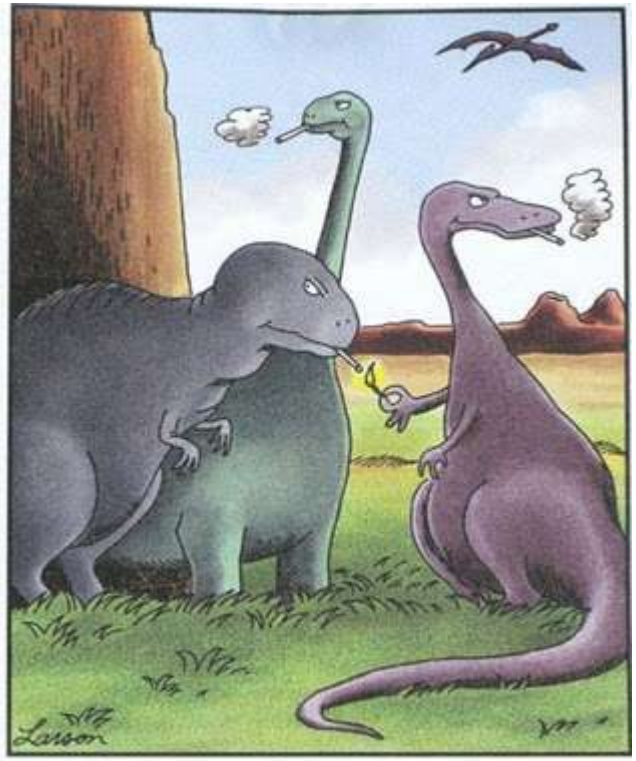
Smoking related interstitial lung diseases

Sterclova M.
Department of Respiratory Medicine, Thomayer Hospital, Prague, Czech Republic



The real reason dinosaurs became extinct

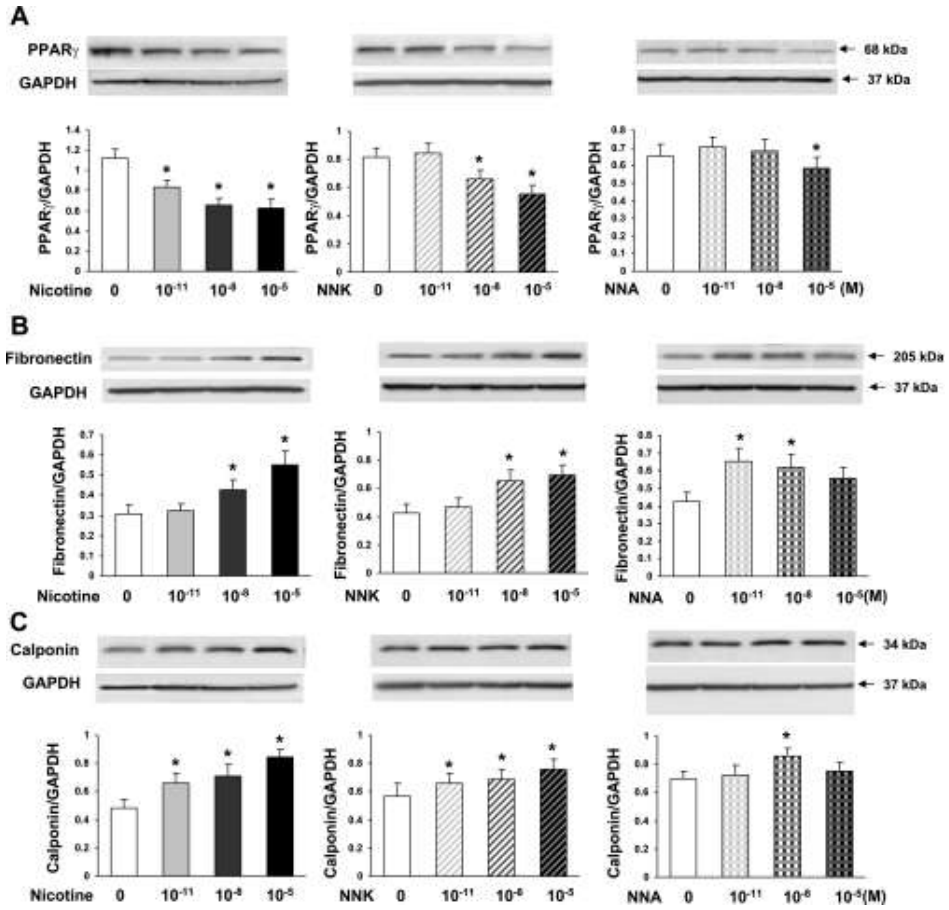
Supported by an IGA Grant No G 1207 (NT13433-4/2012).

1. Effect of age at the time of CS exposure
2. Effect of CS on lungs
3. Pathogenesis of smoking related interstitial lung disorders

5026 BC

1560 France

Ad 1. Effect of age at the time of CS exposure

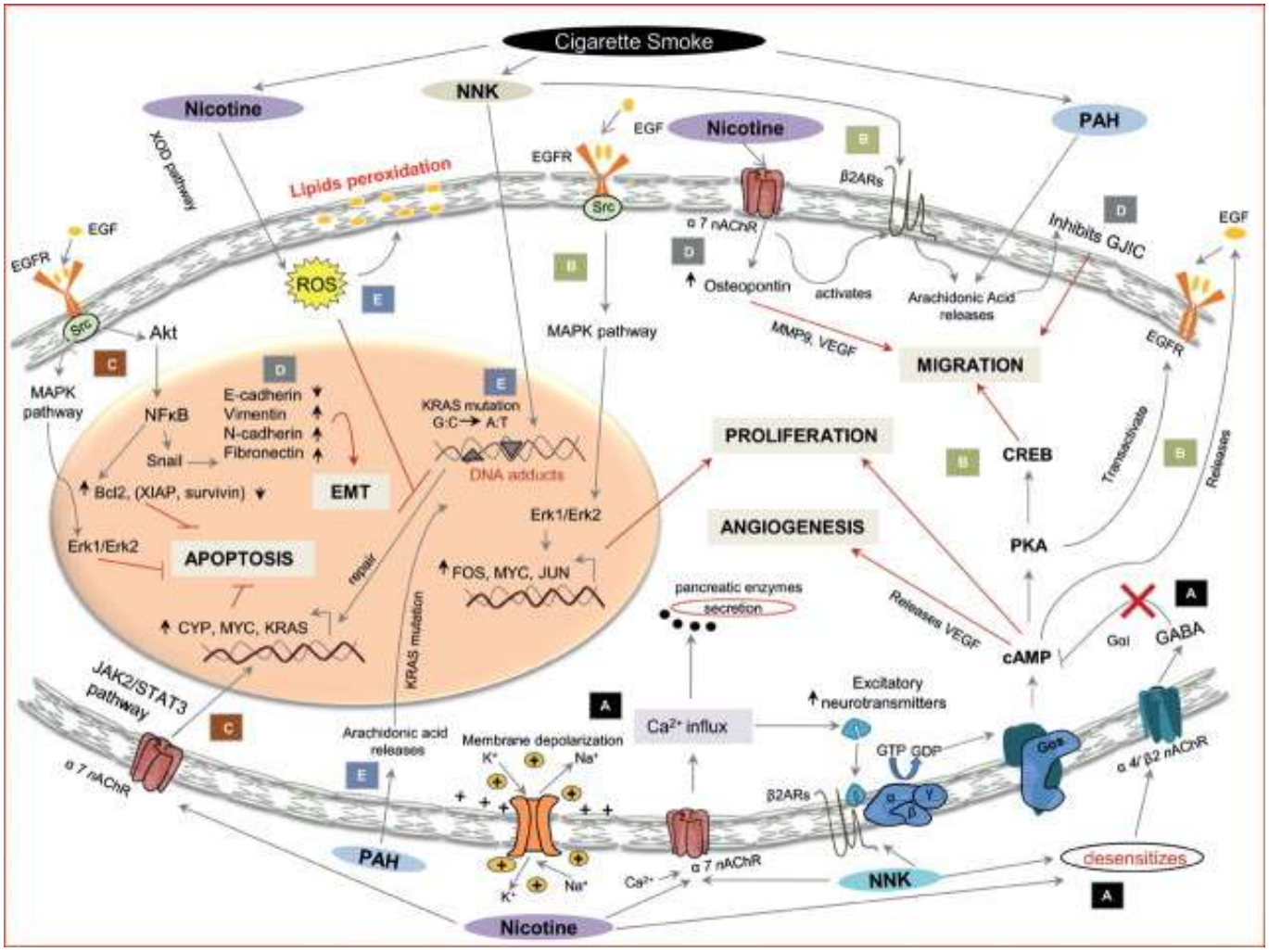


-Third hand smoke - genome instability and faster telomere shortening
-Methylation and downregulation of miRNA (placenta, cord blood, peripheral blood)

-Second hand smoke - higher concentrations of benzol(a)pyrene, toluene, nitrosamines, smaller particles more likely to be deposited in the lung
-Exposure to carcinogens during periods of rapid cell division – genetic abnormalities – lung cancer, fibrogenesis

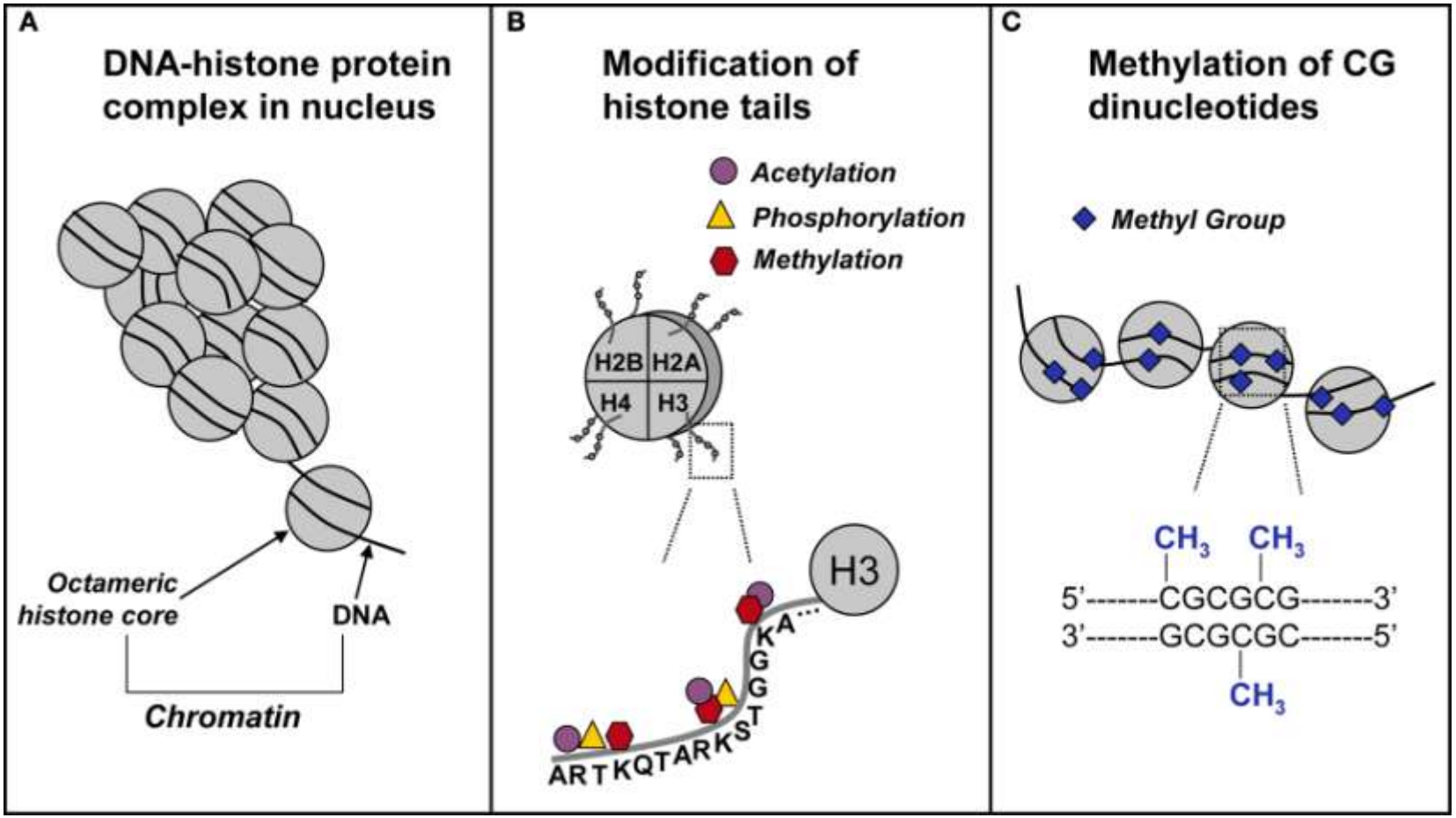
Rehan VK, et al. Am J Physiol Lung Cell Mol Physiol 2011 ;31:L1-L8.

Ad 2. Effect of CS on lung cells



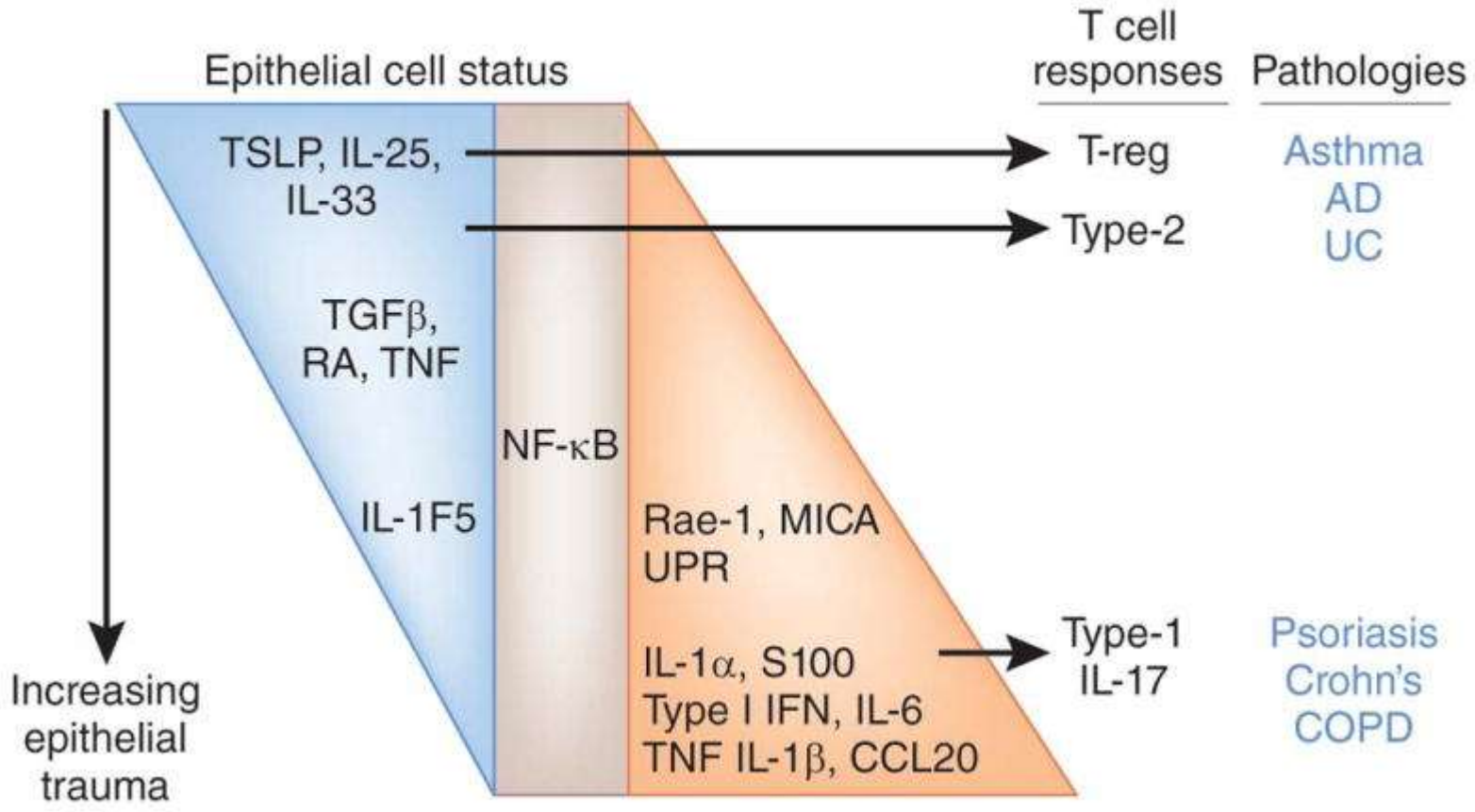
Momi N, et al. Carcinogenesis 2012; 33.1617-28.

Smoking-induced epigenetic events

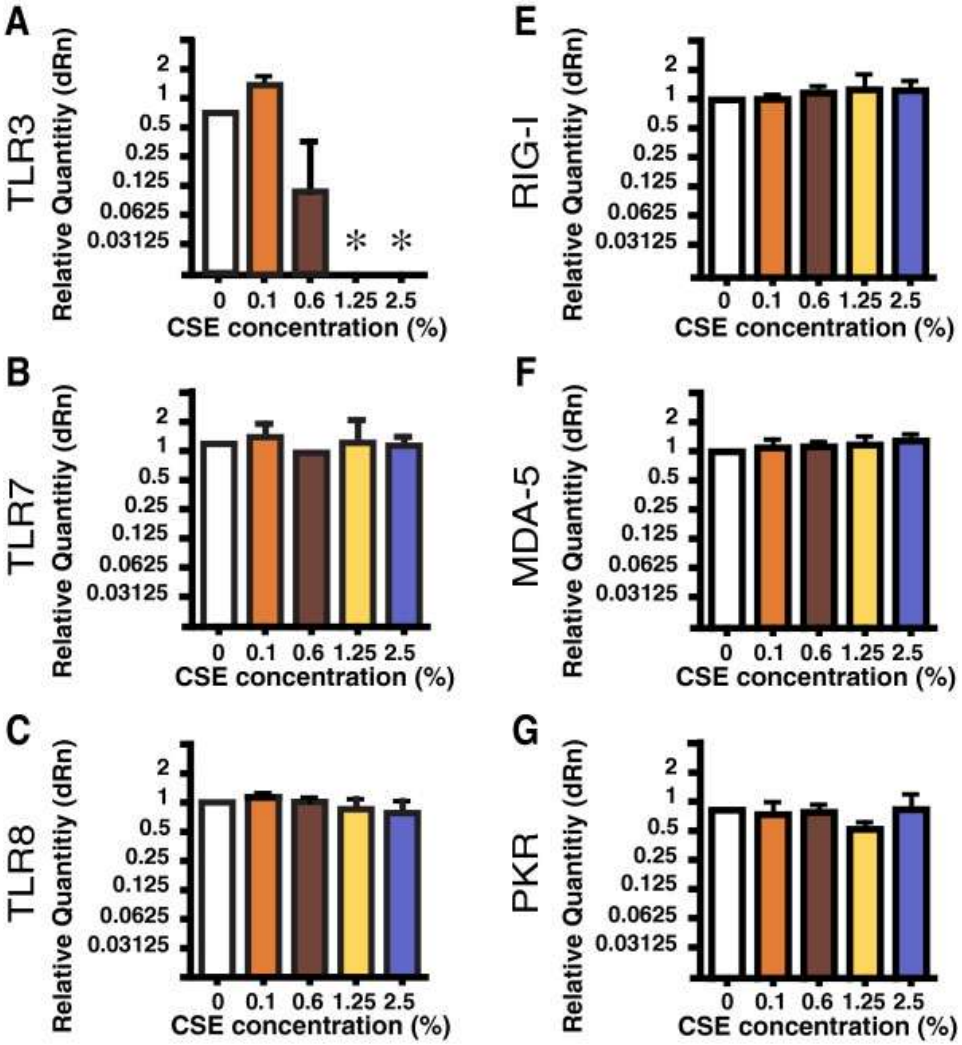


Penner MR, et al. Front Ag Neurosci 2010; 2:9.

Effect of cigarette smoke - epimmunome



Swamy M, et al. Nat Immunol 2010;11: 656–65.



Infection susceptibility

-CS favours colonisation by pathogens
-Enhances bacterial attachment to epithelial cells, promotes changes in virulence by modifying bacterial gene expression

- Reduction in lung Mø TLR3 expression may be one mechanism contributing to the increased incidence of viral respirator infections in smokers and to viral induction of acute exacerbations

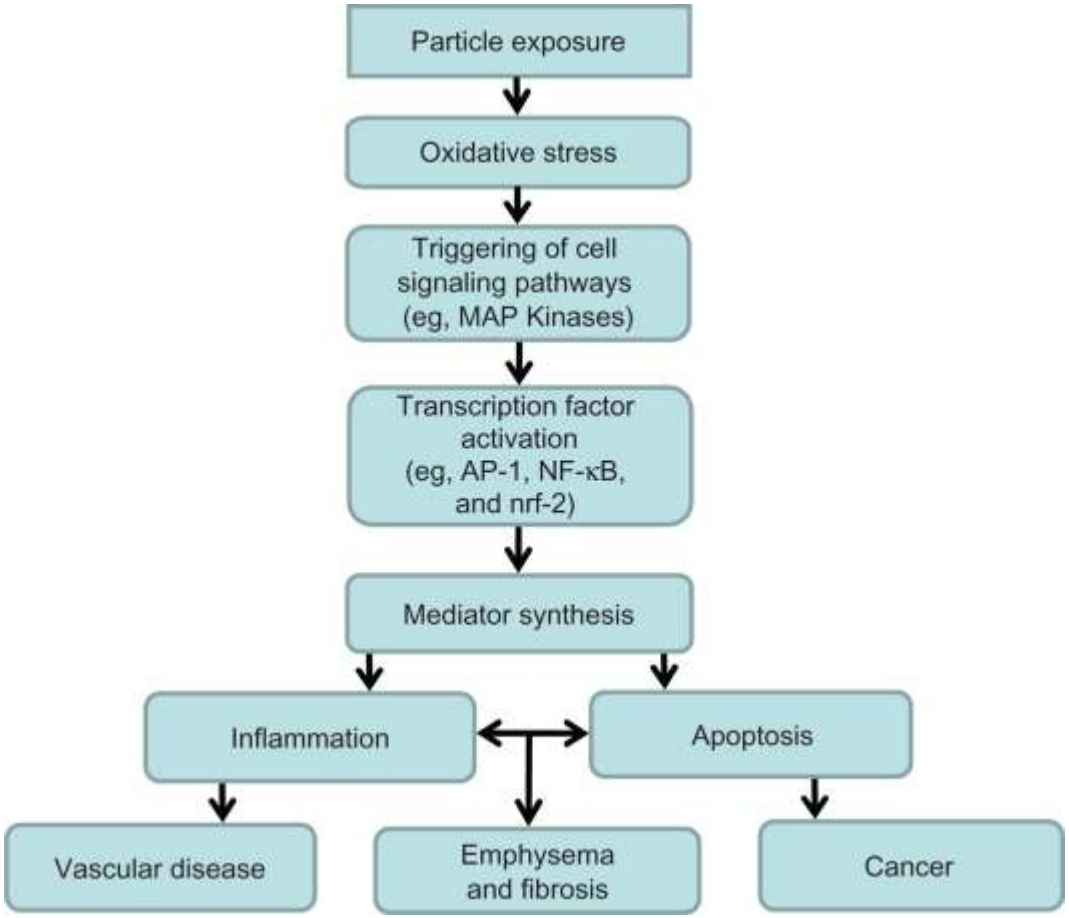
Todt JC, et al. Respir Res 2013; 14:33.
Garmendia J, et al. European Respiratory Journal 2012; 39:467-477.

Mechanisms of nicotine-induced fibrogenesis

- Promotes damage to epithelial/endothelial barriers
- Stimulates the production and release of TGF-β1
- Recruits inflammatory cells
- Activates ROS production
- Activates collagen-producing cells

Jensen K, et al. FASEB Journal 2012; 26:4778-4787.

Particle related effect of cigarette smoke



Sangani RG, et al. International Journal of COPD 2011; 6:191-198.

Modification of environmental exposures prevent/delay onset of short telomere syndrome

Table 4. Relationship between smoking, fibrogenic exposures and pulmonary fibrosis in *TERT* mutation carriers ≥40 years of age.

Exposure	No. of Subjects with Exposure	No. of Subjects without Exposure	P-Value*	Odds Ratio [95% confidence interval]
Smoking, present or past				
Pulmonary Fibrosis	20	8	0.02	4.0 [1.2, 14.5]
No Pulmonary Fibrosis	11	18		
Fibrogenic Exposure**				
Pulmonary Fibrosis	20	8	0.18	2.3 [0.7, 8.1]
No Pulmonary Fibrosis	15	14		
Smoking and/or Fibrogenic Exposure				
Pulmonary Fibrosis	27	1	0.005	13.6 [1.7, 636.8]
No Pulmonary Fibrosis	19	10		

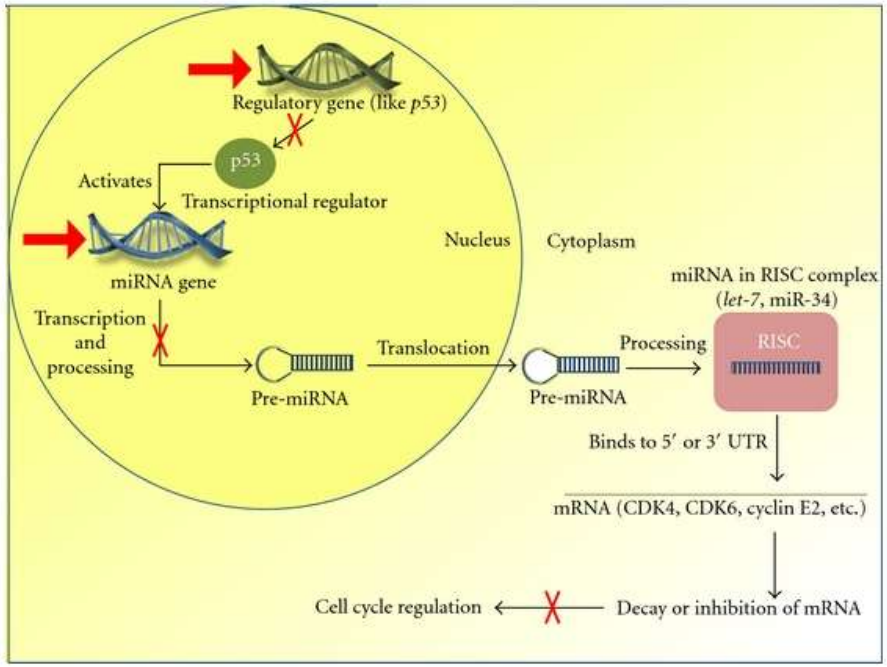
*By Fisher's exact test.

**The self-reported fibrogenic exposures include ingestion of methotrexate and nitrofurantoin; exposure to birds and bird antigens including parakeets, cockatiels, and eagle feathers; occupational exposures to asbestos, welding, carpentry, mining, sandblasting, cement manufacturing, railroad work, insulation; and household exposure to water damage and significant mold.

doi:10.1371/journal.pone.0010680.t004

Diaz de Leon A, et al. PlosOne 2010; 5:e10680.

Cigarette smoke induced dysregulation of microRNA expression

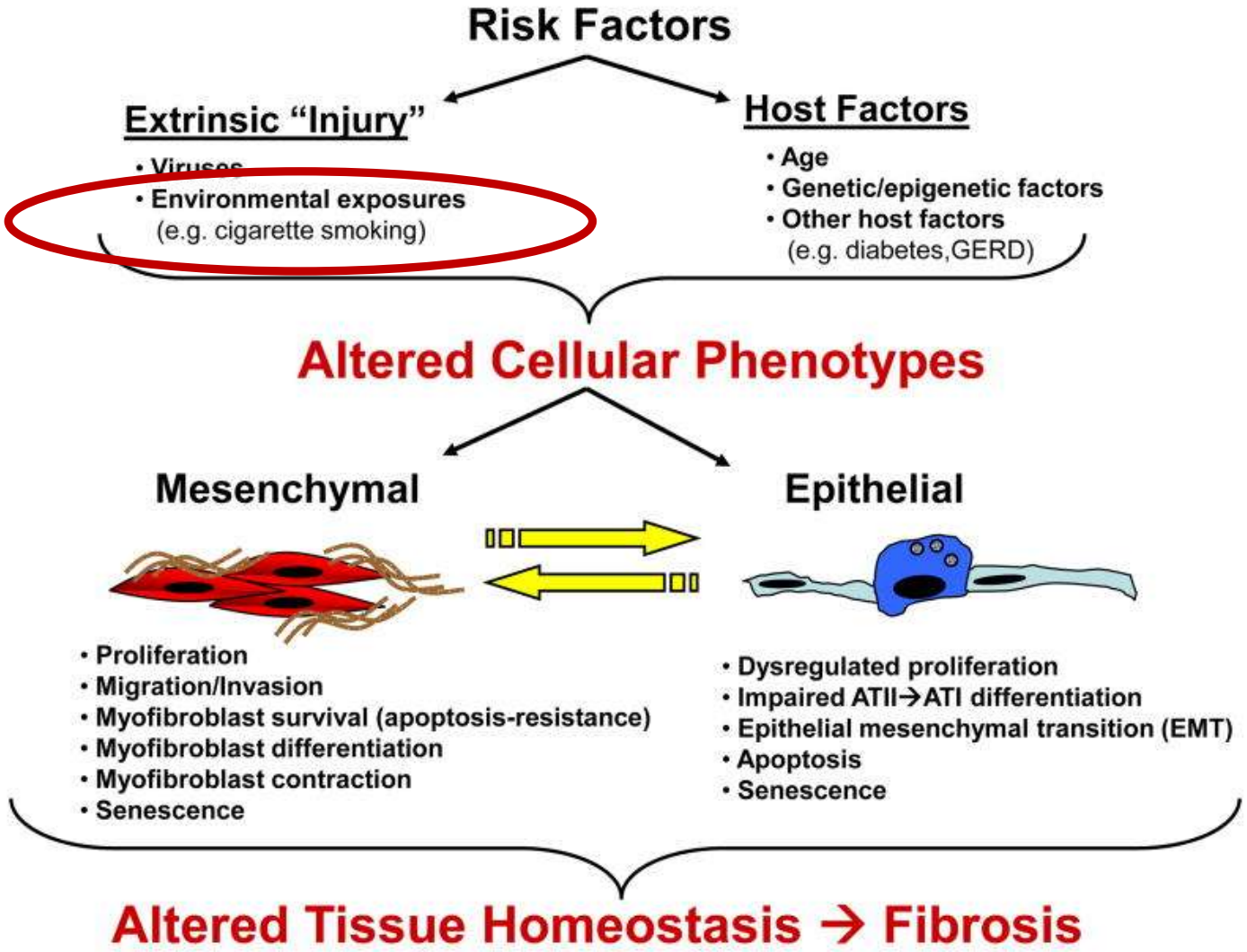


-Repressors of genic expression at the posttrascriptional level, degrading messenger RNA or inhibiting its protein translation

-Correlation between smoke exposure-induced dysregulation of miRNAs and age
-Dysregulation intensity and duration associated
-Short term exposure-reversible changes, adaptive response mech
-Longer exposure-irreversibility of changes in expression

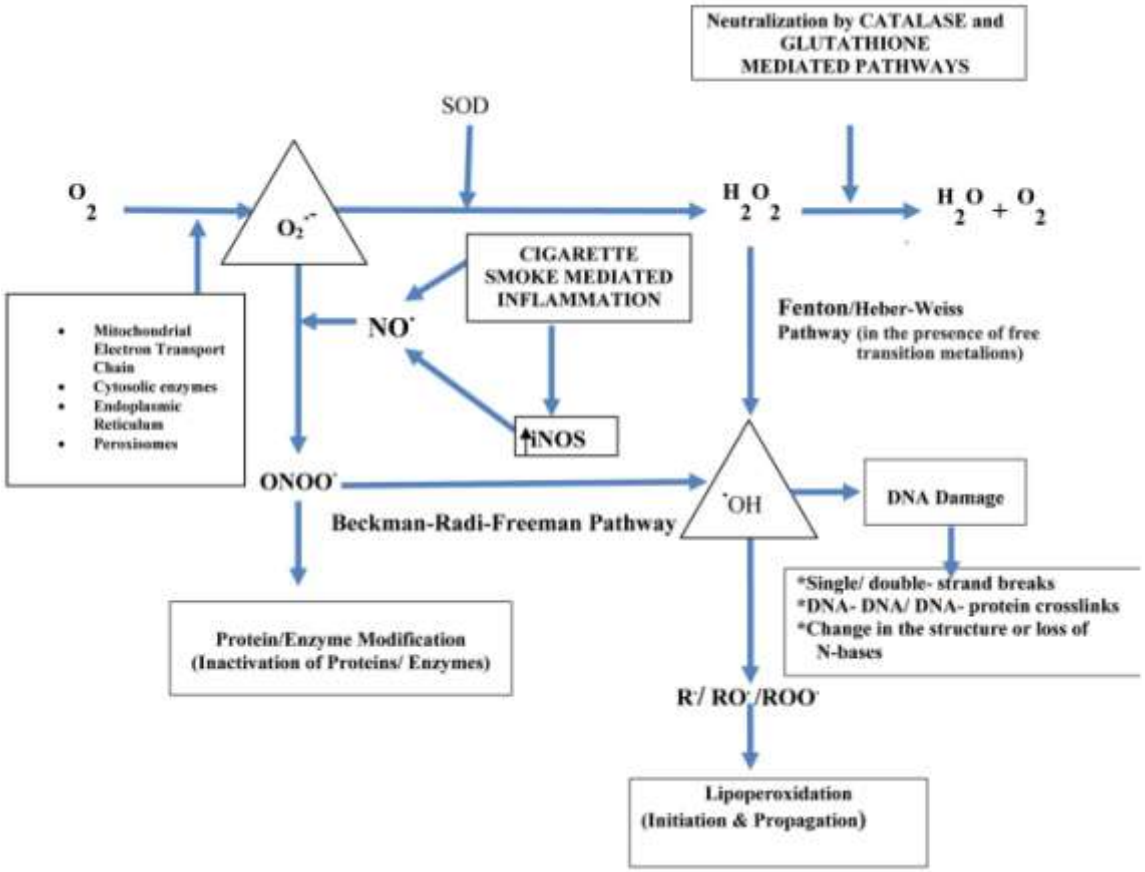
Russ R, et al. Pulm Med 2012; 2012:791234.

Pathogenesis of IPF



Ding Q, et al. Drugs 2011; 71: 981-1001.

Smoking and ILD associated with organic/anorganic antigens exposure



Rajesh P, et al. Journal of Clinical and Diagnostic Research 2013;3: 580 - 588

Smoking and ILD associated with organic/anorganic antigens exposure

TABLE 4: Logistic regression analysis: interactions between *MnSOD* and *CAT*, *iNOS* and *CAT*, *GSTM1* and smoking, *iNOS* and smoking, and *iNOS* and log-cumulative asbestos exposure.

	OR	95% CI	*P* value
MnSOD −9Ala/Val + Val/Val versus Ala/Ala	0.59	0.39–0.91	0.016
CAT −262 TT versus CT + CC	0.53	0.17–1.62	0.266
Interaction[†]	4.49	1.08–18.61	0.038
iNOS LL versus SL + SS	1.08	0.75–1.55	0.687
CAT −262 TT versus CT + CC	0.63	0.24–1.66	0.354
Interaction[‡]	4.78	1.15–19.81	0.031
GSTM1-null versus present	0.63	0.39–1.02	0.062
Smoking	0.55	0.32–0.96	0.036
Interaction[#]	2.67	1.31–5.46	0.007
iNOS LL versus SL + SS	0.85	0.53–1.37	0.505
Smoking	0.70	0.43–1.13	0.143
Interaction[§]	2.00	0.99–4.03	0.054
iNOS LL versus SL + SS	1.91	1.07–3.42	0.030
Log cumulative exposure	4.25	2.79–6.46	0.000
Interaction[*]	0.55	0.31–0.97	0.037

[†]Interaction: *MnSOD* −9Ala/Val + Val/Val versus Ala/Ala * *CAT* −262 TT versus CT + CC.
[‡]Interaction: *iNOS* LL versus SL + SS * *CAT* −262 TT versus CT + CC.
[#]Interaction: *GSTM1*-null versus present * smoking (ever/never).
[§]Interaction: *iNOS* LL versus SL + SS * smoking (ever/never).
[*]Interaction: *iNOS* LL versus SL + SS * log cumulative exposure.

-Association among polymorphisms of genes for enzymes playing role in coping with reactive oxygen and nitric species in asbestosis patients

Franko A, et al. Biomed Res Int 2013; 2013:405743.

Smoking and ILD associated with organic/anorganic antigen exposure

- Protective effect of CS on the development of hypersensitivity pneumonitis
- Long-term exposure to PDE without CS: ↑ in lung weight/body weight ratio, total cell number in bronchoalveolar lavage (BAL) fluid, and content of hydroxyproline in the lung compared to short term exposure
- Short-term exposure to PDE+CS: ↓the lymphocytosis in BAL fluid, and lymphocyte proliferation
- Long-term exposure to PDE+CS: ↑ lung hydroxyproline.

Furuiye M, et al.J Med Dent Sci 2007; 54:87-95.

Smoking and ILD in patients with connective tissue disease

Table 2 Demographic data, the extent of fibrosis and the coarseness of fibrosis compared between smokers with emphysema, smokers without emphysema and lifelong non-smokers in patients with IPF and RA-ILD

	Smokers with emphysema	Smokers without emphysema	Lifelong non-smokers	*P*-value
IPF	$n = 66$	$n = 120$	$n = 63$	
Age (years)	62.8 ± 9.8	63.7 ± 9.1	60.3 ± 12.6	$P = 0.09$
Gender	M/F = 57/9	M/F = 99/21	M/F = 28/35	$P < 0.0005$†
Extent of fibrosis (%)	50.0 ± 19.5	19.1 ± 18.9	59.1 ± 22.8	$P < 0.001$
Coarseness of fibrosis	9.8 ± 1.7	9.4 ± 2.1	8.3 ± 2.3	$P < 0.0001$
RA-ILD	$n = 22$	$n = 24$	$n = 35$	
Age (years)	62.4 ± 6.5	60.8 ± 10.7	55.5 ± 13.3	$P < 0.005$
Gender	M/F = 18/4	M/F = 12/12	M/F = 10/25	$P < 0.0005$†
Extent of fibrosis (%)‡	37.5 ± 23.3	39.8 ± 23.3	31.3 ± 18.3	$P = 0.49$
Coarseness of fibrosis‡	9.1 ± 2.8	8.3 ± 3.5	8.5 ± 2.7	$P = 0.68$

† Group comparisons are made using analysis of variance or chi-square testing.
‡ High-resolution computed tomography scores for extent of fibrosis and coarseness of fibrosis in 75 patients.
IPF, idiopathic pulmonary fibrosis; rheumatoid arthritis-interstitial lung disease.

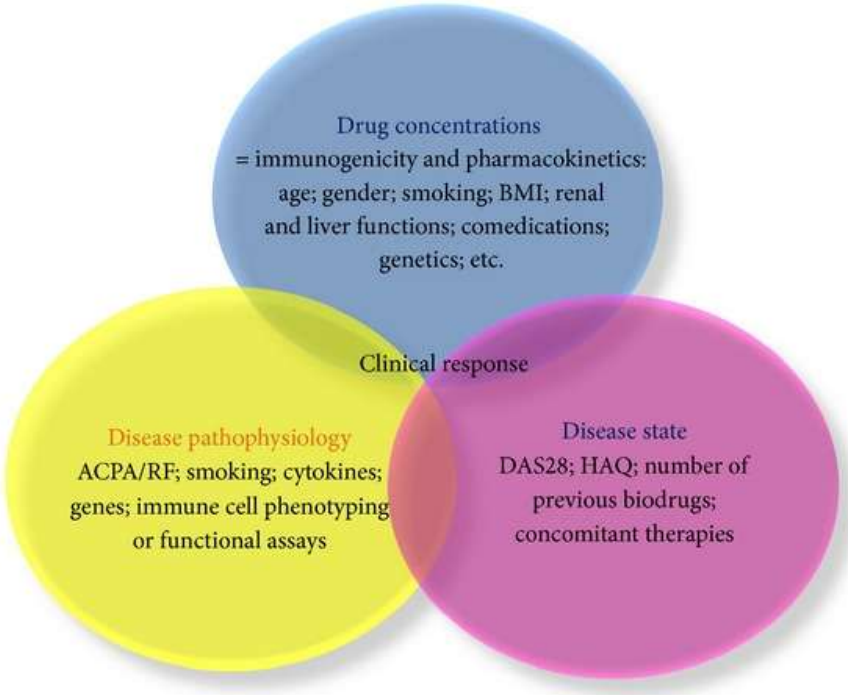
Antoniou KM, et al. Respirology 2013; 18:1191-6.

Smoking and rheumatoid arthritis

- Smoking associated with development of extraarticular manifestations and progressive disease course
- Promotes citrullination of synovial proteins
- Smoking + HLA shared epitopes alleles --- autoimmunity trigger
- ILD in RA males, >10 py UIP
- Lower PY – emphysema, prevalence 48% RA-ILD

Cavagna L, et al. Biomed Res Int 2013; 2013: 759760.

Smoking and rheumatoid arthritis treatment



-Lower infliximab response
-Limit efficiency of corticosteroids to attenuate the transcription of inflammmatory genes
-Induce cytochrome P450 activity

Daien CI, et al. Mediators Inflamm 2014; 2014: 386148.

Smoking and rheumatoid arthritis treatment

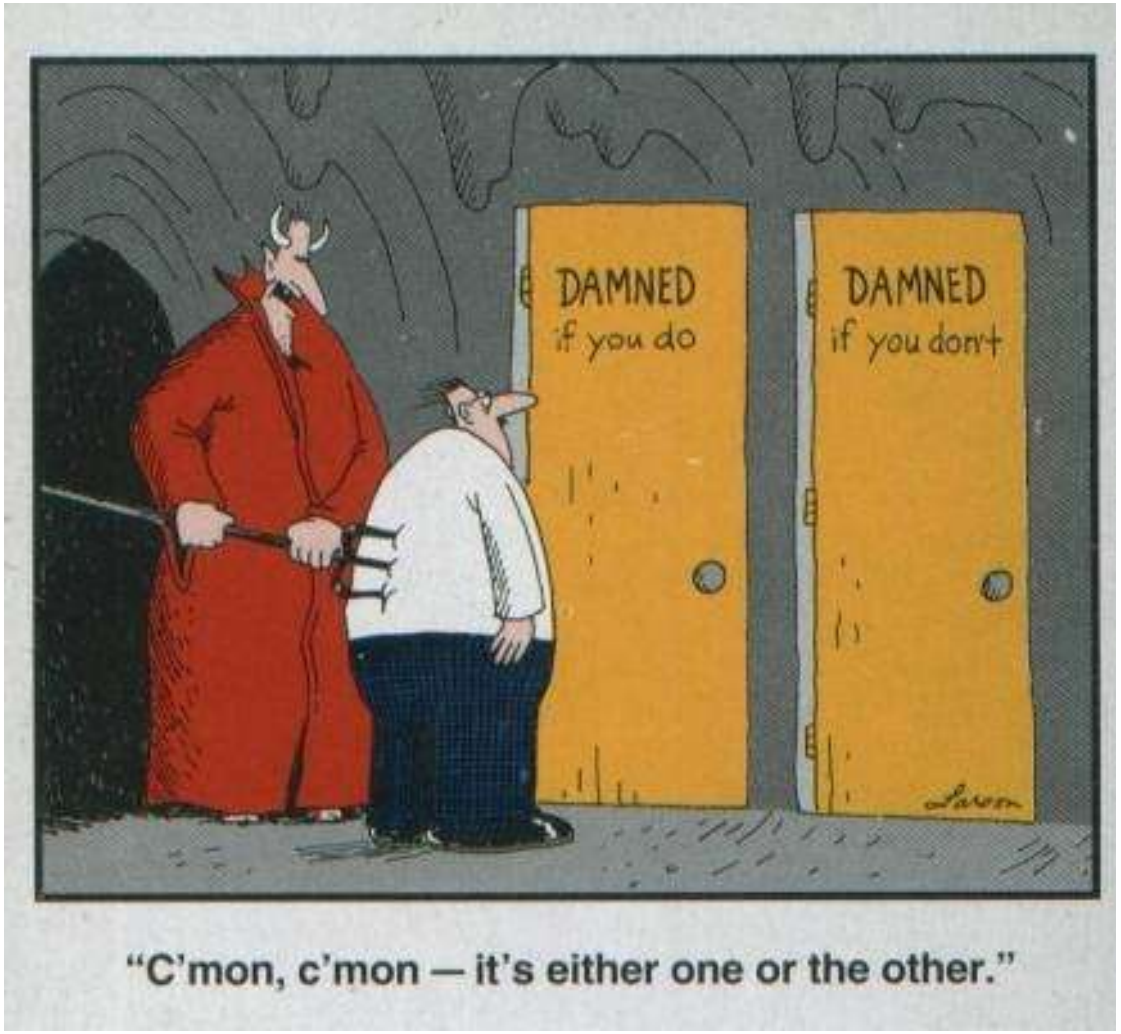
Table 2: Main predictive factors of response to biological therapy.

Factors associated with good response to	Tumor necrosis factor inhibitors	Tocilizumab	Abatacept	Rituximab
Patients characteristics	Male (C) [7–9] Younger (C) [7, 8] Nonsmoker (C) [10, 19–21] Nonobese for IFX (C) [16, 17] Use of MTX (C) [7, 8, 10, 11]	Older (NC) [12]	Younger (NC) [13]	Male (NC) [15]
Disease characteristics	Low HAQ (C) [7, 10, 17, 20] High DAS28 (C) [7, 8, 17] ACPA or RF negativity (C) [20, 31] Low number of previous biological therapies (C) [8]	Low HAQ and high DAS28 [13]	High DAS28 [14] RF positivity (C) [32]	Low HAQ and high DAS28 [15, 32] RF positivity +++ (C) [32] Low number of previous biological therapies (C) [29]
Immunogenicity	Antidrug antibodies against ADA or IFX for response to ETN (NC) [39]			
Genetic background	PTPRC = CD45 (rs10919563) (C) [41, 42], 7 SNPs including EYA4 (rs17301249) and PDZD2 (rs1532269) (NC) [43]			158VV FCGR3A in European countries (C) [44, 45]
Cytokines and immune cells	High TNF bioactivity in blood [5] or in synovium [49] (NC), high LPS-stimulated whole blood IL-1b (NC) [48], low IL-17 (NC) [6] 24-biomarker ETN response signature including autoantibodies and cytokines (C) [53]	High serum IL-6 levels (NC) [54]	Low levels of CD4+ and CD8+ CD28− T cells (NC) [61]	Memory B cells (NC) [57, 58]

C: confirmed; NC: not confirmed. To be confirmed, the data had to be validated at least by two independent teams.

Daien CI, et al. Mediators Inflamm 2014; 2014: 386148.

Systemic sclerodermia - inconsistent results



"C'mon, c'mon — it's either one or the other."

Systemic sclerodermia - inconsistent results

J. Cell Commun. Signal. (2011) 5:67–68
DOI 10.1007/s12079-010-0111-1

BITS AND BYTES

When there's smoke there's…scleroderma: evidence that patients with scleroderma should stop smoking

Andrew Leask

Published in final edited form as:
Arthritis Rheum. 2011 October ; 63(10): 3098–3102. doi:10.1002/art.30492.

Cigarette Smoking is not a Risk Factor for Systemic Sclerosis

Prateek Chaudhary[1], **Xing Chen**[2], **Shervin Assassi**[1], **Olga Gorlova**[2], **Hilda Draeger**[3], **Brock E. Harper**[4], **Emilio Gonzalez**[4], **Terry McNearney**[4,5], **Marilyn Perry**[1], **Frank C. Arnett**[1], and **Maureen D. Mayes**[1]

[1] University of Texas Health Science Center at Houston

[2] University of Texas M.D. Anderson Cancer Center at San Antonio

[3] University of Texas Health Science Center at San Antonio

[4] University of Texas Medical Branch at Galveston

[5] Eli Lilly, Indianapolis

Systemic sclerodermia - inconsistent results

- Significant increase in frequency and severity of vascular and GIT symptoms
- Increase of dyspnoea, ↓ FEV1, FVC, Dlco
- ↑ severity of Raynaud , acid reflux

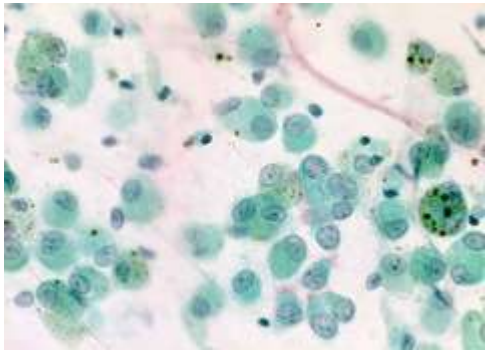
Hudson M, et al. Arthritis Rheum 2011; 63:230-8.

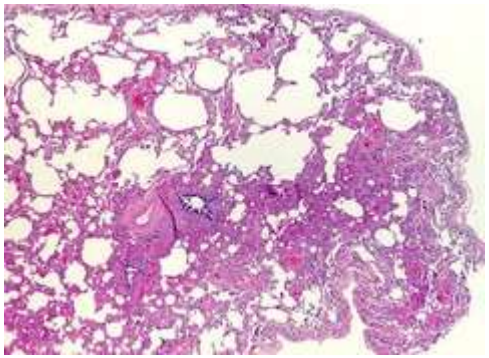
RB-ILD/DIP

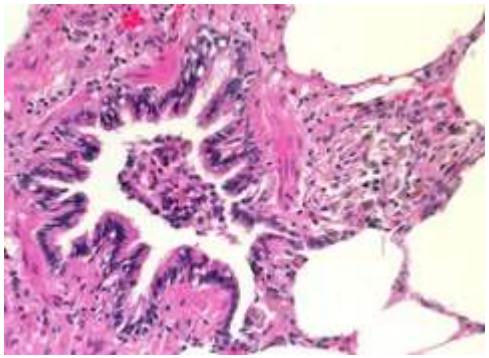
TABLE 2 All causes implicated in desquamative interstitial pneumonia (DIP), other than tobacco smoking

Causes	Ref.	Comments
Occupational exposure to inorganic particles	[1, 2 8–10]	Nature of particles: Si, Mg, Ti, Fe, Ni, Pb, Cr, Au, Ag, Al, K, Ti, BaS, Be, Cu Occupation: tool grinder, arc polisher, tyre manufacturing worker, plastic machinist, Al arc welder, worker exposed to fire-extinguisher powder, diesel fumes
Exposure to mycotoxins	[37–43]	Occupational exposure to aflatoxin (textile worker)
Connective tissue diseases	[44, 45]	
Rheumatoid arthritis	[46]	
Sirolimus	[47]	
Infection	[48–50]	DIP following concurrent CMV and *Aspergillus* pneumonias in a renal transplant recipient (who did not receive sirolimus) Association of DIP and HCV infection Association of DIP and CMV infection in a baby
Use of marijuana	[51]	

CMV: cytomegalovirus; HCV: hepatitis C virus.

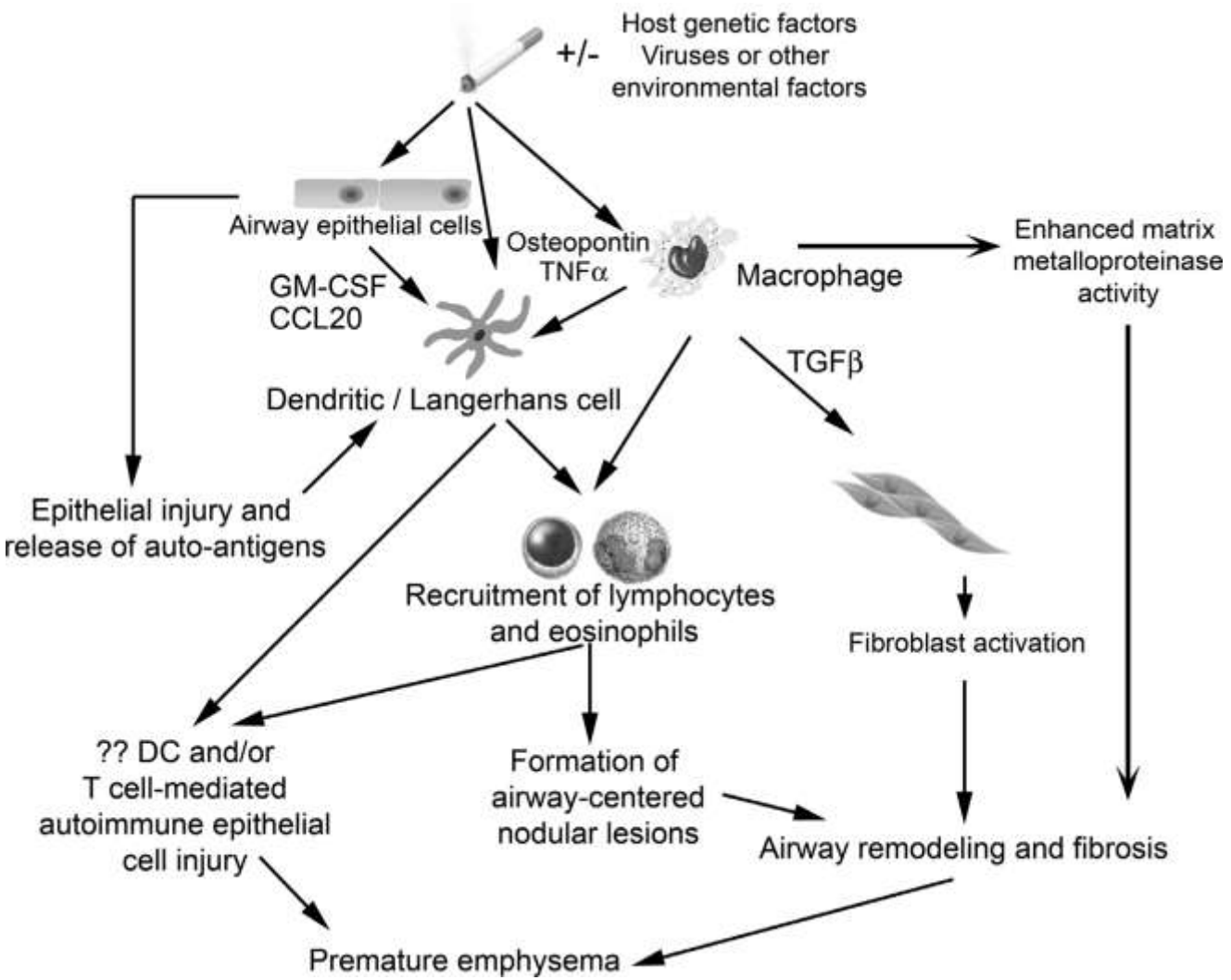






Godbert B, et al. Eur Respir Rev 2013; 22:117-23.

Pulmonary Langerhans cell histiocytosis



Suri SH, et al. Orphanet J Rare Dis 2012; 7:16.

Proteins differently expressed in PLCH and other patients

Table 5 Proteins differently expressed between smoker and no-smoker controls and between PLCH patients and controls.

No. of spot	Protein name	AC	Theoretical pI/Mr (KDa)	Experimental pI/Mr (KDa)	Mascot search result			Mean %V ± SD × 10⁻⁴			1-way ANOVA p value	Folds in			Localization
					No. of matched peptide	Sequence coverage (%)	Score	nsc	sc	PLCH		Nsc-sc	Nsc-PLCH	Sc-PLCH	
					PLCH < nsc and/or sc										
[illegible]	Polymeric immunoglobulin receptor	[illegible]	5.58 / 84.39	5.14 / 67.077	10	18	129	[illegible]	[illegible]	[illegible]	[illegible]	1.04	[illegible]	[illegible]	Cell membrane
[illegible]	Thioredoxin	P10599	4.82 / 11.615	4.67 / 12.066	6	40	63	[illegible]	[illegible]	[illegible]	0.005	[illegible]	2.89	[illegible]	Cytoplasm-Secreted
[illegible]	Plastin-3	P13796	5.2 / 70.81	5.19 / 6[illegible]	10	21	102	[illegible]	[illegible]	[illegible]	0.01	1.45	1.68	[illegible]	Cytoplasm-Cytoskeleton-Cell junction
[illegible]	Serum albumin	P02768	5.92 / 71.317	6.04 / 67.513	8	14	62	[illegible]	[illegible]	[illegible]	0.04	1.63	1.47	[illegible]	Plasma
[illegible]	Serum albumin, fragment Severe	P02768	5.92 / 71.317	6.09 / 31.058	6	9	74	[illegible]	[illegible]	[illegible]	0.049	1.45	2.24	[illegible]	Plasma
30	ADP-ribosylation factor-like protein 3	P36405	6.74 / 20.614	7.37 / 21.404	6	52	107	[illegible]	[illegible]	[illegible]	0.012	2.03	2.14	[illegible]	Membrane
31	Alpha-1B-glycoprotein	P04217	5.58 / 54.006	5.16 / 75.663	8	22	109	[illegible]	[illegible]	[illegible]	0.023	1.17	[illegible]	1.75	Plasma

This table is divided in two parts: the first part includes protein spots significantly down-regulated in no-smoker compared to smoker controls; the second part includes spots up-regulated in non-smoker than smoker controls.

-Oxidative stress, proteolysis, angiogenic factors
-Common pathways in IPF and PLCH

Landi C, et al. J Clin Bioinfoma 2011; 1:31.

MODERN PATHOLOGY (2012) 25, S68–S78

Smoking-related interstitial fibrosis (SRIF), pathogenesis and treatment of usual interstitial pneumonia (UIP), and transbronchial biopsy in UIP

Anna-Luise A Katzenstein

Department of Pathology, SUNY Upstate Medical University, Syracuse, NY, USA

This review focuses on three selected topics of current interest that are related to chronic fibrosing lung disorders and are important for pathologists. First, the clinical and pathologic features of smoking-related interstitial fibrosis (SRIF) are highlighted. SRIF is a common finding in smokers that has striking histologic changes but only mild associated clinical manifestations. It is characterized by marked alveolar septal fibrosis composed of a distinct form of hyalinized collagen deposition. The process is present mainly in subpleural and centrilobular parenchyma and is associated with emphysema and respiratory bronchiolitis. Second, important aspects of the pathogenesis and treatment of usual interstitial pneumonia (UIP) are reviewed. The current theory proposes that UIP is caused by tiny foci of acute lung injury (manifest pathologically by fibroblast foci) that occur and recur in the interstitium over many years. Inflammation may be present as a secondary phenomenon, but is not the primary cause, and therefore anti-inflammatory agents have little effect. The recurrent injury leads to permanent fibrosis, through a process that is considered to represent a form of abnormal wound healing. Multiple therapies have been attempted that are aimed largely at interrupting the fibrosing process, but none have been successful. The cause of the injury is unknown, but a role for aspiration due to gastroesophageal reflux is a popular current theory, and there is some evidence that anti-reflux therapy may be beneficial. Genetic predisposition has been implicated in the etiology of familial cases, and there is evidence that telomere shortening may be important in sporadic cases. Third, the use of transbronchial biopsy (TBB) in diagnosing UIP is reviewed. TBB can provide a surprising amount of information and is especially useful in certain situations, such as elderly or very sick patients in whom surgical lung biopsy carries increased morbidity and mortality.
Modern Pathology (2012) **25,** S68–S78; doi:10.1038/modpathol.2011.154

Keywords: interstitial fibrosis; pulmonary fibrosis; SRIF; TBB; transbronchial biopsy; UIP

Smoking related interstitial fibrosis

Table 2 Contrasting histologic features of SRIF, UIP, and fibrosing NSIP

SRIF	*UIP*	*Fibrosing NSIP*
Hyalinized, ropey, deeply eosinophilic collagen with no to minimal inflammation	Light staining collagen with minimal inflammation	Light staining collagen with admixed inflammation
Mainly subpleural, centrilobular	Random distribution	Relatively diffuse
Relatively uniform involvement	Heterogeneous, patchwork distribution[a]	Relatively uniform involvement
Emphysema, often severe	Emphysema usually absent	Emphysema usually absent
Respiratory bronchiolitis present	+/− Respiratory bronchiolitis	+/− Respiratory bronchiolitis
No/minimal honey-comb change	Honey-comb change present	No/minimal honey-comb change
No/rare fibroblast foci	Fibroblast foci present	No/rare fibroblast foci

[a]Patchwork distribution is defined as the apposition of abnormal areas and normal lung areas in a random pattern without any gradation or areas of transition between them. SRIF and NSIP lack this heterogeneous appearance, but they may be patchy. The difference is that SRIF and NSIP areas blend into the normal areas rather than being sharply demarcated without transition.

Katzenstein AL. Mod Pathol 2012; 25: S68-78.

Eur Respir J 2005; 26: 586–593
DOI: 10.1183/09031936.05.00021005

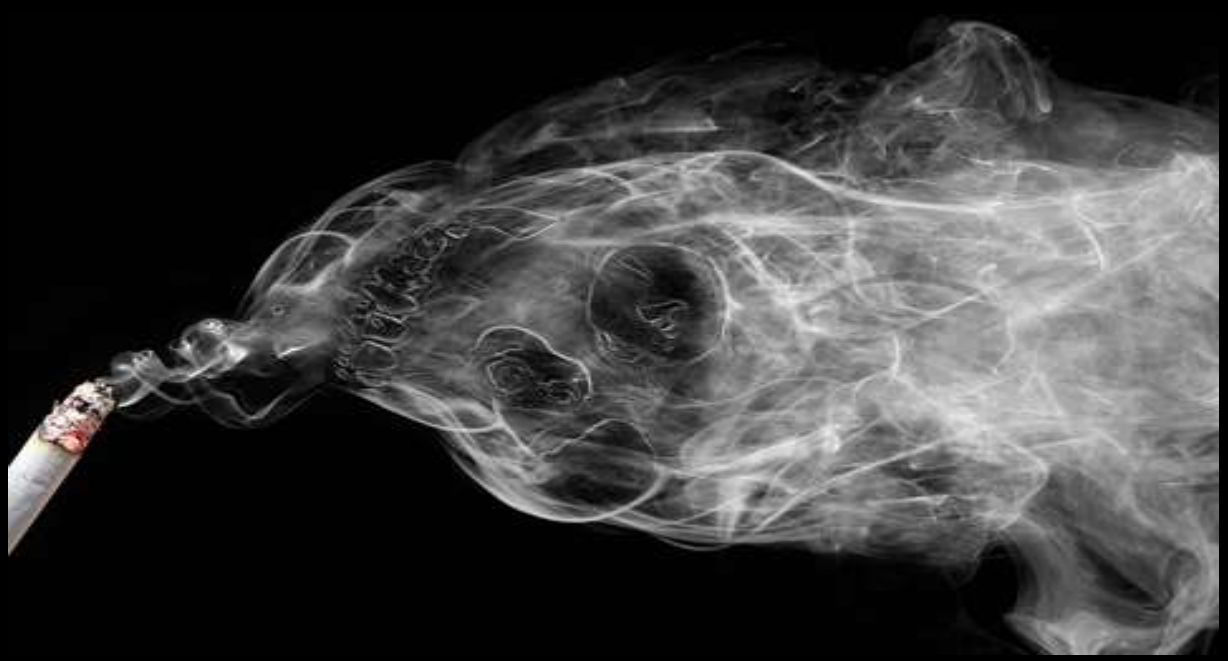
CLINICAL FORUM

Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity

V. Cottin*, H. Nunes[#], P-Y. Brillet[¶], P. Delaval[+], G. Devouassoux[§], I. Tillie-Leblond[ƒ], D. Israel-Biet, I. Court-Fortune[##], D. Valeyre[#], J-F. Cordier* and the Groupe d'Etude et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)**

-Older, male, current or ex-smokers
-Honeycombing, reticulation, traction bronchiectasias, paraseptal emphysema
-PAH in 44%

Conclusions



-IPF
-CPFE
-CTD-ILD

-RB-ILD
-DIP
-PLCH
-AEP
-SRIF


Interstitial Lung Diseases