,[*,†] Bruno Crestani,[‖,¶,#] Paul Soler,[‖,¶,#] Joëlle Marchal-Somme,[‖,¶,#] Adonis Hazoume,[*,†] Jack Gauldie,[‡,§] Andreas Gunther,[**] Olivier Micheau,[*,†] Martin Gleave,[††] Philippe Camus,[*,†,‡‡] Carmen Garrido,[*,†,1] and Philippe Bonniaud[*,†,‡‡,1,2]



Research Article

Hsp27 Modulates p53 Signaling and Suppresses Cellular Senescence

Cornelia O'Callaghan-Sunol, Vladimir L. Gabai, and Michael Y. Sherman

Department of Biochemistry, Boston University Medical School, Boston, Massachusetts

Abstract

The small heat shock protein Hsp27 is expressed at high levels in many tumors and provides protection against anticancer drugs. Here, we show that expression of recombinant Hsp27 at elevated levels leads to protection of MCF10A human mammary epithelial cells from doxorubicin. The protection was associated with suppression of the doxorubicin-induced senescence, where Hsp27 inhibited p53-mediated induction of p21, the major regulator of the senescence program. Similarly, Hsp27 inhibited accumulation of p21 and suppressed senescence in response to the p53 activator nutlin-3, indicating that Hsp27 has a general effect on the p53 pathway. In line with these findings, down-regulation of Hsp27 in HCT116 human colon carcinoma cells that express this heat shock protein at high levels caused senescence in a population of cells and sensitized the rest of the cells to doxorubicin-induced senescence (at low doses) or apoptosis (at high doses of doxorubicin). Induction of senescence by Hsp27 down-regulation associated with activation of the p53 pathway and induction of p21. Interestingly, depletion of Hsp27 caused neither significant proteotoxic nor genotoxic stress, and therefore this heat shock protein seems to have a specific effect on the p53 signaling. Indeed, Hsp27 down-regulation was associated with destabilization of HDM2 and stabilization of p53. These data suggest that Hsp27 may play a general role in regulation of cellular senescence by modulating the p53 pathway. [Cancer Res 2007;67(24):11779–88]

HSP27

- Involved in cell motility
- Involved in cancer prognosis
- Involved in drug resistance

Proteasome inhibitors, doxorubicin

- Antiapoptotic effect
- Suppression of OIS
- Suppression of drug-induced senescence

Cancer Res 2007; 67: (24) 15, 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Common *MUC5B* Promoter Polymorphism and Pulmonary Fibrosis

Max A. Seibold, Ph.D., Anastasia L. Wise, Ph.D., Marcy C. Speer, Ph.D.,*
Mark P. Steele, M.D., Kevin K. Brown, M.D., James E. Loyd, M.D.,
Tasha E. Fingerlin, Ph.D., Weiming Zhang, Ph.D.,
Gunnar Gudmundsson, M.D., Ph.D., Steve D. Groshong, M.D., Ph.D.,
Christopher M. Evans, Ph.D., Stavros Garantziotis, M.D.,
Kenneth B. Adler, Ph.D., Burton F. Dickey, M.D., Roland M. du Bois, M.D.,
Ivana V. Yang, Ph.D., Aretha Herron, B.A., Dolly Kervitsky, B.A., Janet L. Talbert, M.S.,
Cheryl Markin, B.A., Joungjoa Park, B.A., Anne L. Crews, B.A., Susan H. Slifer, Ph.D.,
Scott Auerbach, Ph.D., Michelle G. Roy, B.A., Jia Lin, B.A., Corinne E. Hennessy, M.S.,
Marvin I. Schwarz, M.D., and David A. Schwartz, M.D.

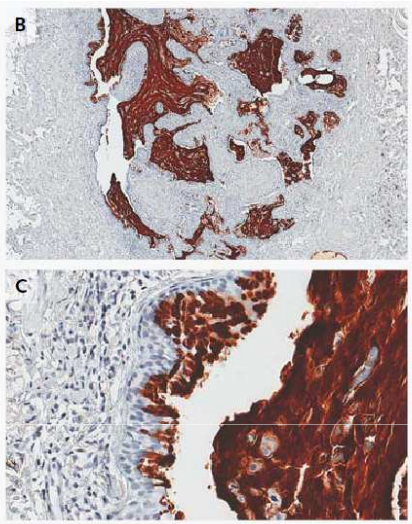


Figure 4. Immunohistochemical Staining of MUC5B in Lung Tissue from Subjects with Idiopathic Pulmonary Fibrosis and Controls.

Immunohistochemical staining showed MUC5B distribution in the cytoplasm of the secretory columnar cells of the bronchi and larger proximal bronchioles in a specimen of lung tissue from a control subject (Panel A). In subjects with idiopathic pulmonary fibrosis, regions of dense accumulation of MUC5B were observed in areas of microscopical honeycombing and involved patchy staining of the metaplastic epithelia lining the honeycomb cysts (Panel B). Accumulation was also observed in the mucous plugs within the cysts (Panel C).

N Engl J Med 2011;364:1503-12.

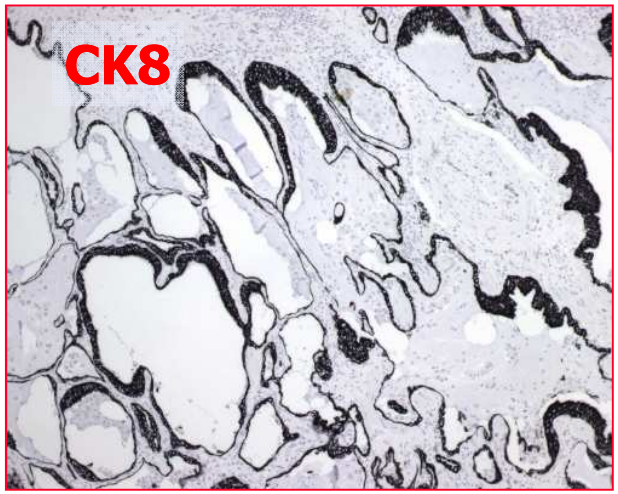
Honeycombing: bronchiolar dysplasia ?

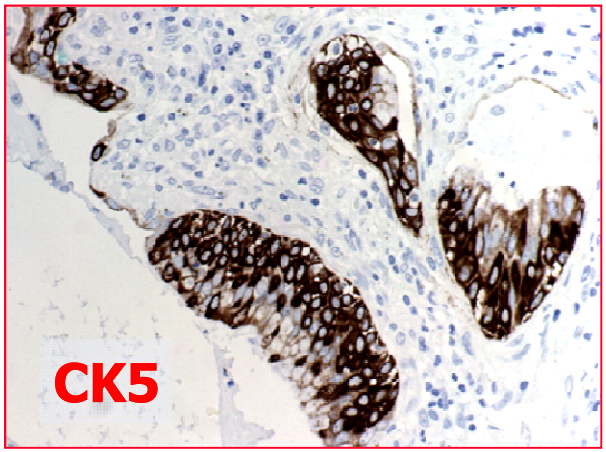
0023-6837/02/8210-1335$03.00/0
LABORATORY INVESTIGATION
Vol. 82, No. 10, p. 1335, 2002
Printed in U.S.A.

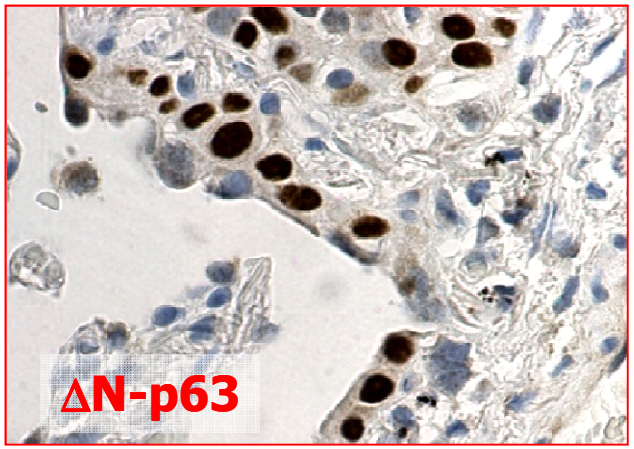
Abnormal Re-epithelialization and Lung Remodeling in Idiopathic Pulmonary Fibrosis: The Role of ΔN-p63

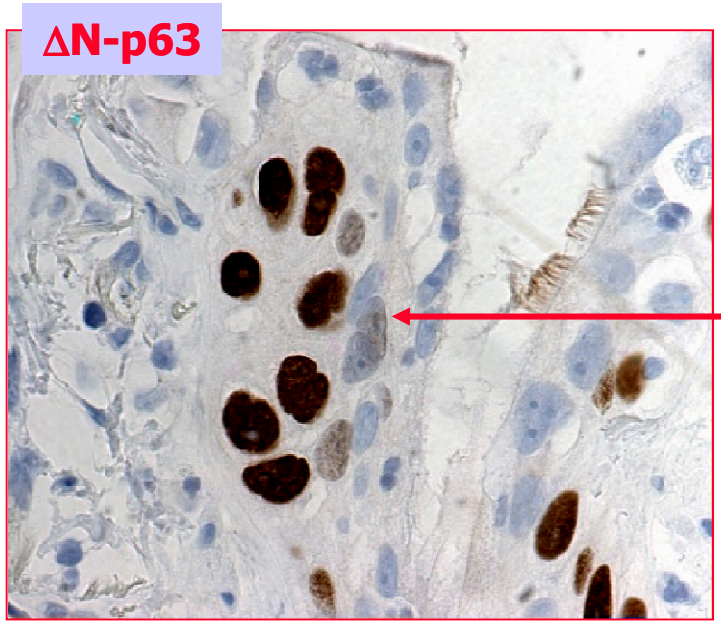
Marco Chilosi, Venerino Poletti, Bruno Murer, Maurizio Lestani, Alessandra Cancellieri, Licia Montagna, Paola Piccoli, Giulia Cangi, Gianpietro Semenzato, and Claudio Doglioni

Basal cell hyperplasia and atypia

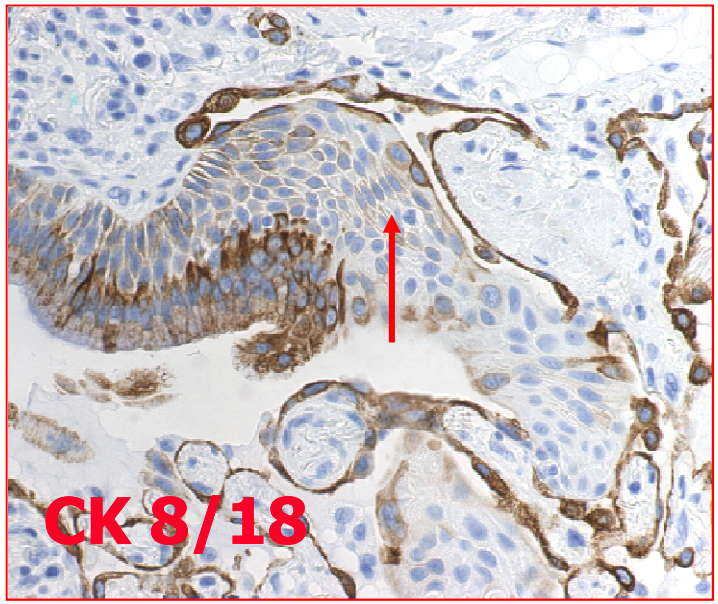


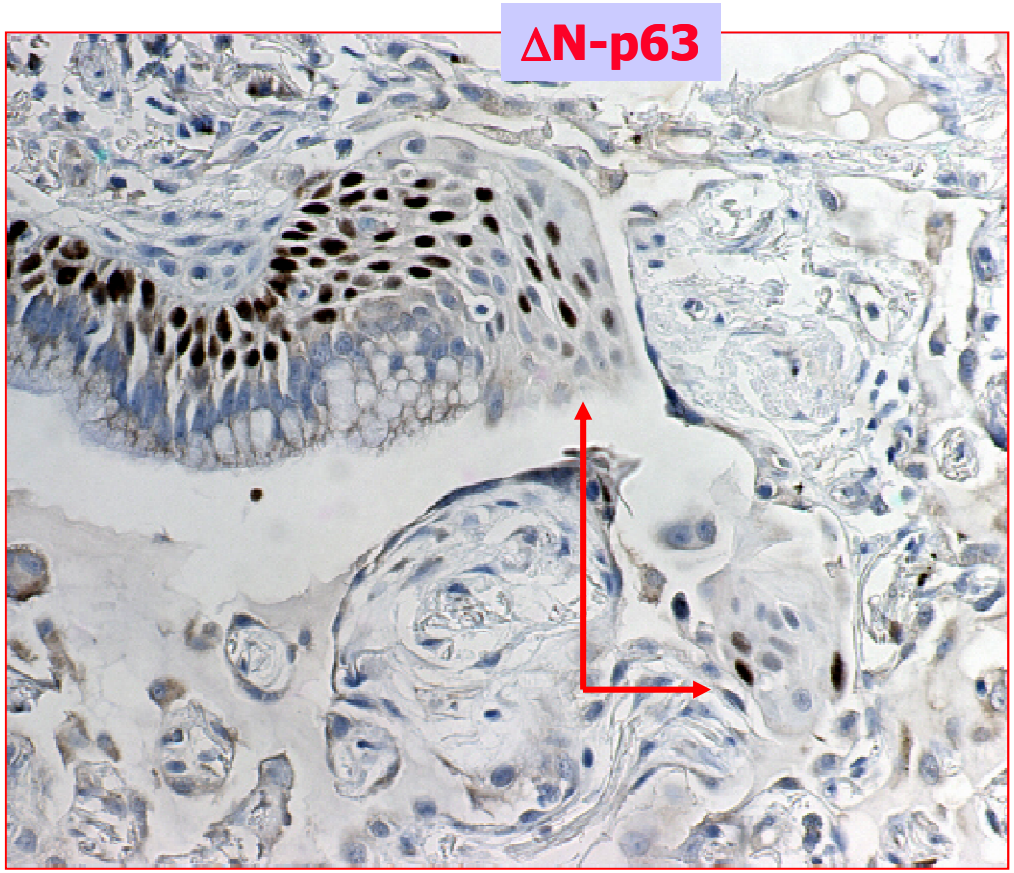






Abnormal basal cells





From metaplasia to squamous carcinoma in IPF

Patients with idiopathic pulmonary fibrosis (IPF) have an increased incidence of lung carcinoma (LC) when compared to general age-matched population (up to 48%) in different series, and different studies suggest that this increase is independent of the effect of cigarette smoking

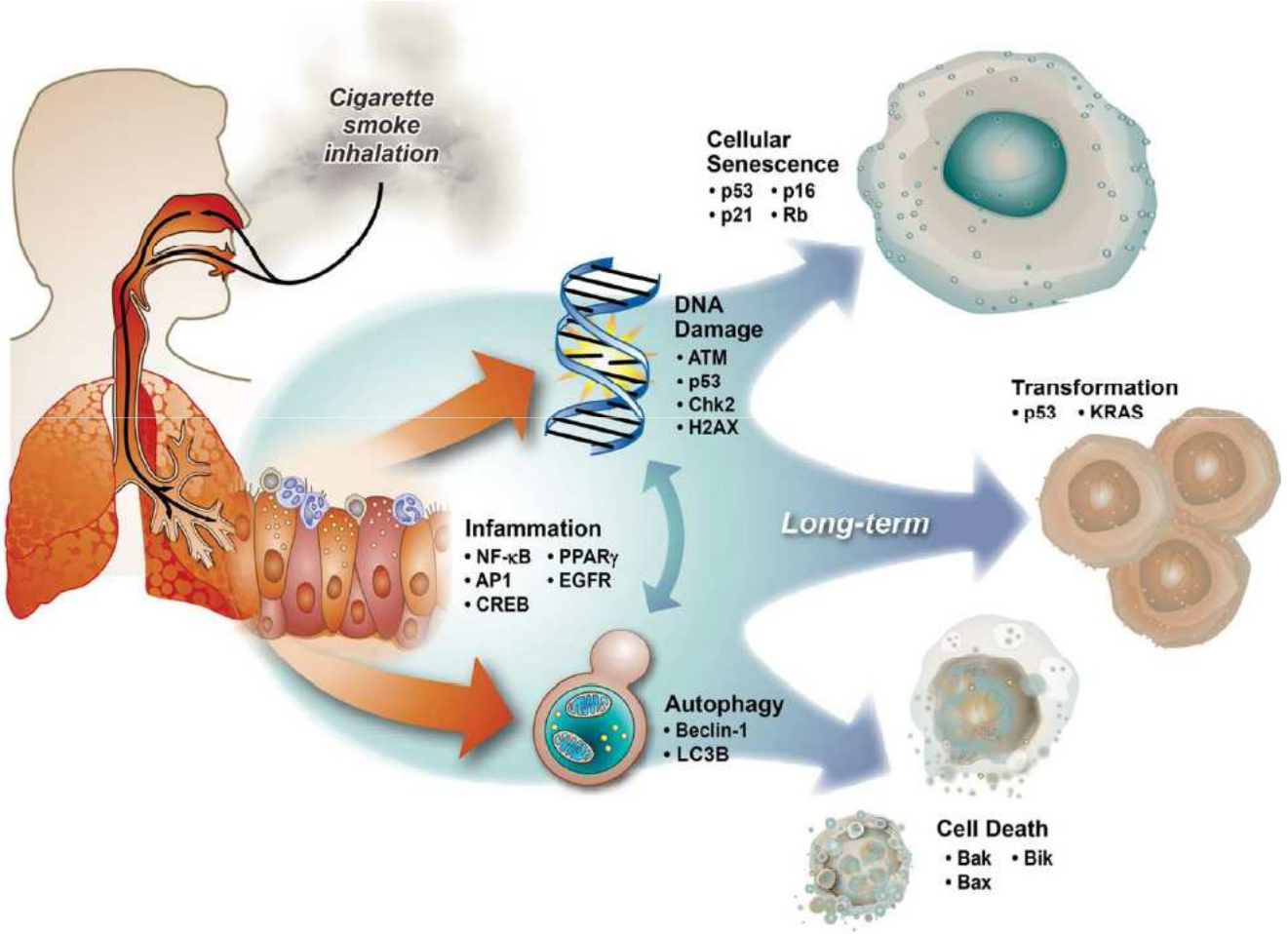
[*haddad 1968, Turner-Warwich 1980; Panos 1990; Aubrey-2002; Hubbard 2000; Artinian 2004, Daniels 2005, Le Jeune 2007, Matsushita 1995, Ozawa 2009]*.

Am J Respir Cell Mol Biol. 2013 Oct 10. [Epub ahead of print]

Molecular Processes That Drive Cigarette Smoke-Induced Epithelial Cell Fate of the Lung.

Nyunoya T, Mebratu Y, Contreras A, Delgado M, Chand HS, Tesfaigzi Y.

LRRI, Albuquerque, New Mexico, United States.



Molecular Processes that Drive Cigarette Smoke-Induced Epithelial Cell Fate of the Lung. Cigarette smoke exposure induces inflammation, DNA damage, and autophagy that cause lung epithelial cells to undergo cell death, cellular senescence, and/or transformation.

Pathology International 1999; **49**: 1060–1066

Original Article

Pulmonary fibrosis and lung carcinoma: A comparative study of metaplastic epithelia in honeycombed areas of usual interstitial pneumonia with or without lung carcinoma

Mitsugu Hironaka and Masashi Fukayama

Department of Pathology, Jichi Medical School, Tochigi, Japan

Usual interstitial pneumonia (UIP), or idiopathic pulmonary fibrosis, has been considered to be associated with a high risk for lung carcinoma. To investigate this well-known but still equivocal relationship, we reviewed the clinical features of UIP autopsy cases with or without lung carcinoma (n = 32 and 38, respectively), and compared the morphology and cell kinetics of metaplastic epithelia in the honeycombed areas (n = 11, each group). Thirty-two of 70 UIP autopsy cases showed lung carcinomas. Clinically, UIP with lung carcinoma showed a male predominance (P = 0.001), a higher rate of smoking history (P = 0.001) and a later onset of UIP (P = 0.02), compared with UIP without lung carcinoma. Most of the carcinomas were peripheral in origin (90%), and 65% were topographically associated with honeycombed areas or the border between honeycombing and non-fibrotic areas. Quantitative assessment of the metaplastic epithelia in the honeycombed areas revealed that squamous metaplasia, but not cuboidal cell metaplasia or bronchial cell metaplasia, occurred more frequently in UIP with lung carcinoma than in UIP without lung carcinoma (P = 0.02). There were no significant differences between the two groups with regard to the labeling indexes of Ki-67 and p53 in the metaplastic epithelia, including squamous metaplasia. The degree of atypical squamous metaplasia was not different between the two groups. The quantitative predominance of squamous metaplasia in the honeycombed areas may not be a precursor for lung carcinoma, but might reflect a constitutional susceptibility of UIP patients to develop a lung carcinoma.

noma in hepatitis B or C,[2,3] gastric cancer in chronic *Helicobacter pylori* infection[4,5] and colon cancer in ulcerative colitis.[6] Usual interstitial pneumonia (UIP), or idiopathic pulmonary fibrosis, is a persistent inflammatory disease of the lung that results in fibrosis and remodeling of the peripheral airway (honeycombing). A close relationship between UIP and lung carcinoma has also been suspected,[7–13] but it remains uncertain whether UIP is a homogeneous group of chronic inflammations with regard to not only their etiology but also to their susceptibility to develop into lung carcinomas. To investigate this well-known but still equivocal relationship, we first evaluated the clinical and pathological characteristics of UIP with or without lung carcinoma, as determined at autopsy.

Meyer and Liebow observed atypical epithelial proliferation in the honeycombed area, such as multilayered columnar, cuboidal, or squamous epithelium, and regarded the proliferation of atypical epithelia as a precancerous lesion in UIP.[8] However, the significance of the epithelial changes in the honeycombing has not yet been carefully studied in relation to lung carcinoma arising from UIP. Furthermore, the quantitative and qualitative differences in the epithelia in the honeycombed area between UIP with and without lung carcinoma have not been studied. As the limitation of a study using an autopsy lung compared to biopsy material, some secondary changes directly related with death might have blurred the original UIP-related changes, but it has a merit to examine

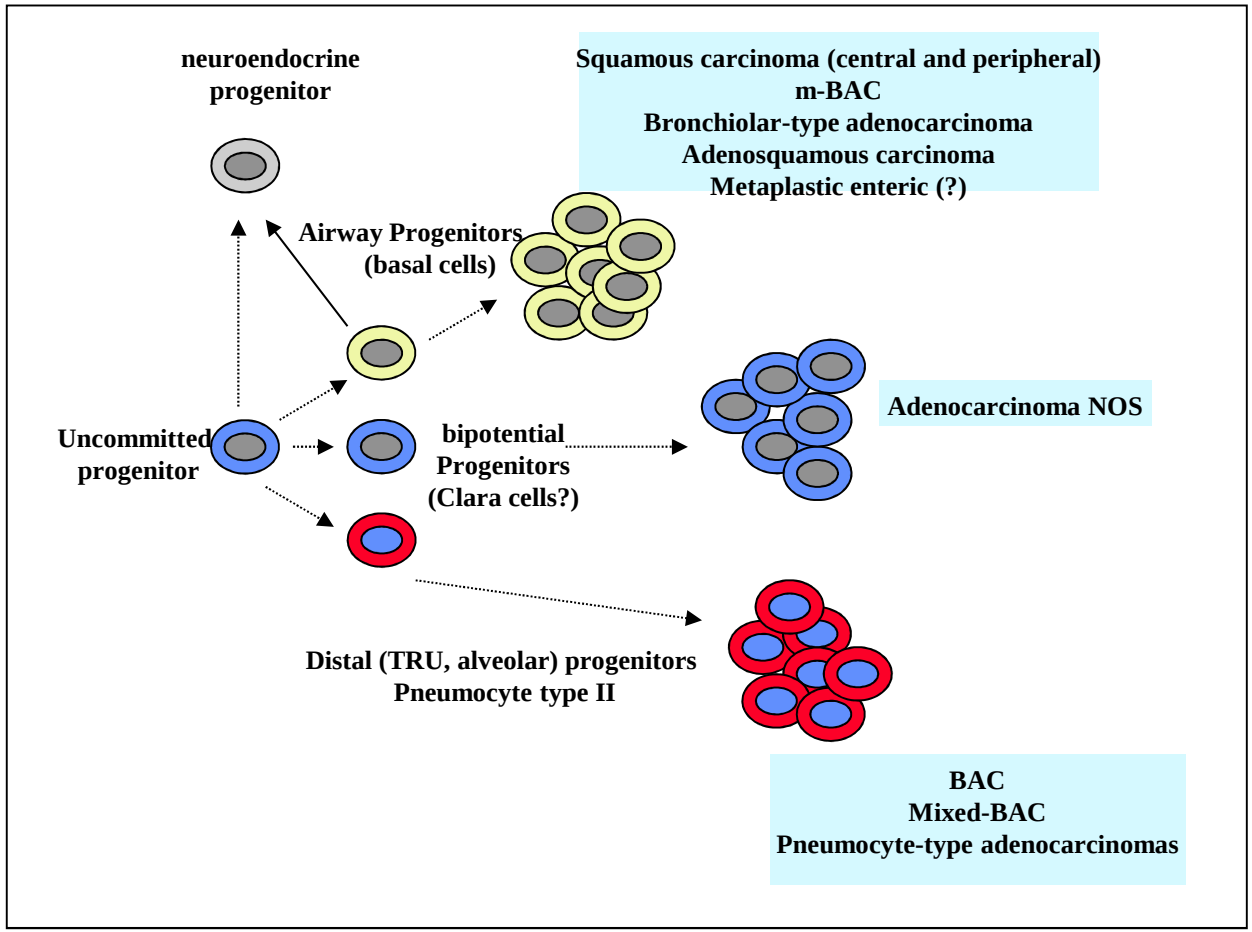
..90% peripheral…

…65% topographically associated with honeycombing…

Mixed Adenocarcinomas of the Lung

Place in New Proposals in Classification, Mandatory for Target Therapy

Marco Chilosi, MD; Bruno Murer, MD



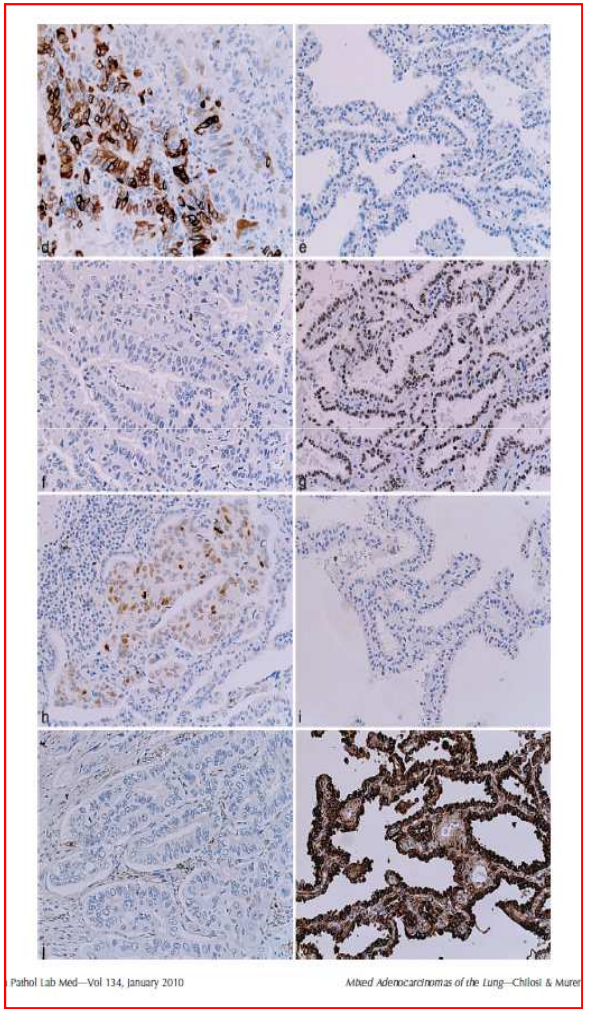
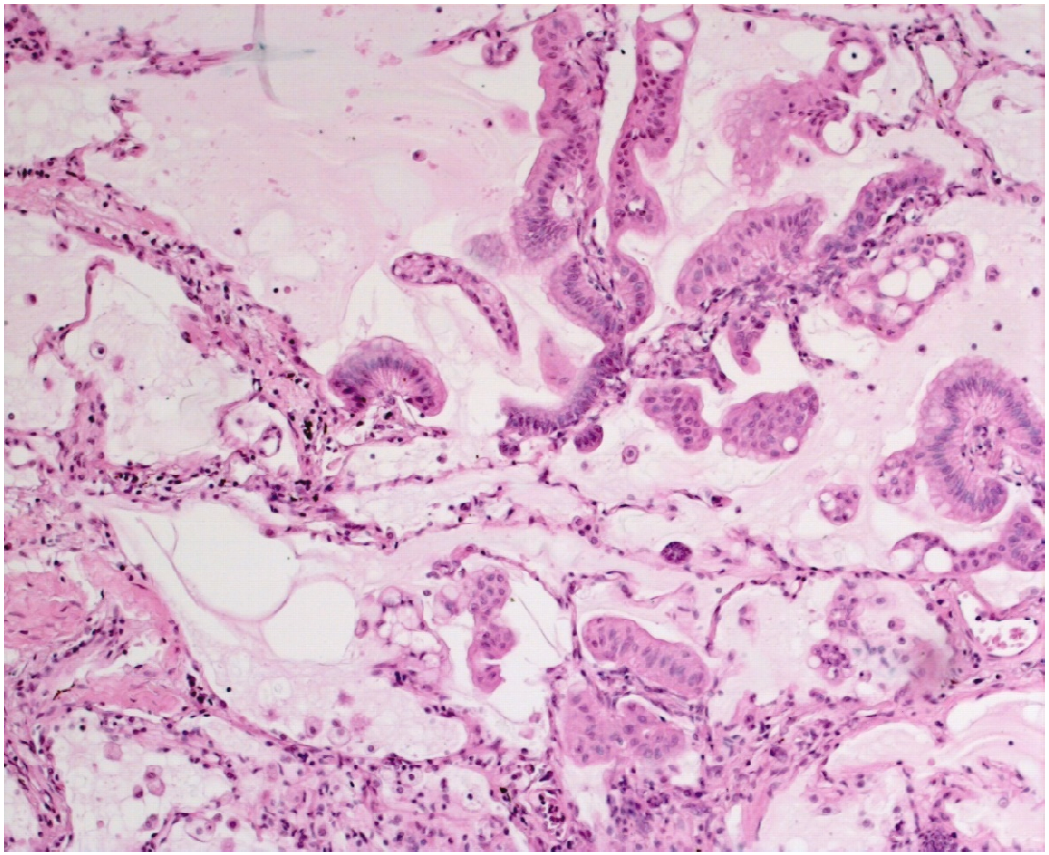


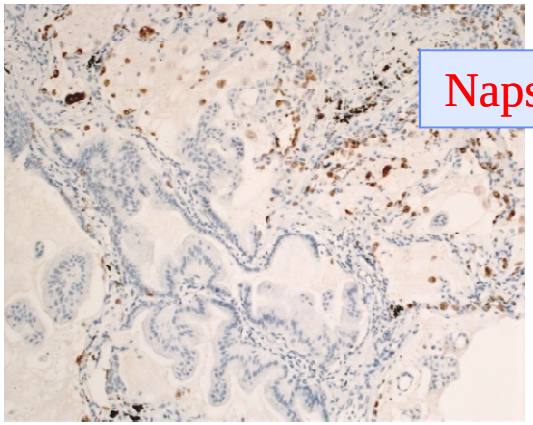
TABLE 2: Frequency of subtypes observed in IPF-related adenocarcinomas compared with non-IPF carcinomas

Adenocarcinoma type ***(according to WHO)***	**N° IPF carcinomas our series**	**% IPF carcinomas our series**	**% Reported series in general population**
Invasive mucinous(m-BAC)	3/15	20%	0% (#) <1% (ref.)
Enteric differentiation	7/15	46,6%	11% 12% (ref. §) 15,9% (#)
Pneumocyte phenotype	5/15	33,3	78,4% (#)

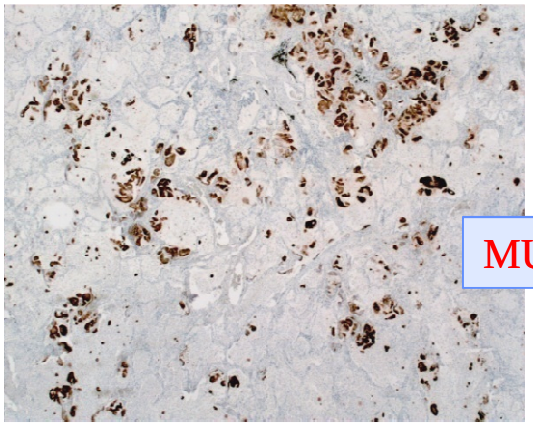
(#) our control group of 88 cases of non-IPF adenocarcinomas
(§) Mazziotta 2005
(^) according to Yatabe, 2004

ADK mucinous (m-BAC) in IPF (#3)

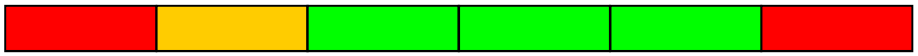




Napsin-A

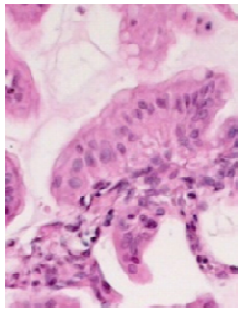
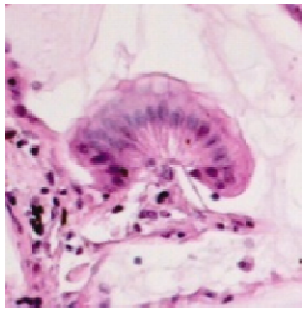
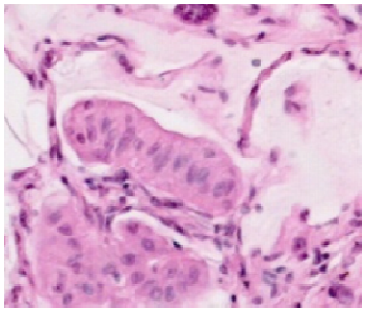
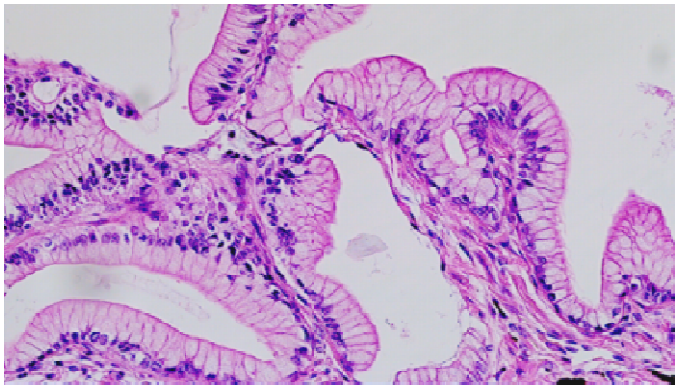


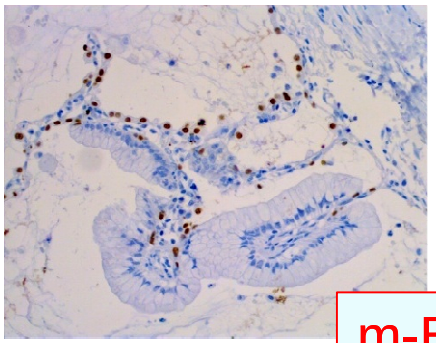
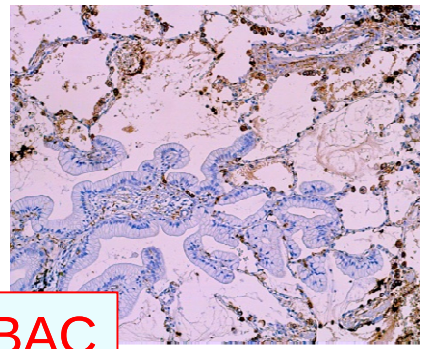
MUC5AC



CK7 CK20 TTF1 SPA NAPS MUC5AC

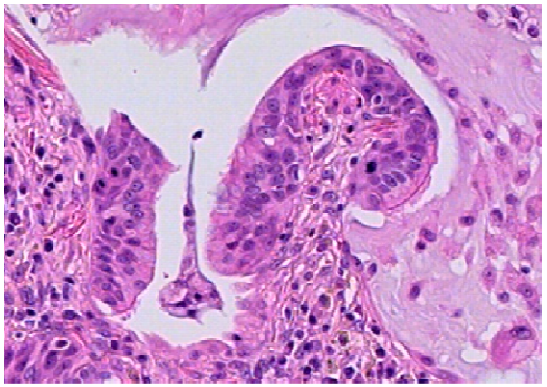
The “*worm-sign*” in m-BAC

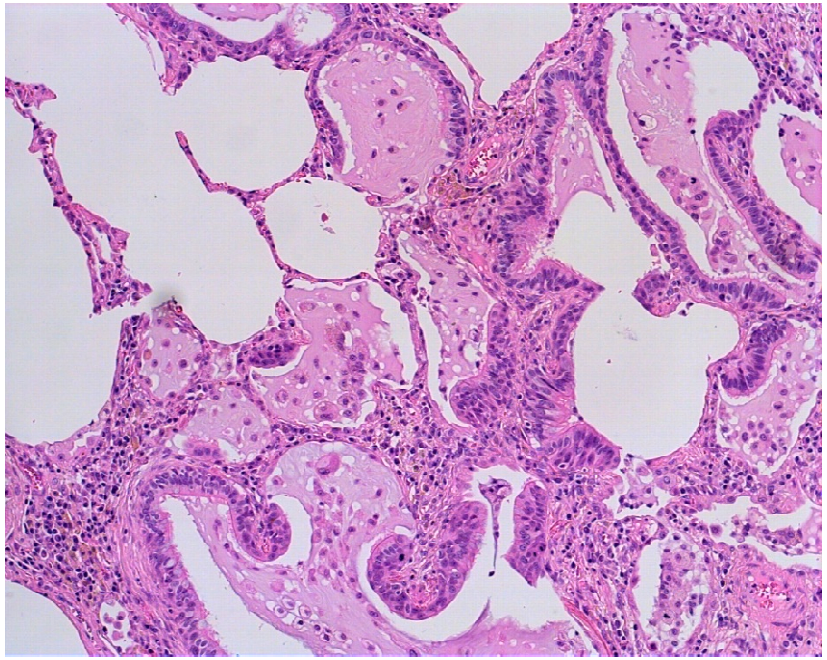






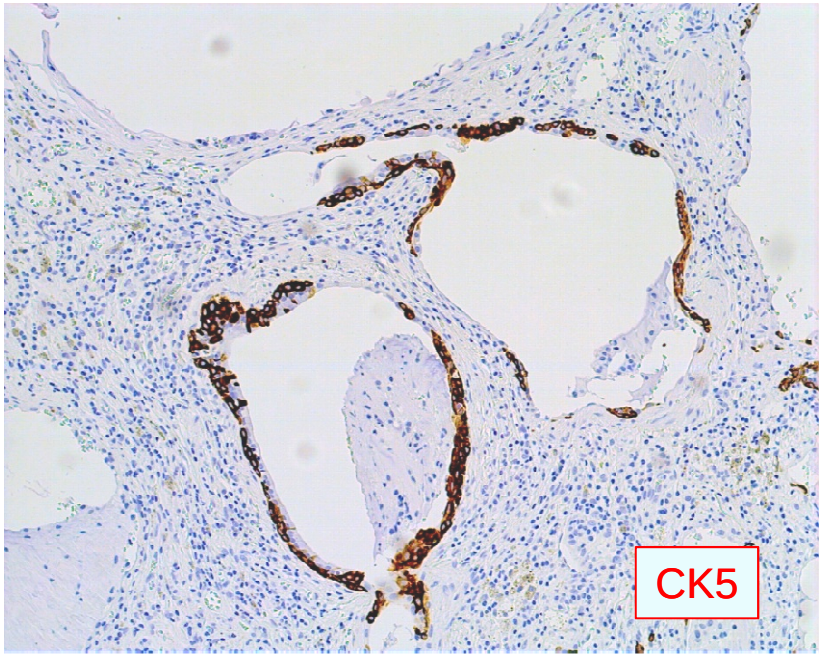



m-BAC

The “*worm-sign*” in IPF/UIP







Pathology International 2007; **57**: 233–244 doi:10.1111/j.1440-1827.2007.02098.x

Review Article

Epidermal growth factor receptor mutations in lung cancers

Yasushi Yatabe[1] **and Tetsuya Mitsudomi**[2]

Departments of [1]*Pathology and Molecular Diagnostics and* [2]*Thoracic Surgery, Aichi Cancer Center, Nagoya, Japan*

Table 2 Characteristics of two biological subtypes in bronchioloalveolar carcinoma

	Mucinous BAC	Non-mucinous BAC
Female	12/16 (75%)†	44/54 (81%)†
Smoker	5/16 (31%)†	10/54 (19%)†
Clinical symptom	Mucinous sputa	Mostly no symptom
Radiographic appearance	Air-bronchogram, more frequent in multinodular presentation	Ground-glass attenuation Solid nodular presentation
Phenotype		
CK7	Positive (>95%)	Positive (>95%)
CK20	Mostly positive (70–90%)	Negative
TTF-1	Mostly negative	Positive (>90%)
CDX2	Possible to be positive	Negative
Genotype		
KRAS	Frequent (60–70%)	Occasional (5–10%)
EGFR	Almost none (<1%)	Frequent (>50%)

†Authors' experience.

BAC, bronchioloalveolar carcinoma; CDX2, caudal type homeobox transcription factor 2; CK, cytokeratin; *EGFR*, *epidermal growth factor receptor*; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; TTF-1, thyroid transcription factor-1.

TABLE 2: Frequency of subtypes observed in IPF-related adenocarcinomas compared with non-IPF carcinomas

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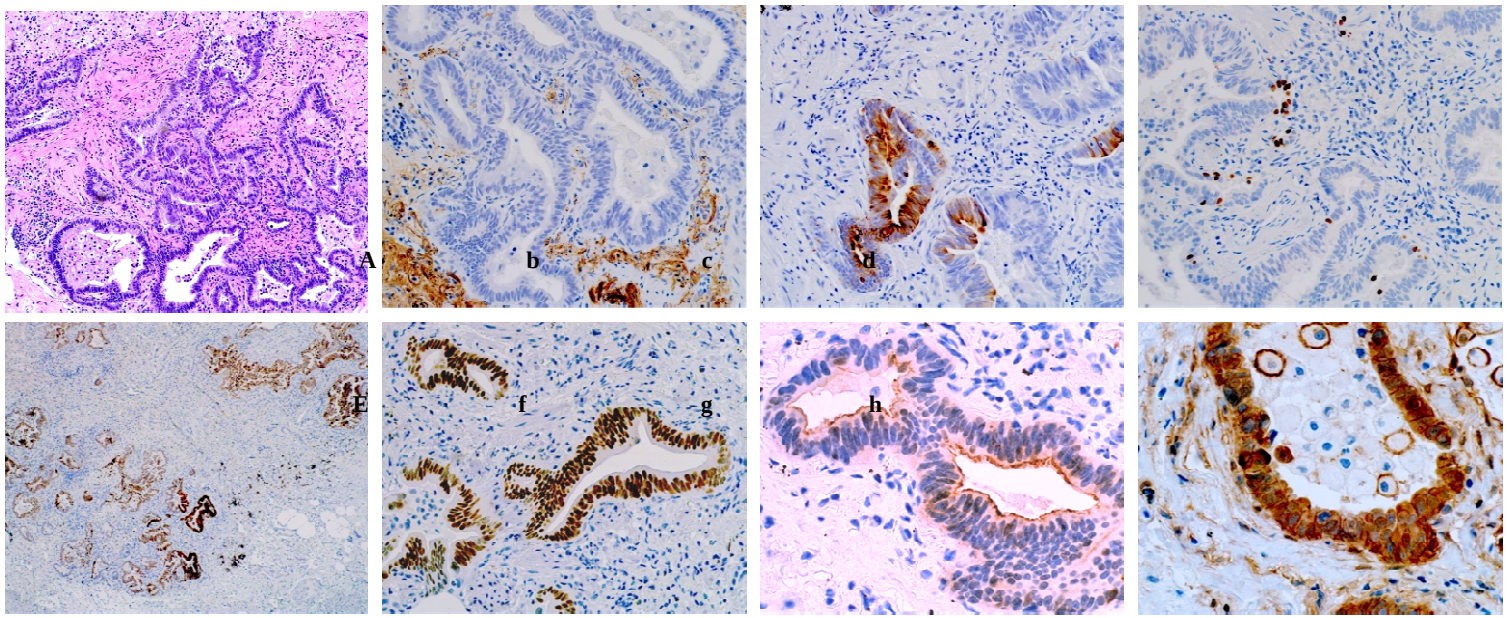
Pneumocyte phenotype	5/15	33,3	78,4% (#)

(#) our control group of 88 cases of non-IPF adenocarcinomas
(§) Mazziotta 2005
(^) according to Yatabe, 2004

Enteric-type ADK in IPF *Case #6*



Metaplastic enteric adenocarcinoma developed in IPF (a: H&E). The acinar component express an incomplete intestinal phenotype: SPA – (b), CK20 +/-,(c), TTF1 – (d), cdx-2 + (e,f), villin + (g), beta-catenin + (nuclear h).

Journal of Biology

BioMed Central

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Research article

Hyperactive Wnt signaling changes the developmental potential of embryonic lung endoderm

Tadashi Okubo and Brigid LM Hogan

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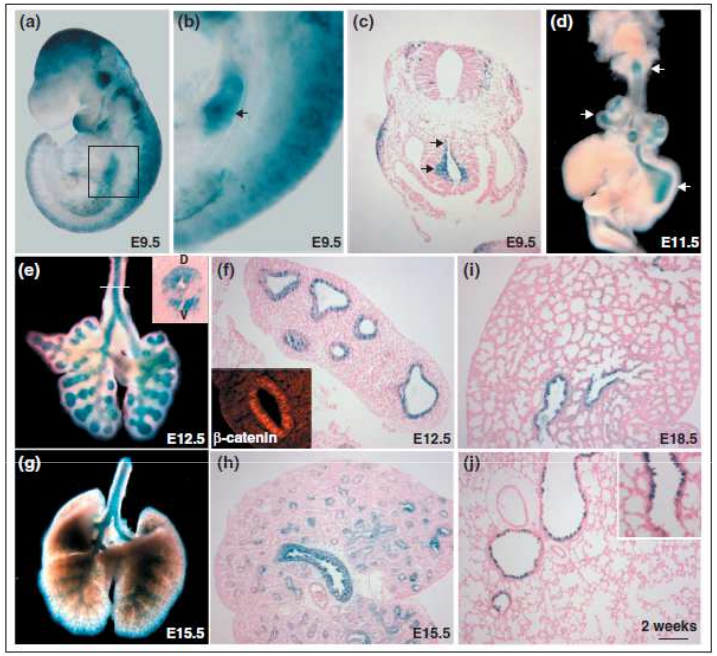
Accepted: 23 April 2004

Abstract

Background: Studies in many model systems have shown that canonical signaling through the pathway downstream of ligands of the Wnt family can regulate multiple steps in organogenesis, including cell proliferation, differentiation, and lineage specification. In addition, misexpression of the Wnt-family member Wingless in *Drosophila* imaginal disc cells can lead to transdetermination of progenitors from one lineage to another. Conditional deletion of the β-catenin component of the Wnt signaling pathway has indicated a role for Wnt signaling in mouse lung endoderm development. The full range of effects of this pathway, which includes the transcription factor Lef1, has not been explored, however.

Results: To explore this issue, we expressed a constitutively active β-catenin-Lef1 fusion protein in transgenic embryos using a lung-endoderm-specific promoter from the *surfactant protein C* gene. Transgenic lungs appeared grossly normal, but internally they contained highly proliferative, cuboidal epithelium lacking fully differentiated lung cell types. Unexpectedly, microarray analysis and *in situ* hybridization revealed a mosaic of cells expressing marker genes characteristic of intestinal Paneth and goblet cells and other non-lung secretory cell types. In addition, there was strong ectopic expression of genes such as *Cdx1* and *Atoh1* that normally regulate gut development and early allocation of cells to intestinal secretory lineages.



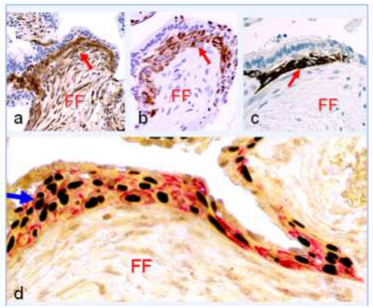
Conclusions:

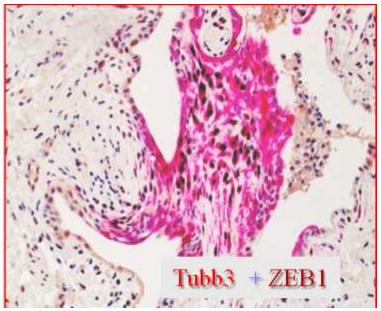
Our results show that hyperactive Wnt signaling in lung progenitors expressing a lung-specific gene can induce a dramatic switch in lineage commitment and the generation of intestinal cell types. We discuss the relevance of our findings to the poorly understood pathological condition of intestinal metaplasia in humans.

From “bronchiolar Dysplasia to carcinoma in IPF/UIP

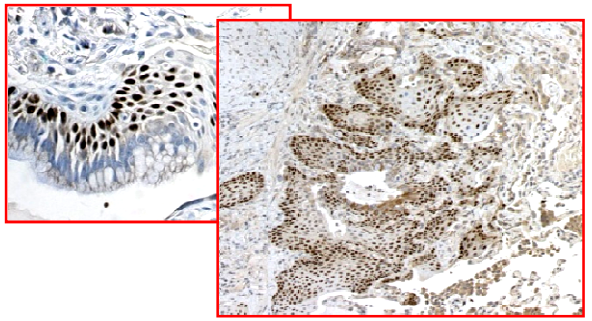
Hyper-expression

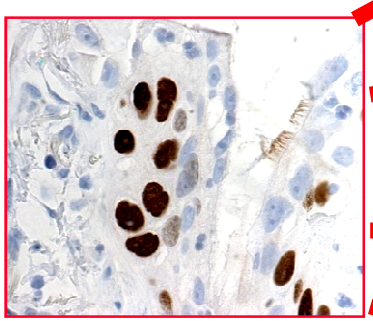
- N-beta-Catenin
- Laminin-5g2
- Hsp27
- Tubb3
- P63
- ZEB1
- MUC5B
- S100A4
- Fascin
- C-Myc





Squamous carcinoma





adenocarcinoma

Goblet-metaplasia

m-BAC

Abnormal stem (basal) cells

WNT-abnormal activation

Intestinal-type adenocarcinoma

Chilosi *et al. Respiratory Research* 2012, **13**:3
http://respiratory-research.com/content/13/1/3

RESPIRATORY RESEARCH

REVIEW Open Access

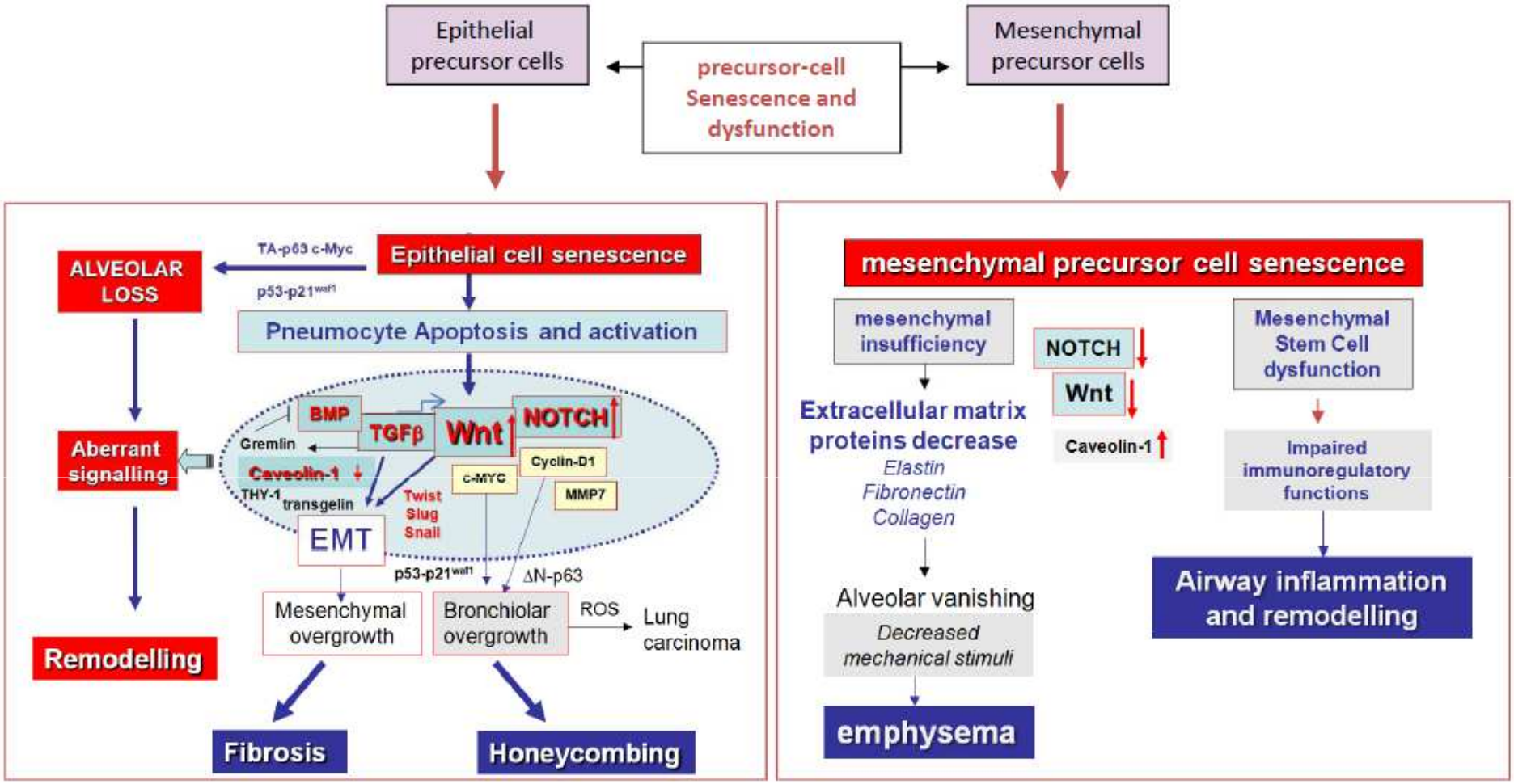
The pathogenesis of COPD and IPF: Distinct horns of the same devil?

Marco Chilosi[1*], Venerino Poletti[2] and Andrea Rossi[3]

Abstract

New paradigms have been recently proposed in the pathogenesis of both chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), evidencing surprising similarities between these deadly diseases, despite their obvious clinical, radiological and pathologic differences. There is growing evidence supporting a "double hit" pathogenic model where in both COPD and IPF the cumulative action of an accelerated senescence of pulmonary parenchyma (determined by either telomere dysfunction and/or a variety of genetic predisposing factors), and the noxious activity of cigarette smoke-induced oxidative damage are able to severely compromise the regenerative potential of two pulmonary precursor cell compartments (alveolar epithelial precursors in IPF, mesenchymal precursor cells in COPD/emphysema). The consequent divergent derangement of signalling pathways involved in lung tissue renewal (mainly Wnt and Notch), can eventually lead to the distinct abnormal tissue remodelling and functional impairment that characterise the alveolar parenchyma in these diseases (irreversible fibrosis and bronchiolar honeycombing in IPF, emphysema and airway chronic inflammation in COPD).

Keywords: COPD, IPF, precursor cell senescence, telomere dysfunction, Wnt, Notch, Caveolin-1


Epithelial precursor cells
precursor-cell Senescence and dysfunction
Mesenchymal precursor cells
ALVEOLAR LOSS
TA-p63 c-Myc
Epithelial cell senescence
p53-p21waf1
Pneumocyte Apoptosis and activation
Aberrant signalling
BMP
TGFβ
Wnt
NOTCH
Gremlin
Caveolin-1
THY-1 transgelin
Twist Slug Snail
c-MYC
Cyclin-D1
MMP7
EMT
p53-p21waf1
ΔN-p63
Mesenchymal overgrowth
Bronchiolar overgrowth
ROS
Lung carcinoma
Remodelling
Fibrosis
Honeycombing
mesenchymal precursor cell senescence
mesenchymal insufficiency
Extracellular matrix proteins decrease
Elastin
Fibronectin
Collagen
Alveolar vanishing
Decreased mechanical stimuli
emphysema
NOTCH
Wnt
Caveolin-1
Mesenchymal Stem Cell dysfunction
Impaired immunoregulatory functions
Airway inflammation and remodelling
IPF
COPD

Abnormal Lung Aging in Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis

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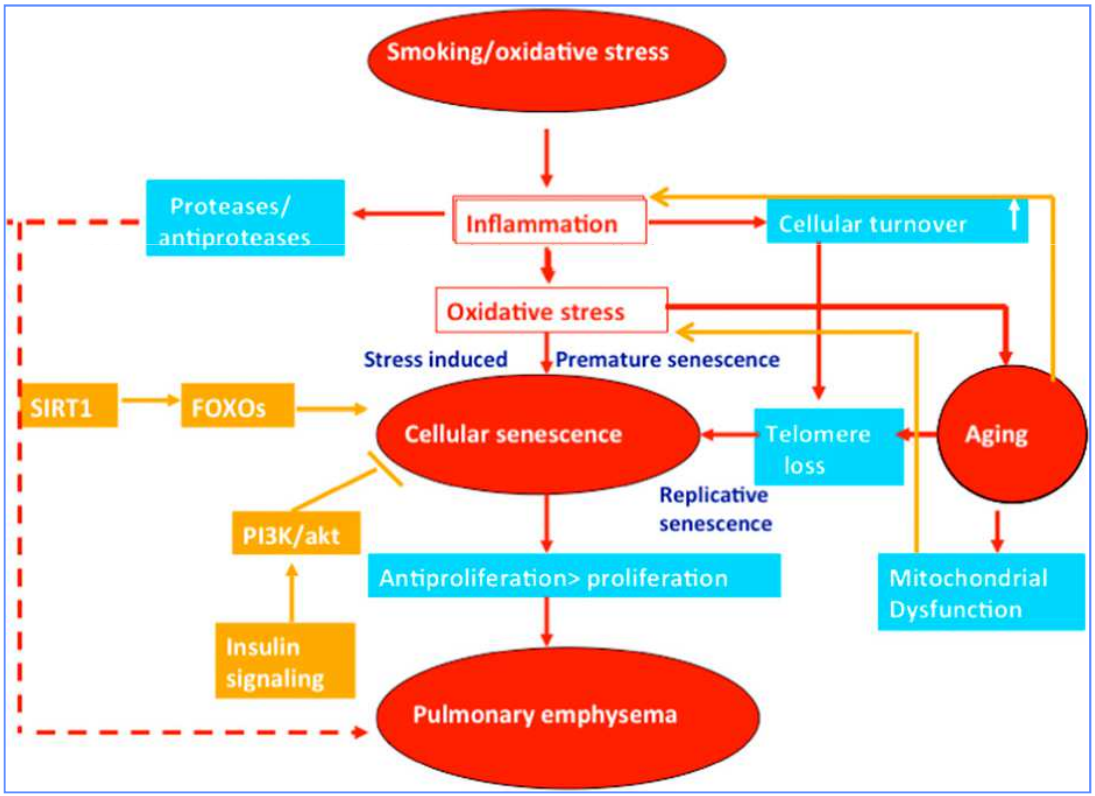
Aging is a natural process characterized by progressive functional impairment and reduced capacity to respond appropriately to environmental stimuli and injury. The incidence of two common chronic respiratory diseases (chronic obstructive pulmonary disease [COPD] and idiopathic pulmonary fibrosis [IPF]) increases with advanced age. It is plausible, therefore, that abnormal regulation of the mechanisms of normal aging may contribute to the pathobiology of both COPD and IPF. This review discusses the available evidence supporting a number of aging mechanisms, including oxidative stress, telomere length regulation, cellular and immunosenescence, as well as changes in a number of antiaging molecules and the extracellular matrix, which are abnormal in COPD and/or IPF. A better understanding of these abnormalities may help in the design of novel and better therapeutic interventions for these patients.

Keywords: chronic obstructive pulmonary disease; fibrosis; interstitial lung disease; inflammation; repair



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