Pathogénie de la Fibrose Pulmonaire Idiopathique

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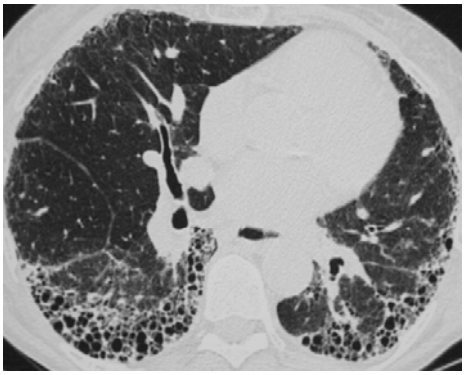
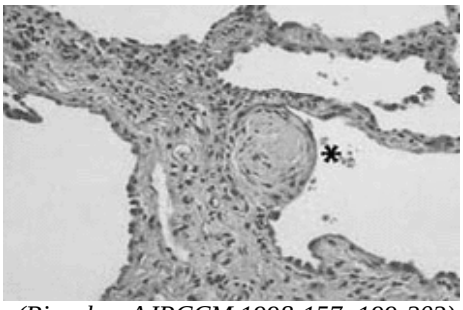
Paris, France

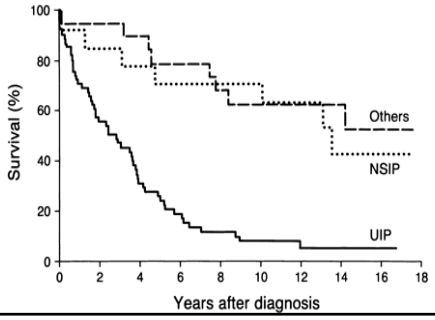
Fibrose Pulmonaire idiopathique

- Incidence: 5-10/100 000
- Grave
- Définition plus restrictive depuis 2000

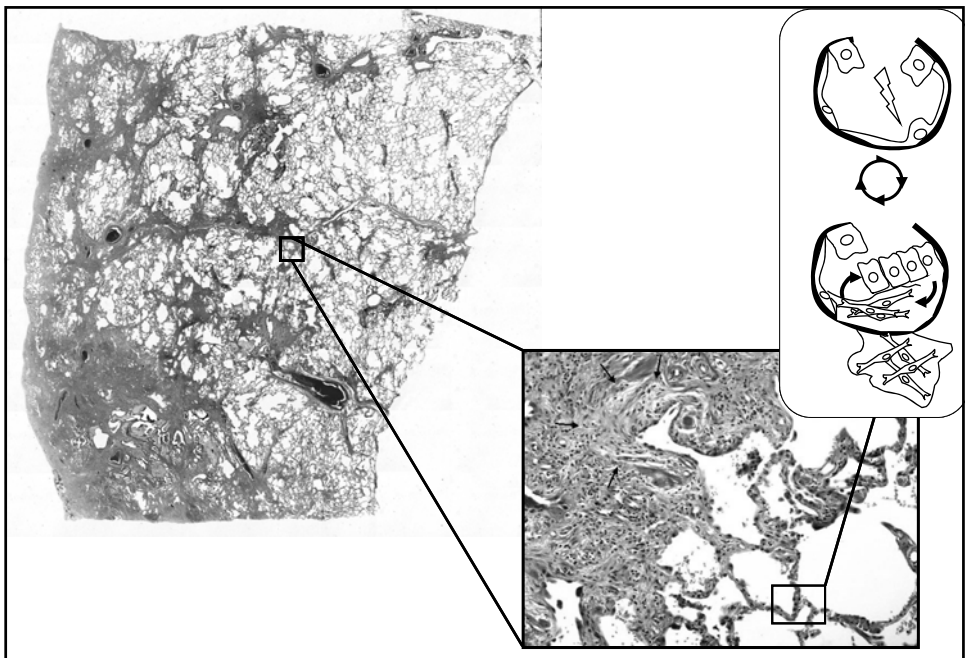
→ Pneumopathie interstitielle commune *(UIP)*



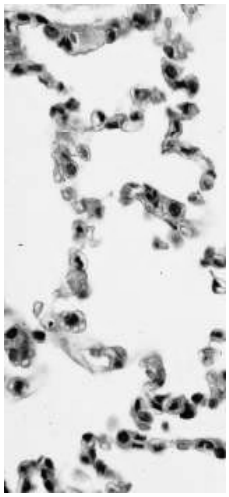




(Bjoraker, AJRCCM 1998;157: 199-203)



(Dr Claire Danel, Pathology Lab, Bichat Hospital)



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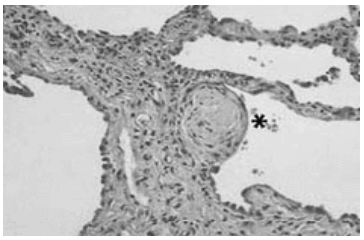
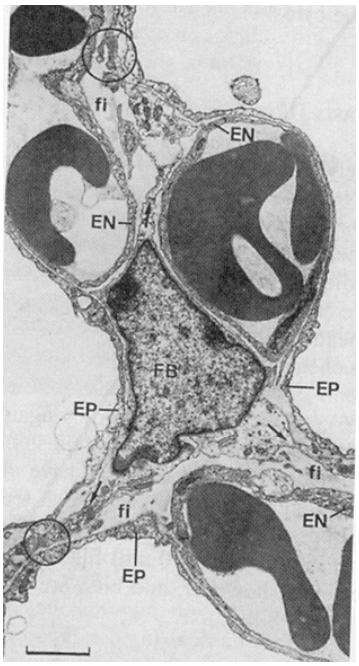
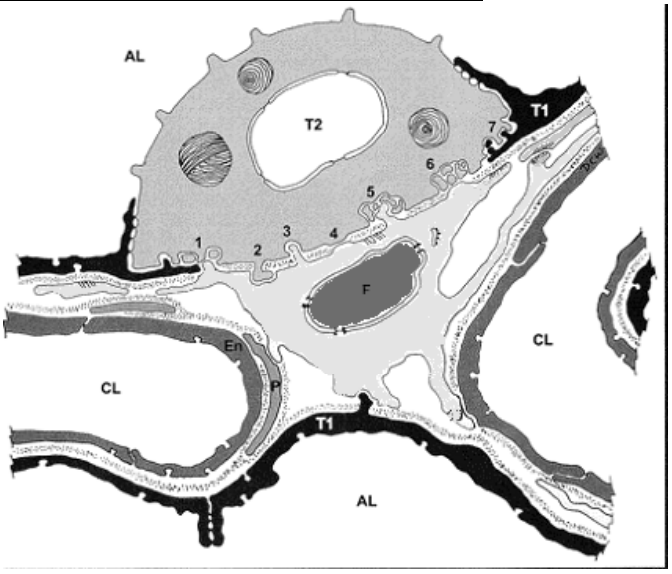




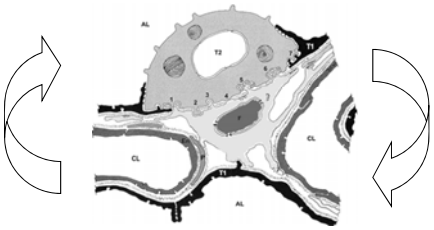
Weibel, E., and R. Crystal. 1997.
In The Lung. Lippincott Raven, Philadelphia. 685-695

Interactions P2 - Fibroblastes

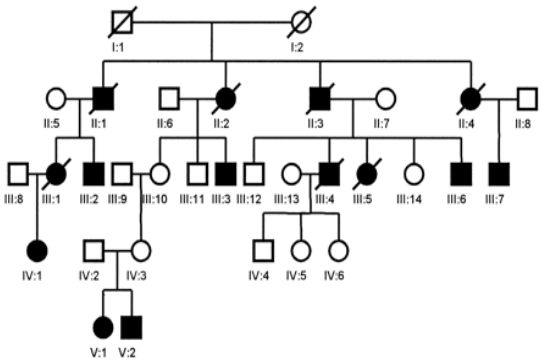


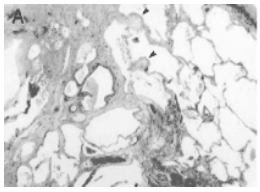
(Sirianni, AJRCCM 2003;168:1532-1537)

Les leçons des formes familiales de fibrose

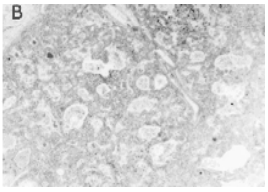


- Mutations apoprotéines du surfactant
  - SFTPC
  - *SFTPA2, ABCA3*
- Télomérase
  - TERT, TERC, Dyskerin
  - *Tsakiri, PNAS 2007; Armanios, NEJM 2007*





UIP



NSIP-C

Exon 5+128 SP-C
Mutation T→A

↓

Mutation L188Q proSP-C
(région C terminale)

↓

Accumulation de SP-C
Cytotoxique in vitro

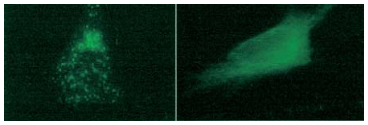
↓

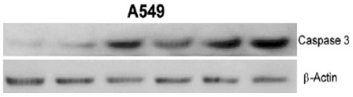
Fibrose
(ht°z)

(Thomas, AJRCCM 2002;165:1322-8)

Effet in vitro de mutations SFTPC

Transfection de SP-C muté (A549)





- Accumulation dans le RE
  →stress du RE
  →réponse UPR
  (*unfolded protein response*)
  →Activation voies apoptose

Mutation SFTPC
↓
Apoptose pneumocyte

Mulugeta, AJRCMB 2005

FPI sporadique

Anomalies épithéliales alvéolaires

- **Apoptose des cellules épithéliales alvéolaires**
  - **dans les zones « saines »**
  - **à proximité des foyers fibroblastiques**

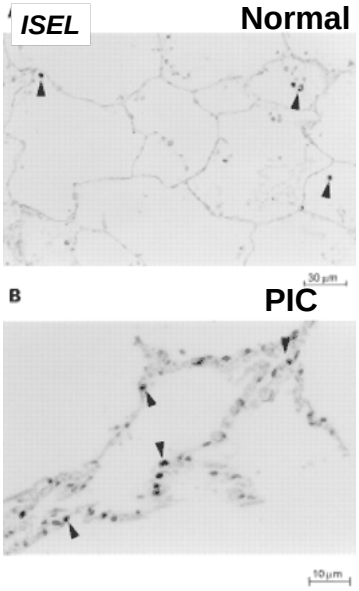
    Uhal Am J Physiol 1998;
    Barbas-Filho, J Clin Pathol 2001

- **↗↗ Expression Fas et FasL ↑**

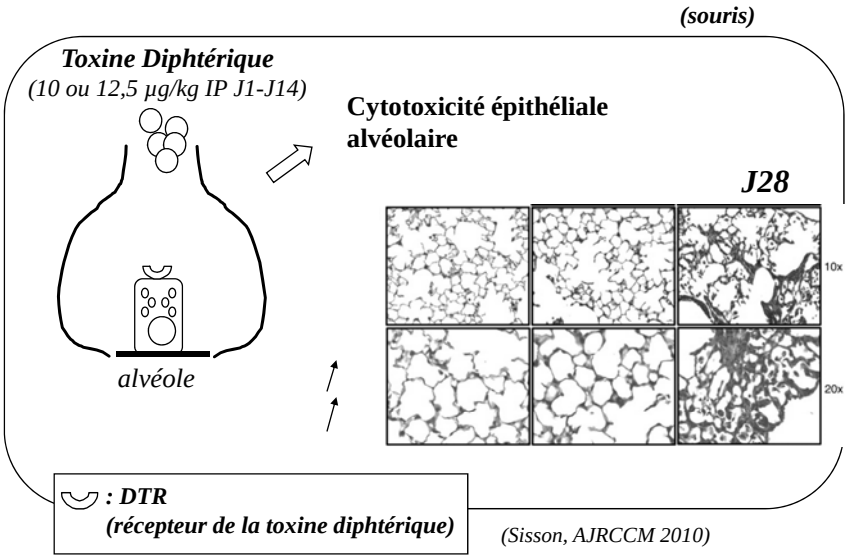
  Kuwano, AJRCMB 1999;20:53

- **Stress du tériculum endoplasmique**

  Korfei, AJRCCM 2008



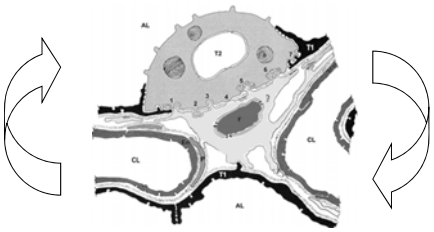
(Barbas-Filho, J Clin Pathol 2001;54:132-8)



(Sisson, AJRCCM 2010)

Souris SPC-DTR

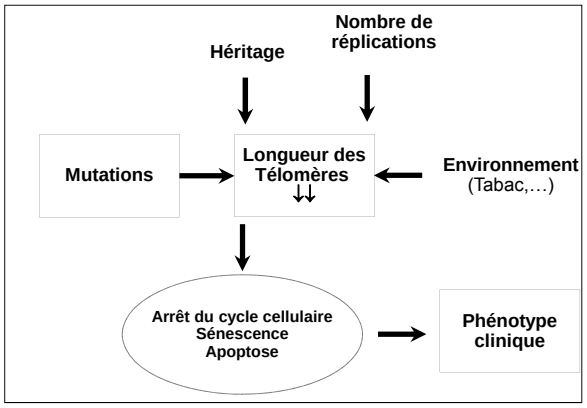
Les leçons des formes familiales de fibrose



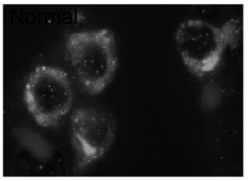
- Mutations apoprotéines du surfactant
  - SFTPC
  - *SFTPA2, ABCA3*
- Télomérase
  - TERT, TERC, Dyskerin
  - *Tsakiri, PNAS 2007; Armanios, NEJM 2007*

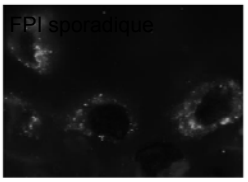
Télomères courts:
- 40% des FPI familiales
- 25% des FPI sporadiques

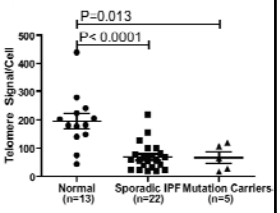
Cronkhite, AJRCCM 2008



Télomères P2





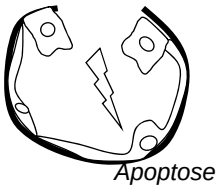


Alder, PNAS 2008

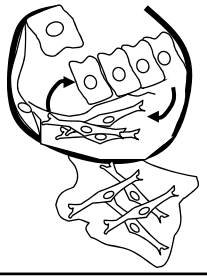
La FPI est une épithéliopathie alvéolaire

L'hypothèse de Moises Selman

(Ann Intern Med 2001)



Apoptose



Stimulus ⇦

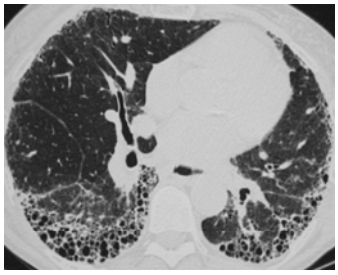
Tabac,
Polluants de l'air,
Anomalies des protéines du surfactant
Virus,
micro-inhalations sur RGO
Autres…?

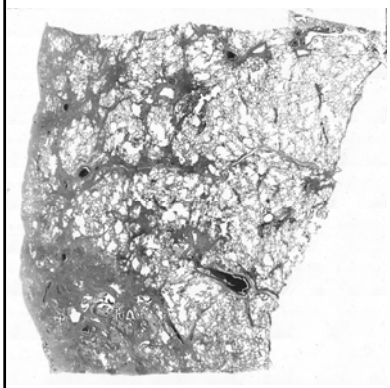
Lésions épithéliales alvéolaires répétées

Réparation aberrante

INFLAMMATION ?

Fibrose

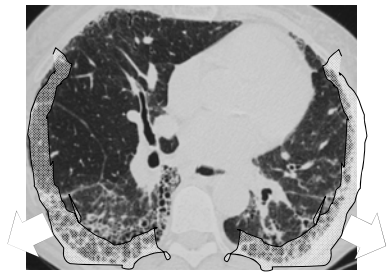


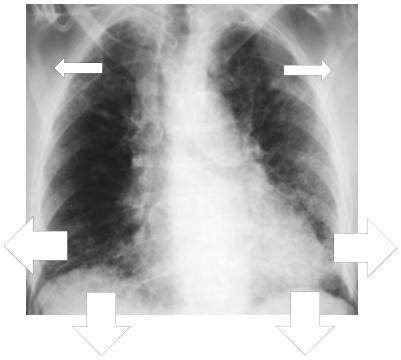


Prédominance spatiale :
- Lobes inferieurs
- Régions sous-pleurales
- Périphérie du lobule

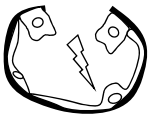
Hypothèses ?
- RGO (Tcherakian, Thorax 2010)
- Contraintes mécaniques
- Rôle de la plèvre
- Sources de fibroblastes

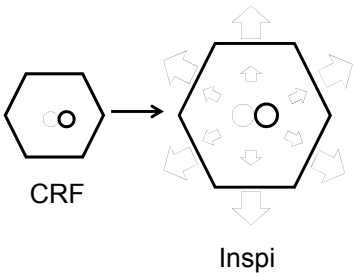
(Dr Claire Danel, anatomie pathologique, Hôpital Bichat)





Contraintes mécaniques ?



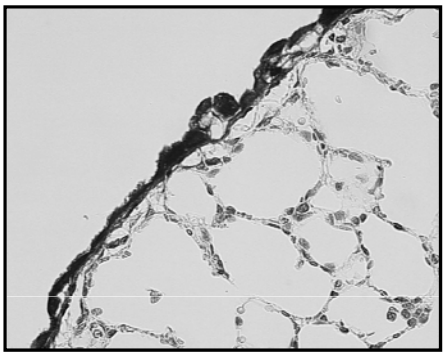


(Dr Claire Danel, anatomie pathologique, Hôpital Bichat)

Implication des cellules mésothéliales ?

AdLacZ + AdDL

J6

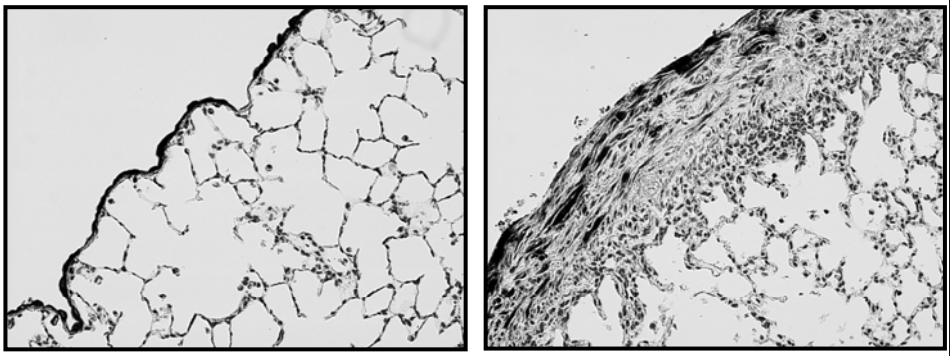


AdLacZ + AdTGF-β1

J2

(Decologne, J Immunol 2007)

Implication des cellules mésothéliales ?



AdLacZ + AdDL **AdLacZ + AdTGF-β1**

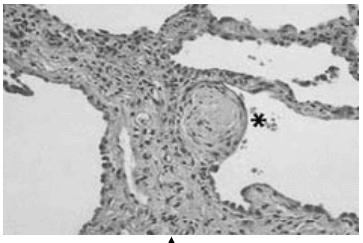
J6 **J6**

(Decologne, J Immunol 2007)

Origine des fibroblastes

Amplification du pool local

Transition épithelio-mesenchymateuse



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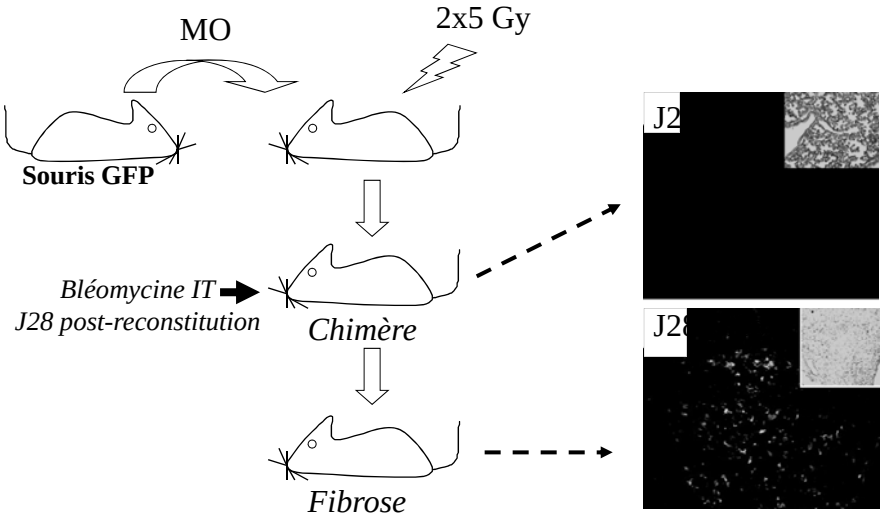
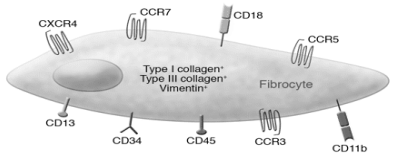
Recrutement de précurseurs circulants

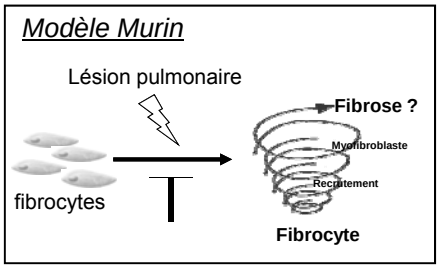
Origine des fibroblastes ?

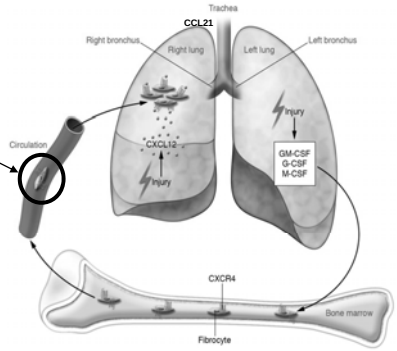


(Hashimoto, J Clin Invest 2004;113:243-252)

Fibrocytes

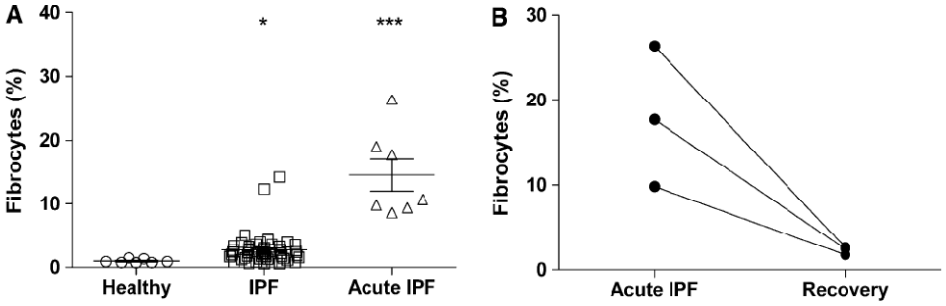






(Strieter, J Clin Invest 2007)

Fibrocytes circulants



(Moeller, AJRCCM 2009)

Le modèle classique est-il mort ?

Stimulus

~~**Inflammation chronique**~~

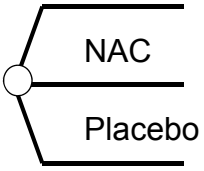
Corticoïdes
I°suppresseurs

Fibrose

PANTHER trial
IPF Network NIH

- Patients avec FPI peu évoluée
  (CVF > 50%;DLCO > 30%; Dc <4 ans)

Pred + AZA + NAC



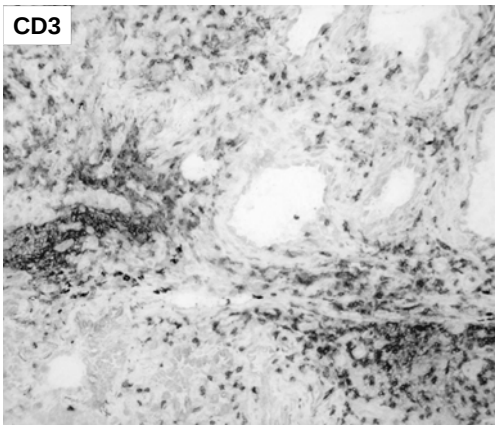
N=390
60 sem

Etude PANTHER
(Communiqué de presse NIH)

	Pred/Aza/NAC	Placebo
Mortalité	11%	1%
Hospitalisations	29%	8%
Effets indésirables graves	31%	9%

Pas de différence dans la fonction pulmonaire

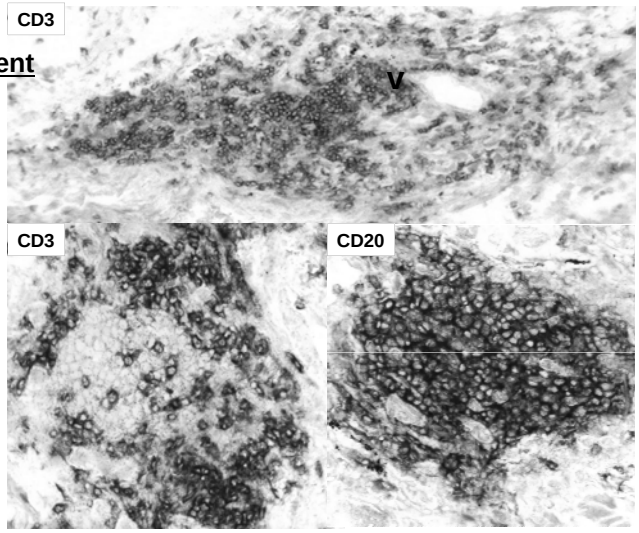
Infiltration diffuse par des cellules immunes



Marchal-Somme J, *J Immunol*, 2006

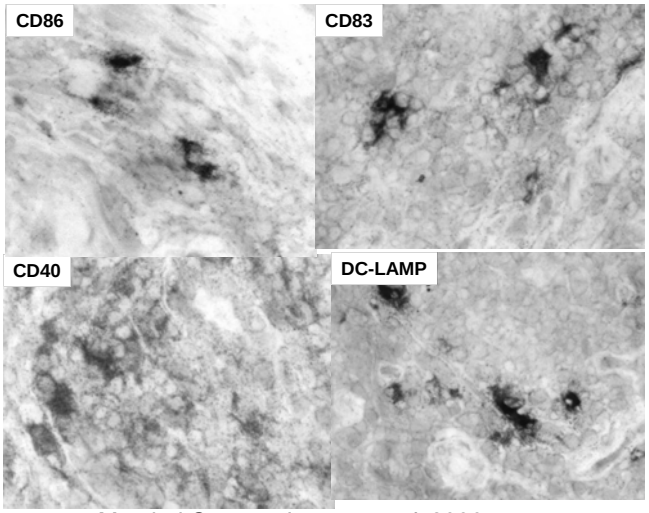
Agrégats lymphoïdes

<u>Principalement</u>
CD4+
CD45Ro+
CD28+



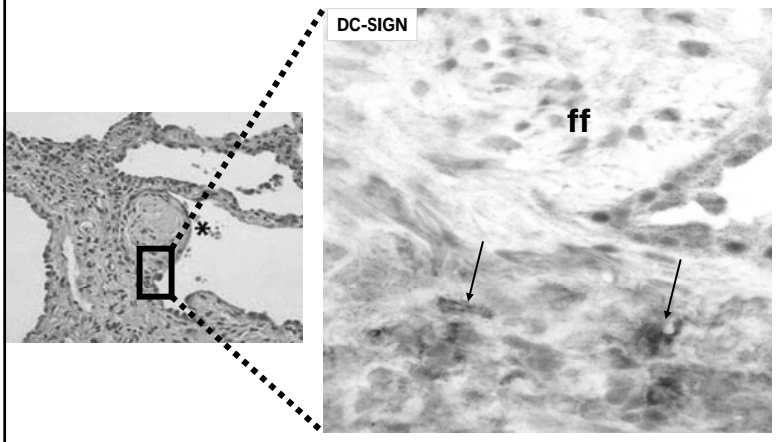
Marchal-Somme J, *J Immunol*, 2006

Les agrégats lymphoïdes sont infiltrés par des CDs matures



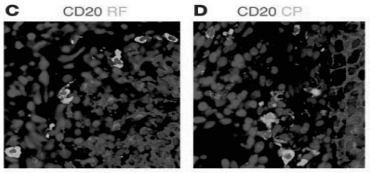
Marchal-Somme J, *J Immunol*, 2006

Les CDs sont absentes des foyers fibroblastiques



(J.Marchal-Somme, *AJRCCM* 2007)

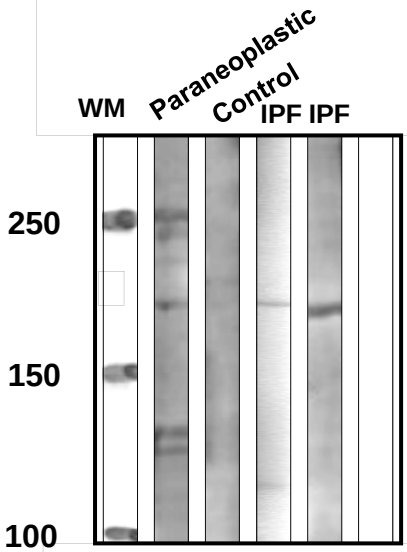
Lymphoïdogénèse
Rôle dans la PR
(Rangel-Moreno, J Clin Invest 2006)



IgG biotinylée Fibrinogène citrulliné

Un rôle physiopathologique
dans la FPI ?

Immunoblot *(extraits placentaires)*

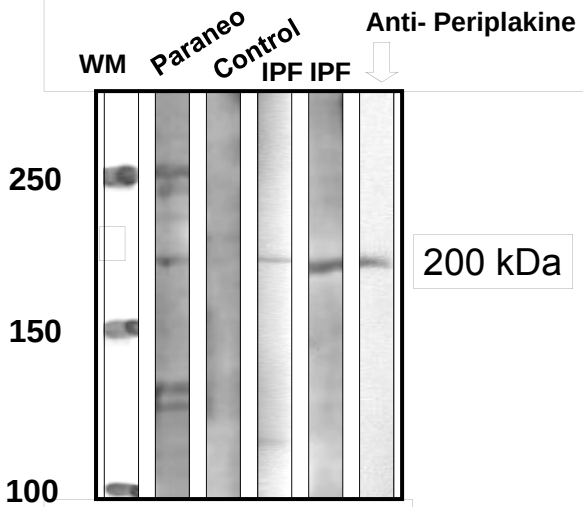


200 kDa

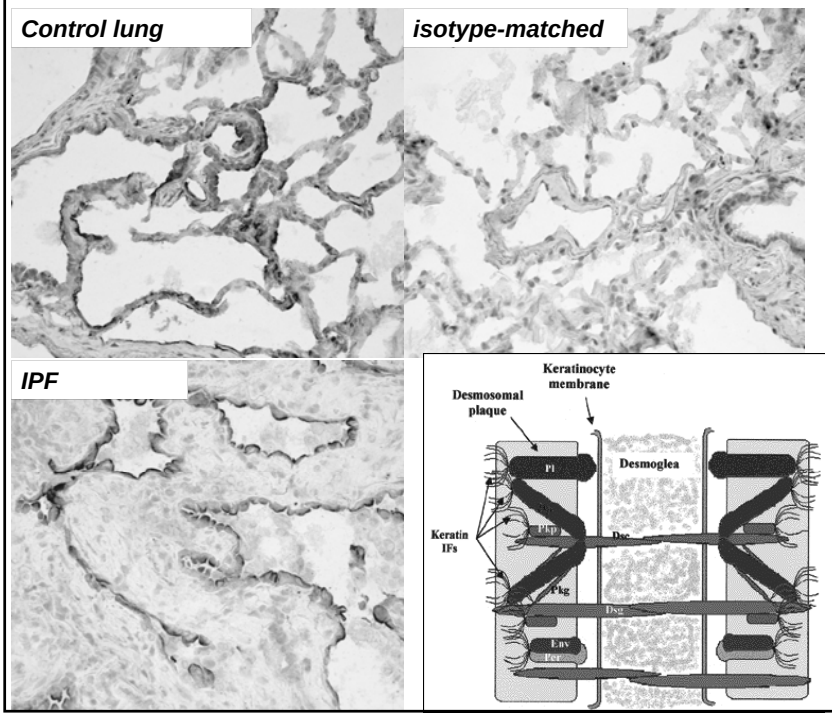
Analyse protéomique
(MALDI-TOF)

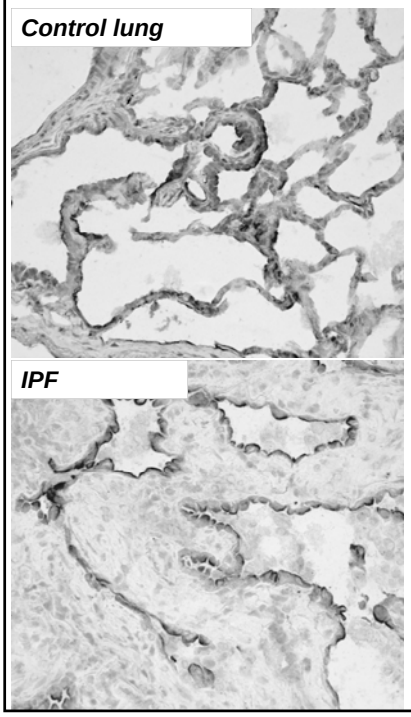
Periplakine

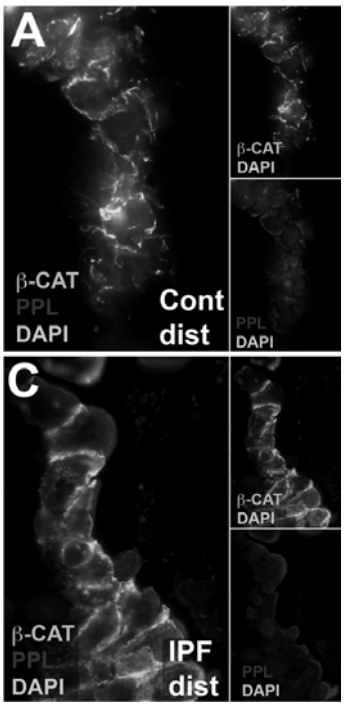
Immunoblot *(extraits placentaires)*



(Taille et al, AJRCCM 2011)







Détection des Ac circulants anti-périplakine

	Ac (+) *n*	Ac (-) *n*	%
FPI *(n=40)*	**16**	**24**	***40%***
CT-PF *(n=10)*	**1**	**9**	
BPCO *(n=10)*	**0**	**10**	
Témoins *(n=40)*	**0**	**40**	

(Taille et al, AJRCCM 2011)

Données cliniques

	IPF patients		
	Ab (+) ***(n=16)***	**Ab (–)** ***(n=24)***	p
Age	72 ± 2	70 ± 2	NS
Gender (% male)	81%	75%	NS
Smokers or ex smokers	81%	70%	NS
Pack/year	27 ± 6	26 ± 5	NS

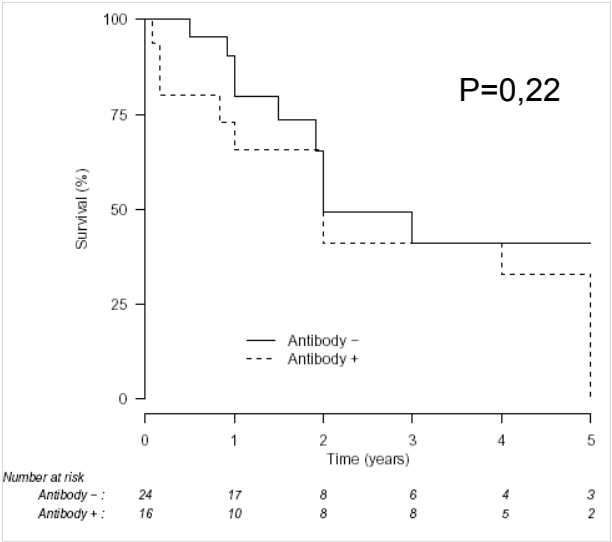
(Taille et al, AJRCCM 2011)

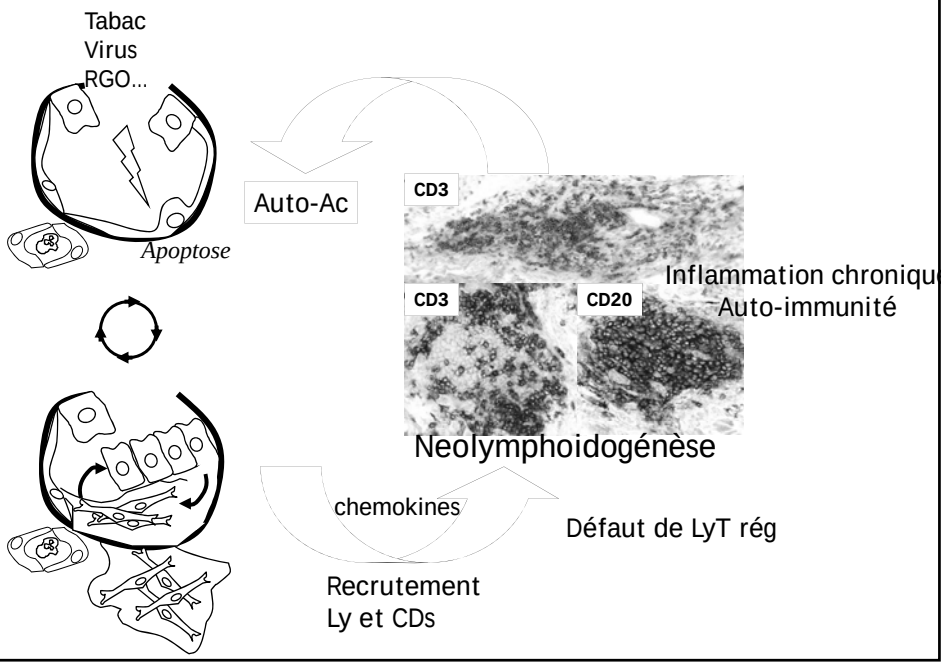
Les Ac anti-périplakine sont associés à une maladie plus sévère

	Ab (+) ***(n=16)***	**Ab (-)** ***(n=24)***	**p**
CPT *[% pred]*	56 ± 3	68 ± 3	***0.008***
CVF *[% pred]*	66 ± 3	79 ± 5	***0.02***
DLCO *[% pred]*	32 ± 3	47 ± 5	***0.03***
PaO_2 *[mmHg]*	62 ± 4	73 ± 2	***0.05***

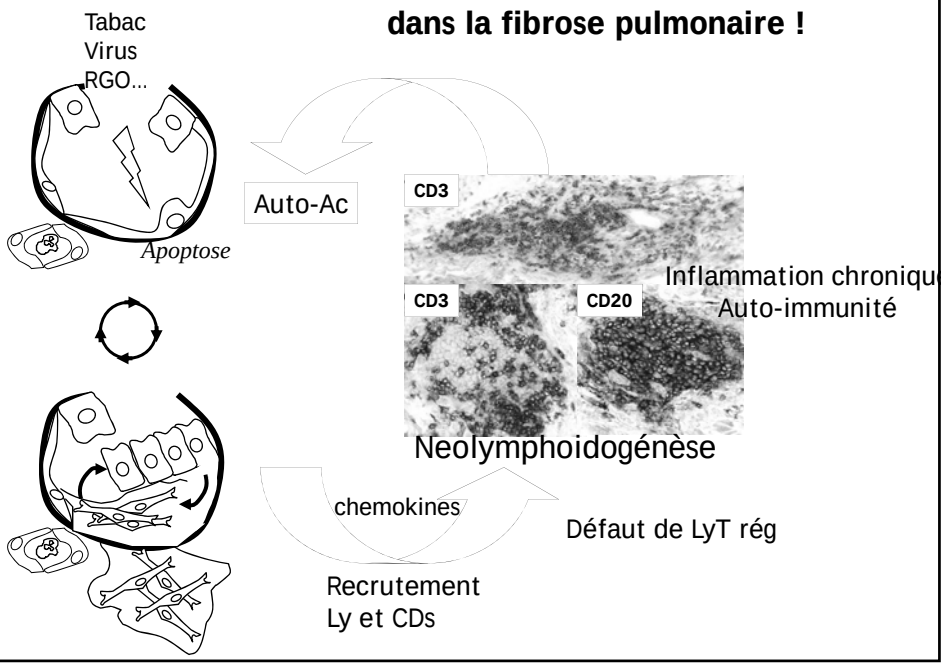
⇨ Étude prospective N=150 (CIRC APHP, Cohorte COFI)

Pas de lien avec la survie

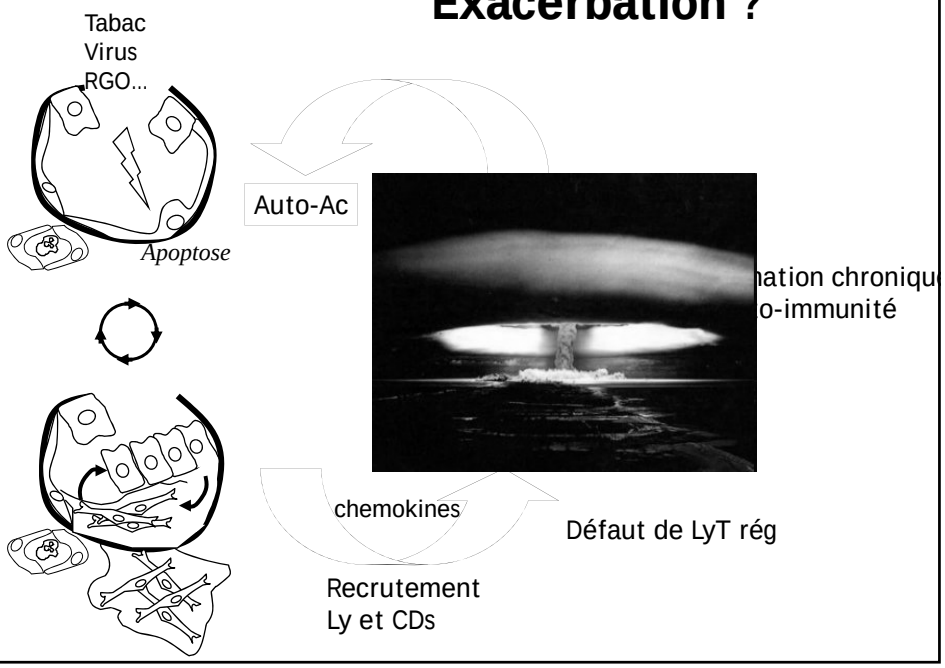




Il y a encore une place pour l'inflammation dans la fibrose pulmonaire !



Exacerbation ?



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