Sclérodermie systémique: physiopahtologie

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Systemic Sclerosis (SSc): a tripartite disease

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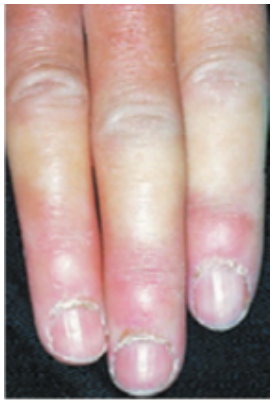
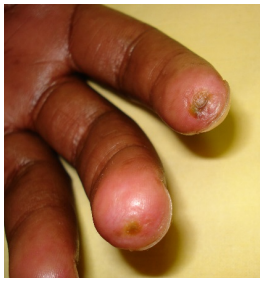
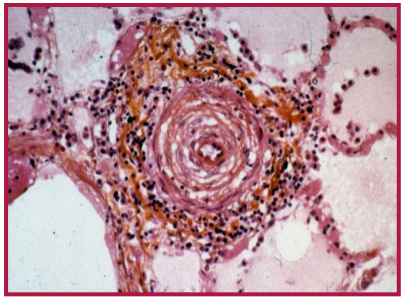
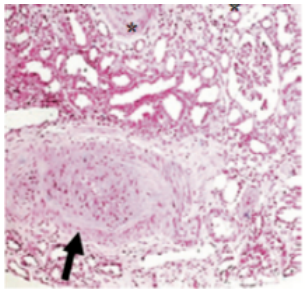
Vascular hyperreactivity









Courtesy or Prof. L. Mouthon;
Gabrielli *et al., NEJM* 2009;
Denton *et al., Lancet* 2017

Systemic Sclerosis (SSc): a tripartite disease

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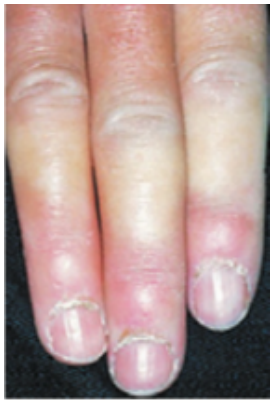
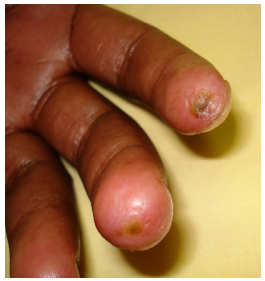
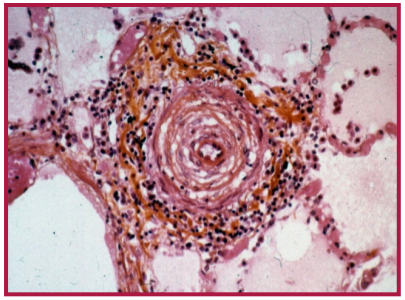
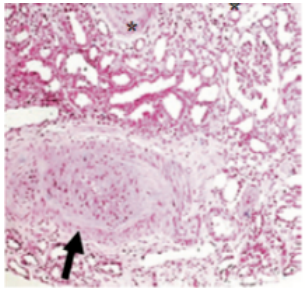
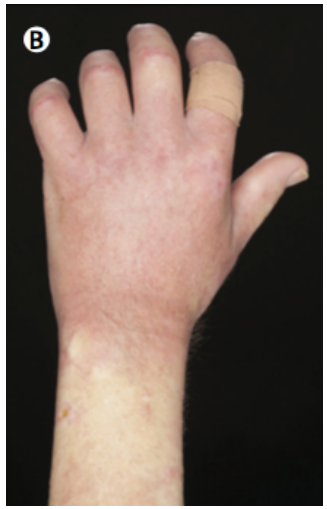
Fibrosis

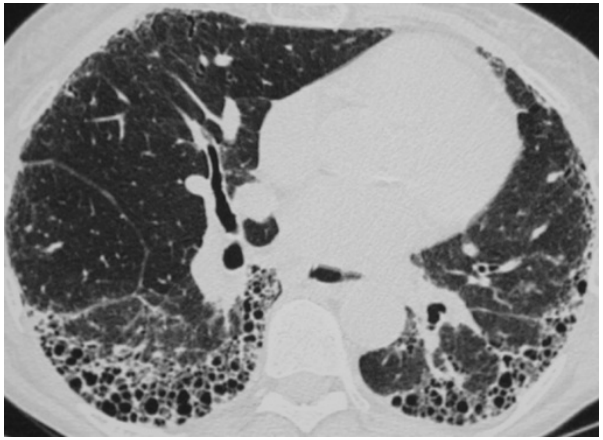












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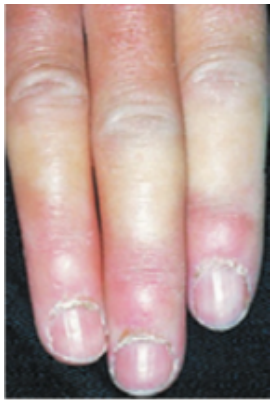

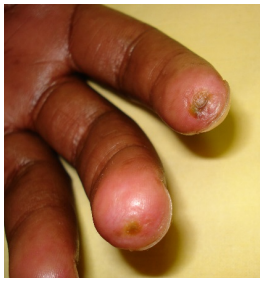

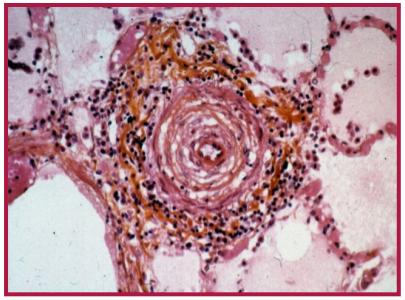

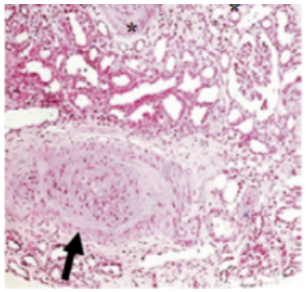

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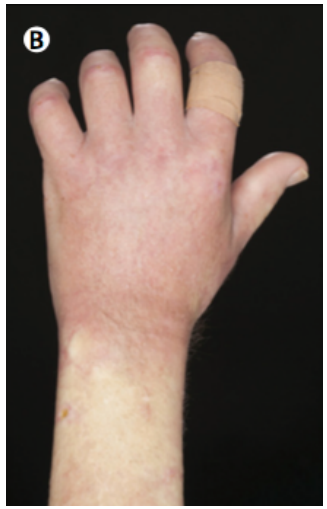
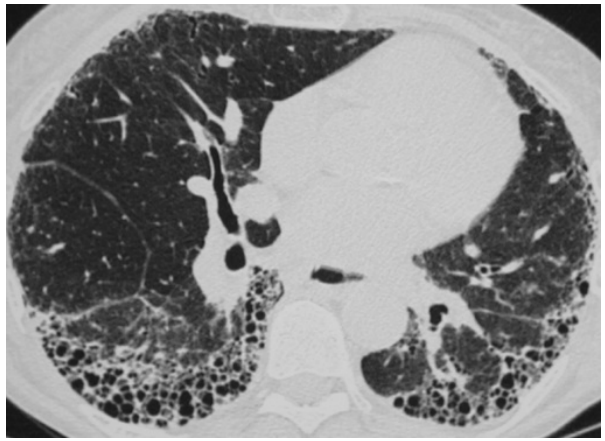
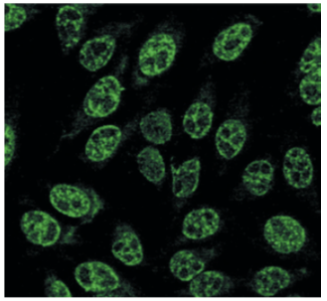
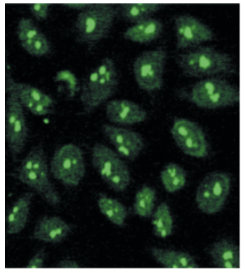
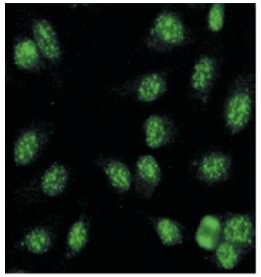


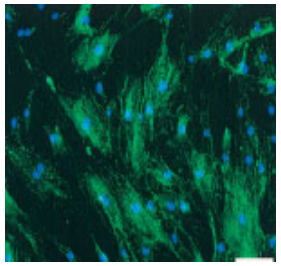


Autoimmunity









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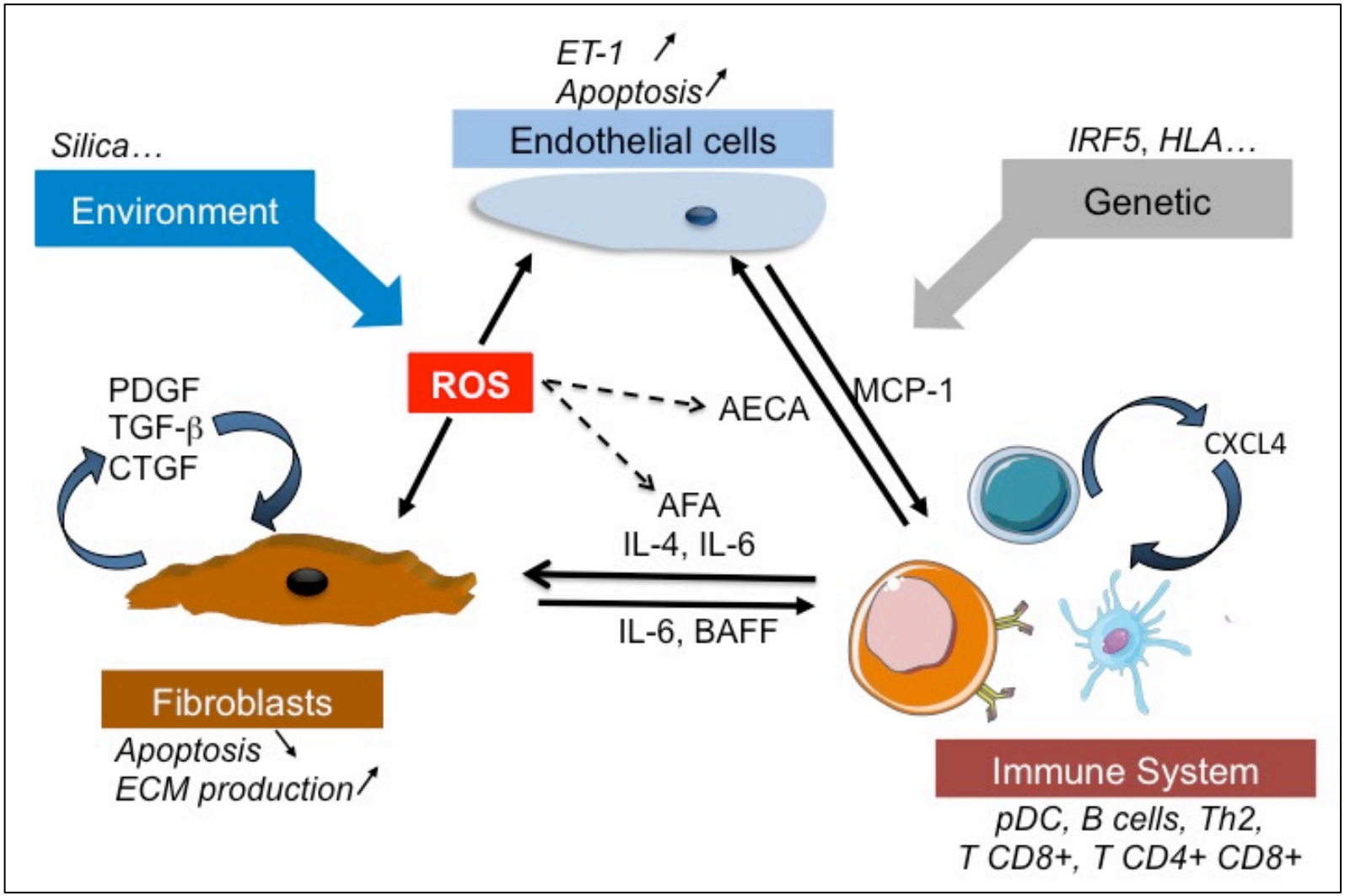
Denton *et al., Lancet* 2017

No perfect mouse model !

		Experimental model	Vasculopathy	Fibrosis	Inflammation	Autoantibodies	Limits/specificities
Genetic models	Spontaneous	Tsk-1 [46]					Unclear various organs defects
		Tsk-2 [52]					Unclear various organs defects
		UCD-200 UCD-206 [54]					Chicken model with poor background
		TβRIIΔk and TBRI^{CA} [56, 57]					Absence of autoimmunity
	Genetic modification	Caveolin 1$^{-/-}$ [61]					Not well characterized
		Fra-2$^{-/-}$ [61]					Not well characterized
		Fli1$^{\Delta CAT/\Delta CTA}$ [58]					Not well characterized/ absence of autoimmunity
		Fli1 endothelial cell KO [58]					Not well characterized/ absence of autoimmunity
Inducible models		Bleomycin induced model [65]					Overestimation of drug effects
		ROS-induced model [62]					TGF-β independent model
		Topo I/CFA's adjuvant induced SSc [61]					Unclear function of anti-topoisomerase I antibody
		Angiotensin II induced SSc [61]					Poor links with human SSc
		Sclerodermatous GVHD [61]					Not well characterized

Dumoitier *et al.*, *Presse Médicale* 2014

Systemic Sclerosis (SSc): pathophysiology



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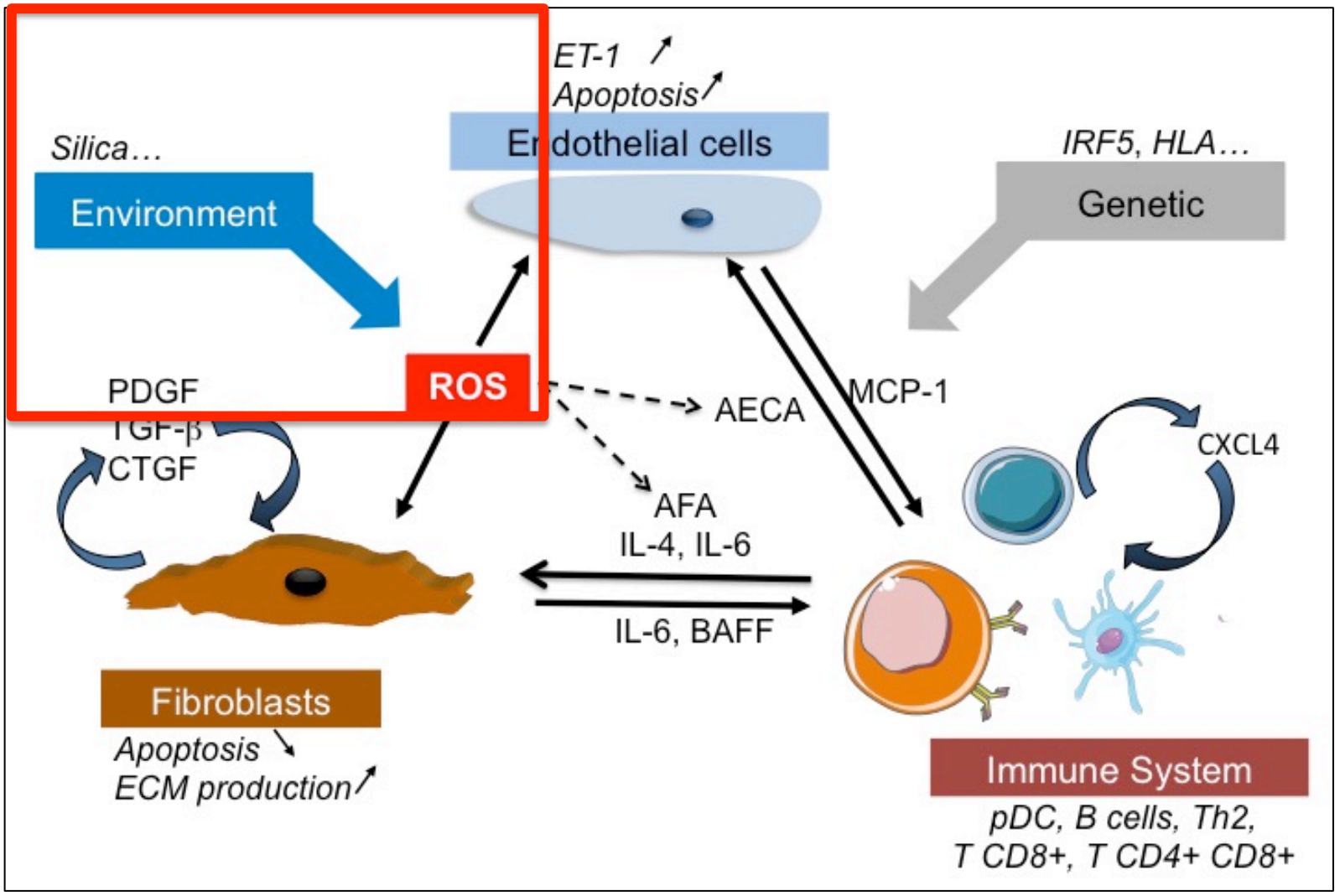


Dumoitier *et al.*, *Presse Médicale* 2014

Systemic Sclerosis (SSc): environnement

- Agents chimiques :
  - Silice => OR: 2,81 (cas-témoins) – OR: 17,5 (cohorte)
  - Solvant s=> OR: 2,00 (cas-témoins)
  - Implants mammaires siliconés => OR 1,68 (cas-témoins) 2,13^{ns} (cohorte)
  - Résines époxy => OR 2,97(cas-témoins)
  - Pesticides - soudures – tabac => NON

Rubio-Rivas *et al.*, *Clin Rheum* 2017

  - Quels solvants ?
    - Solvants aromatiques OR: 2,72
    - Trichloréthylène OR: 2,07
    - Solvants halogénés OR: 1,49
    - Kétones OR: 4,20

Zhao *et al., JCRPRRM 2016*

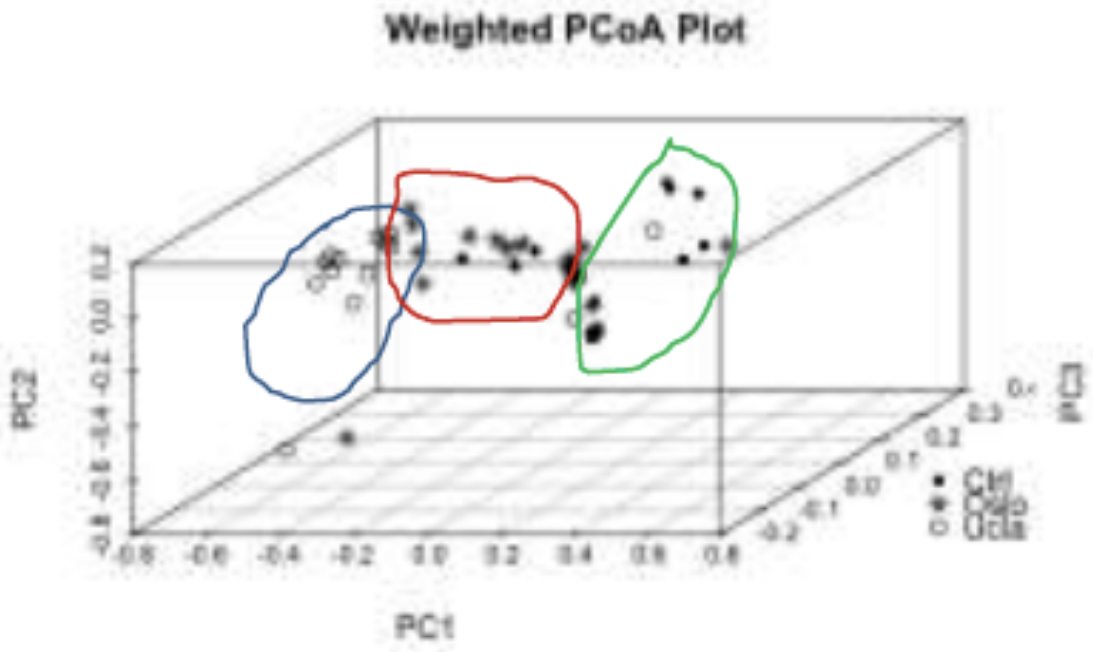
- Agents infectieux:
  - Quelques associations avec la présence d'ADN viral CMV / PVB19

Ferri *et al., Clin Exp Rheum 1999;*
Lunardi et al., Nat Med 2000

2015 – **Systemic sclerosis disease state is associated with specific alterations in gastrointestinal microbiotal in two independent cohorts**
Elizabeth Volkmann et al.

- 2 cohortes de 17 patients sclérodermiques (UCLA et Oslo) comparées à une cohorte de sujets sains (HC)

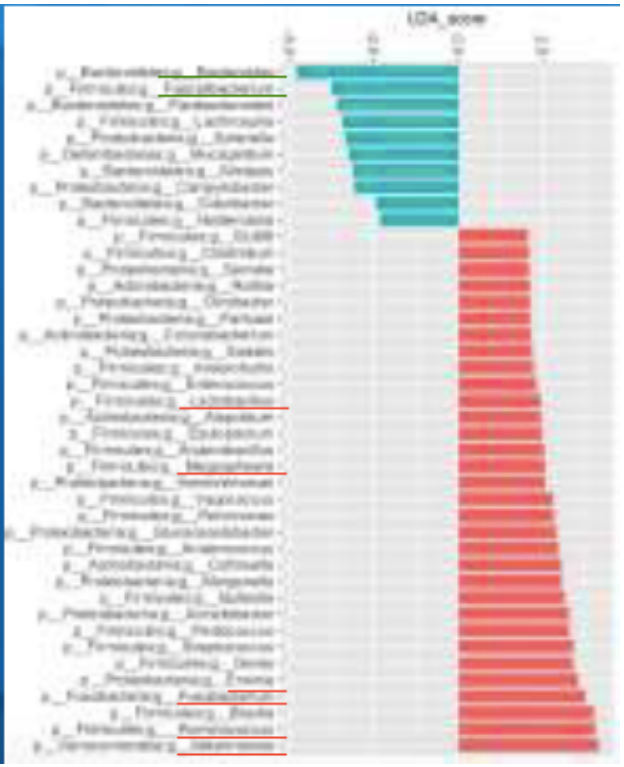
HC vs OSLO
R2= 0.126
P=0.002



HC vs UCLA
R2= 0.355
P=0.001

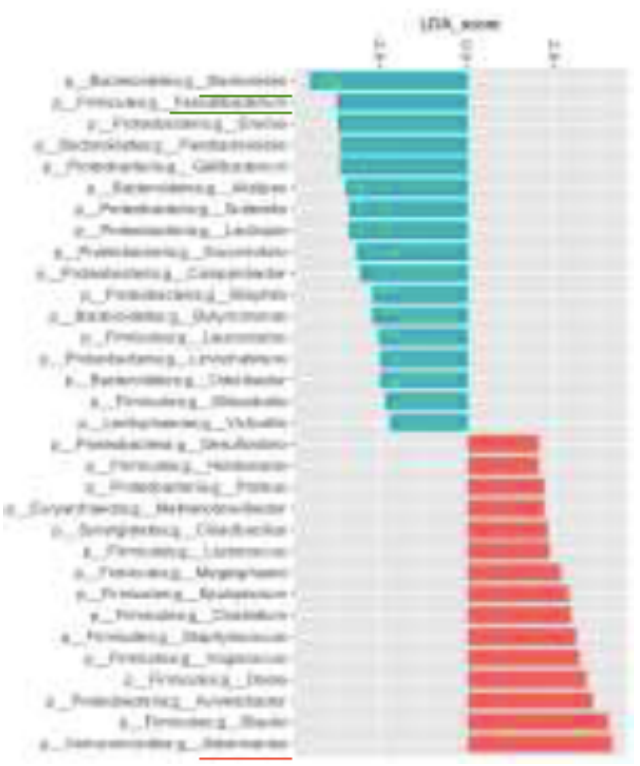
2015 – **Systemic sclerosis disease state is associated with specific alterations in gastrointestinal microbiotal in two independent cohorts**
Elizabeth Volkmann et al.

UCLA vs HC



OSLOvs HC

UCLA vs OLSO

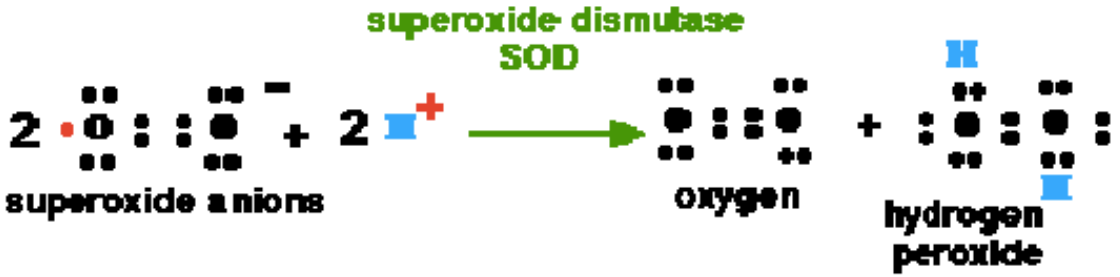


2015 – **Systemic sclerosis disease state is associated with specific alterations in gastrointestinal microbiotal in two independent cohorts**
Elizabeth Volkmann et al.

- **Eléments du microbiote associés à ScS:**
  - Augmentés
    - *Fusobacterium* (UCLA)
    - *Akkermansia* (UCLA)
    - *Ruminococcus* (UCLA)
    - *Lactobacillus* (UCLA Oslo)
  - Diminués
    - *Bacteroides* (UCLA Oslo)
    - *Faecalibacterium* (UCLA)

Stress Oxydatif

NADPH oxidase
myeloperoxidase



Arguments directs:

synthèse d'O2 •– par les monocytes et des fibroblastes de sujets atteints de ScS *(SAMBO, J Invest Dermatol. 1999)*

Prolifération des fibroblastes et production de collagène dépendante de FRO dans la ScS
(SAMBO, Arthritis Rheum, 2001)

Arguments indirects:

Phénomènes d'ischémie –reperfusion: production d'anions superoxydes (O2 •–) (HERRICK, Clin Exp Rheumatol. 2001)

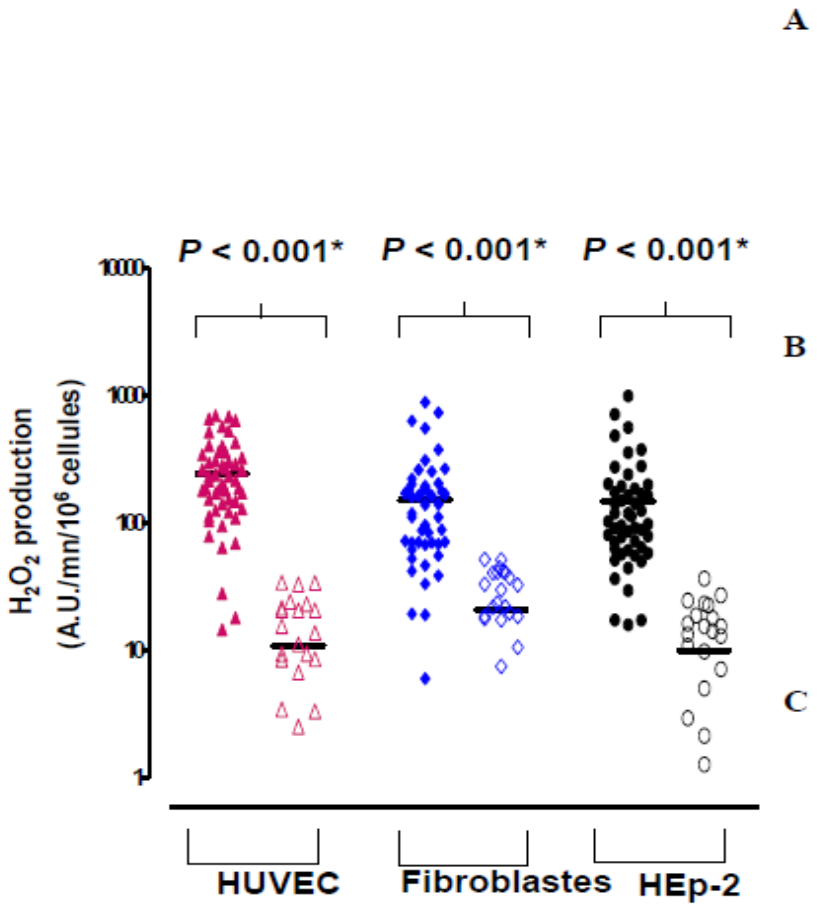
Toxicité de la silice et de la bléomycine médiée par le stress oxydatif (FUBINI, Free Radic Biol Med. 2003)

protéines oxydées sériques (carbonyls et advanced oxidation protein products, AOPP)(ALLANORE, Am J Med. 2004)

marqueurs de peroxydation lipidique dans le sérum

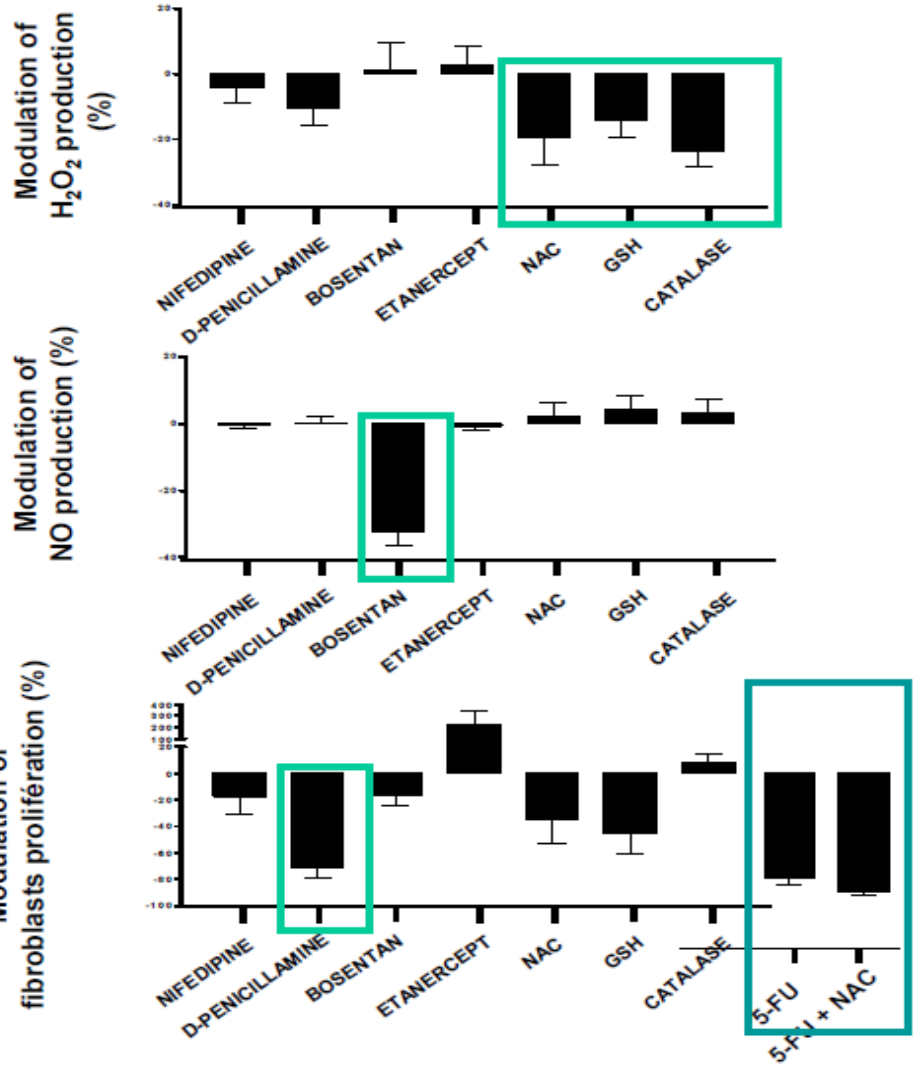
Stress Oxydatif

Generation of H2O2 in the presence of SSc serum



Servettaz A et al, Ann Rheum Dis 2007

Effect of drugs and anti-oxydizing molecules



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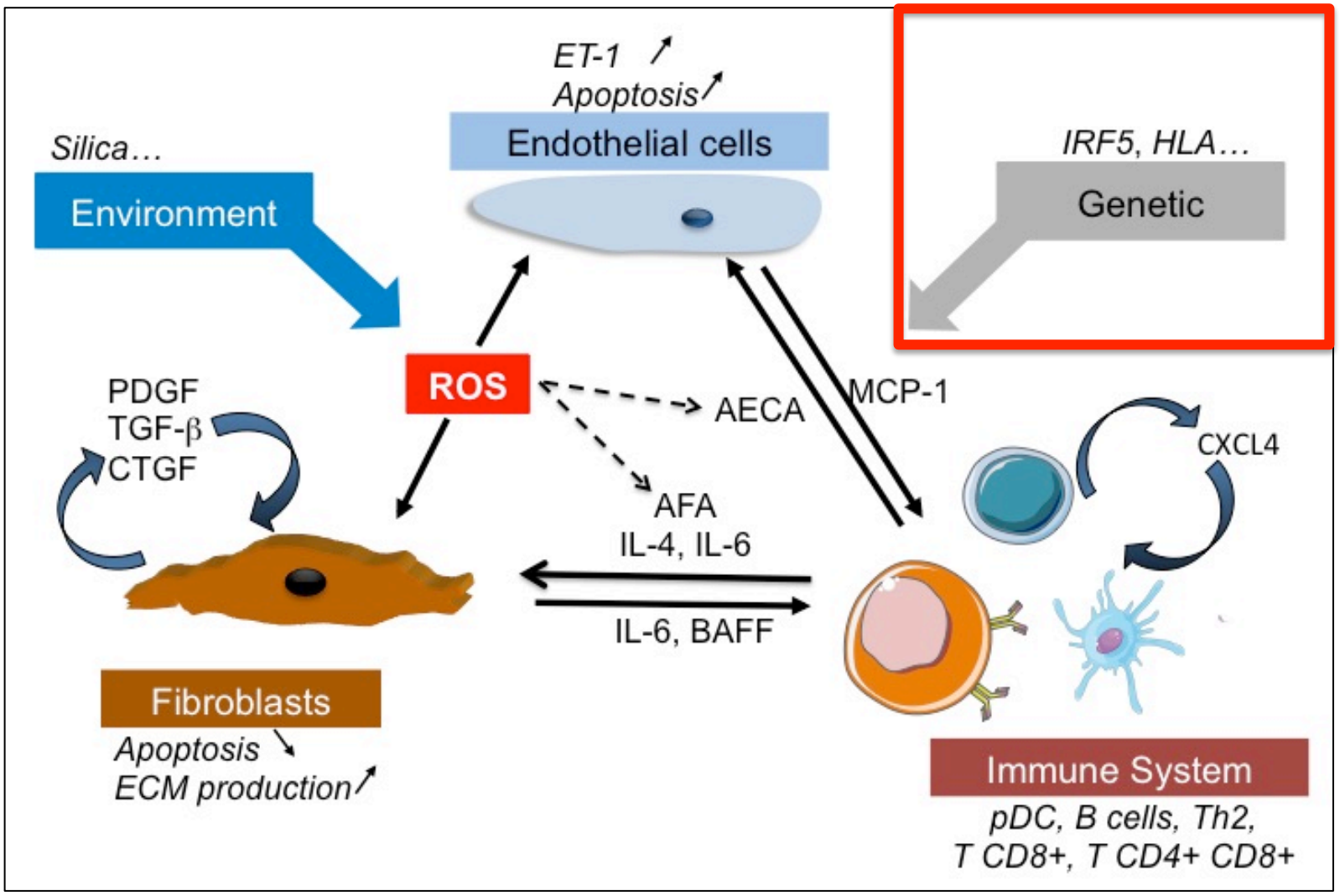

Dumoitier *et al.*, *Presse Médicale* 2014

Prédisposition Génétique

Systemic sclerosis: susceptibility genes

Fibrosis	Vascular involvement	Autoimmunity
Fibrillin-1 (FBN1)	***VEGF***	**CMH-HLA: HLA II and autoantibodies** (*HLA-DRB1*01-DBQ1*0501 associated to ACA)*
Fibronectin (FN))	***Endothelin and its receptors***	**Lymphocytic activation : STAT4,TBX21 regulators of TH1-TH2 balance;**
Secreted Protein Acid and Rich Cystein (SPARC) or osteonectin	***Hypoxia-inducible factor 1A***	***Protein tyrosine phosphatase nonreceptor type 22 (PTPN22),***
Connective tissue growth factor (CTGF)	***Endothelial nitric oxide synthase (eNOS/NOS3) and inducible NOS (iNOS/NOS2)***	*B cell scaffold protein with ankyrin repeats 1 (BANK1)*
TGF-β	***Fibrinogen***	*B lymphocyte kinase (BLK);*
Serotonin 5-HT2A receptor	***Stromal cell-derived factor 1 (SDF-1/CXCL12):)***	*Tumour necrosis factor alpha-induced protein 3 (TNFAIP3);*
Interleukine-1α et 1β		*Interleukin-23 receptor*
Matrix metalloproteinase (MMP)		**Innate immunity: IRF5, control of IFN production**

Romano E, Clin Exp Rheumatol, 2011

Loci associés à la sclérodermie systémique	*p*
Localisés dans la région HLA	
TNFα (microsatellite α13)	$p < 0.05$
D6S422, chr 6p22.3 (haplotypes 165, 171, 292, 305, 307)	$p < 0.05$
Non localisés dans la région HLA	
D1S419	$p < 0.05$
D14S277	$p < 0.05$
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D1S255, chr1p32-31 (haplotypes 97, 127, 209, 230, 233)	$p < 0.01$
D1S2800, chr1q42.3 (haplotypes 85, 169, 208, 212, 265, 267)	$p < 0.01$
D5S410	$p < 0.0001$
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D7S510, chr7p12-11 (haplotypes 95, 177, 188, 208, 245)	$p < 0.01$
D7S661	$p < 0.01$
D8S514, chr8q24.12 (haplotypes 156, 222, 272)	$p < 0.05$
D14S63	$p < 0.05$
D15S978	$p < 0.05$
D19S220	$p < 0.05$
D19S221, chr19p13.2 (haplotypes 85, 105, 161, 200)	$p < 0.01$
D20S107	$p < 0.01$
D22S423, chr22q13.1 (haplotypes 83, 137, 146, 248, 307)	$p < 0.05$
DXS1068	$p < 0.01$
DXS8055, chrXq21-23 (haplotypes 223,272, 316, 272)	$p < 0.01$

Chr : chromosome ; HLA: human leukocyte antigen ; TNFα : tumor necrosis factor α

Chairta *et al.*, *Hum Immunol* 2017

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<u>Implication dans l'immunité:</u>
- chimiokines
- cytokines
- interleukines
- intégrines

Chairta *et al.*, *Hum Immunol* 2017

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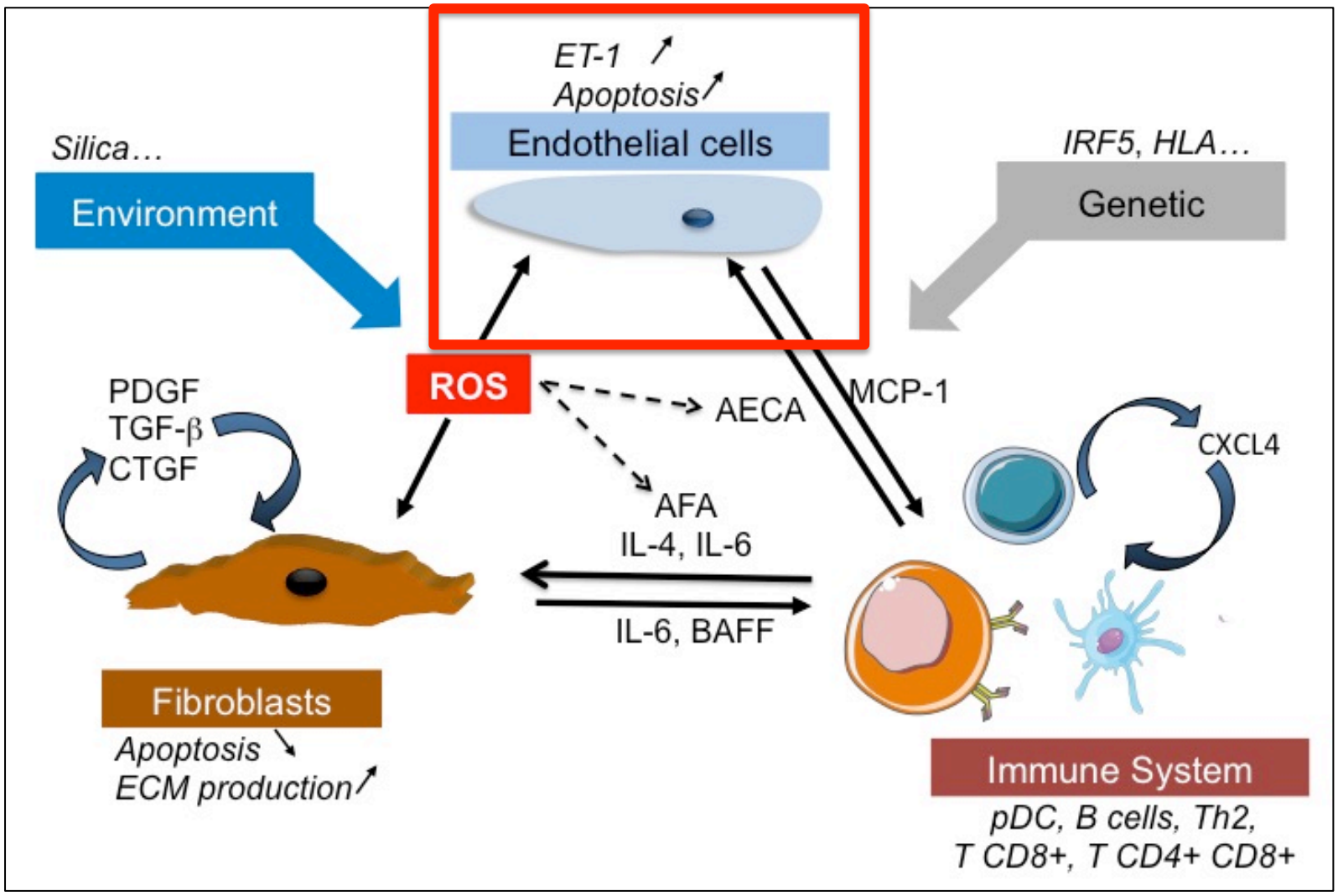
Méta-analyse GWAS européo-japonaises
(4436 cas 14751 contrôles):
- SNPs **GSDMA** $p = 1.4 \times 10^{-10}$
- SNPs **PRDM1** $p = 6.6 \times 10^{-10}$

Implication dans auto-immunité

Terao *et al.*, *Ann Rheum Dis* 2017

Chairta *et al.*, *Hum Immunol* 2017

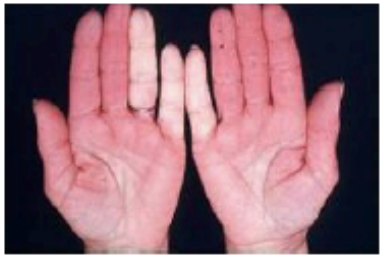
Systemic Sclerosis (SSc): pathophysiology



Dumoitier *et al.*, *Presse Médicale* 2014

A disease of the endothelium

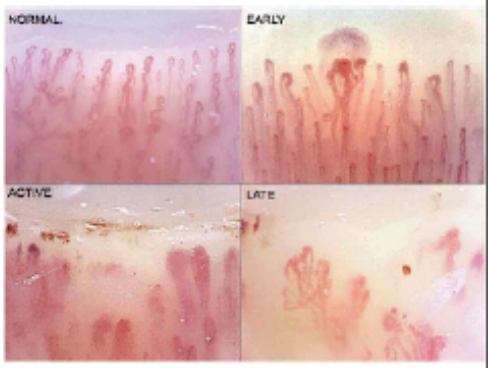
Major dysfunction of endothelial cells *(Matucci-Cerinic, Semin Arthritis Rheum. 2003)*



Apoptosis at early stages (AECA ?) *(Sgonc,J Clin Invest. 1996)*

Loss of physiological barrier: permeabilisation of vessels

Abnormal vascular tone regulation



Increased endothelin-1 synthesis *(Mayes, Arthritis Rheum, 2003)*

Defective prostacyclin synthesis

Perturbed NO synthesis *(Cotton, J Pathol. 1999; Herrick, Clin Exp Rheumatol. 2001)*

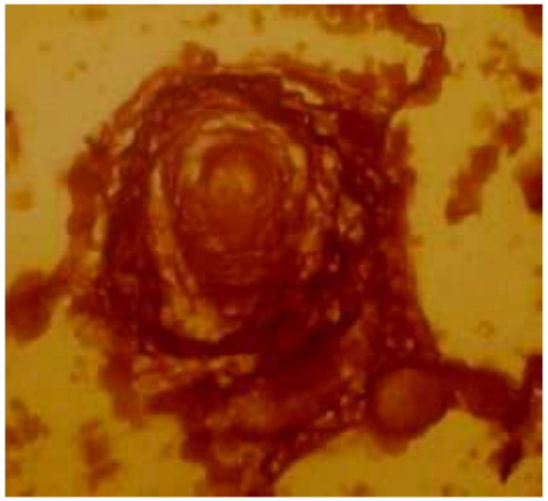
Perturbed angiogenesis: VEGF decreased of not detectable *(Distler O., Circ Res, 2004)*

Synthesis of MCP-1 and VCAM-1: recruitment of lymphocytes *(Anderegg, Arch Dermatol Res. 2000)*

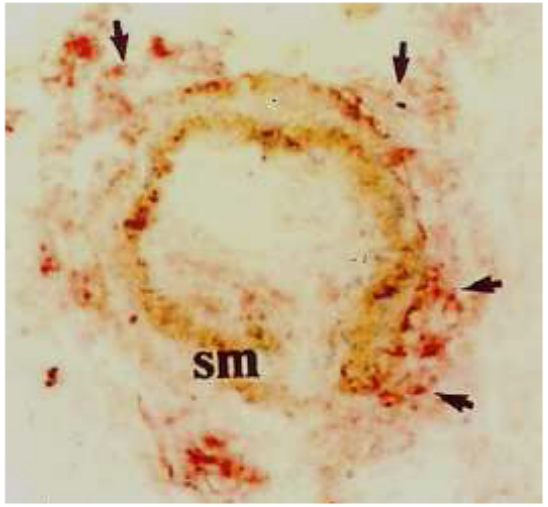
Synthesis of TGFβ and PDGF: activation of fibroblasts *(Cotton,J Pathol, 1998)*

Endothelin-1 expression in pulmonary and renal vasculature

PAH

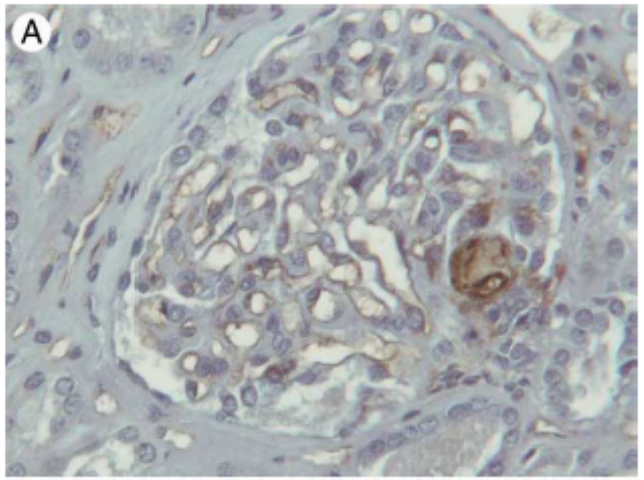


Sirius red stain - collagen

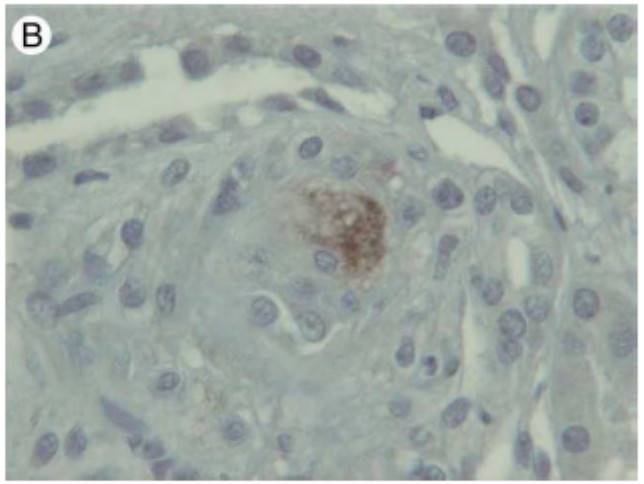


Immunolocalisation of ET-1 ligand

Scleroderma renal Crisis



ET-1 in glomerular thrombosis and along glomerular basement membranes



ET-1 in arteriolar thrombosis

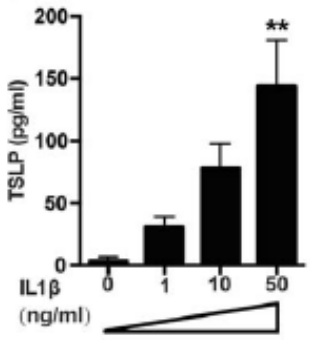
Mouthon et al. Human Pathol 2010

Platelets Induce Thymic Stromal Lymphopoietin Production by Endothelial Cells

Contribution to Fibrosis in Human Systemic Sclerosis

Marie-Elise Truchetet,[1] Béatrice Demoures,[2] Jorge Eduardo Guimaraes,[3] Anne Bertrand,[4] Paôline Laurent,[2] Valérie Jolivel,[2] Isabelle Douchet,[2] Clément Jacquemin,[2] Liliane Khoryati,[2] Pierre Duffau,[1] Estibaliz Lazaro,[1] Christophe Richez,[1] Julien Seneschal,[4] Marie-Sylvie Doutre,[4] Jean-Luc Pellegrin,[4] Joël Constans,[4] Thierry Schaeverbeke,[4] Patrick Blanco,[1] and Cécile Contin-Bordes,[1] on behalf of the Fédération Hospitalo-Universitaire ACRONIM

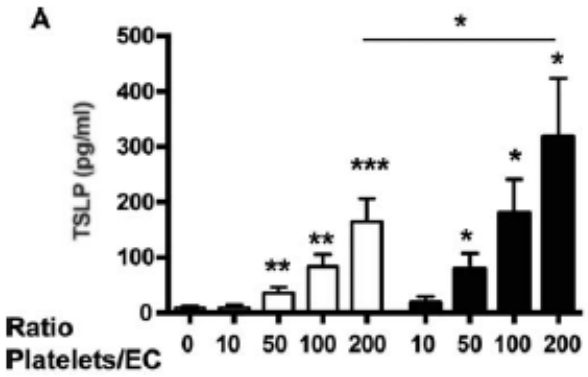
ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 11, November 2016, pp 2784–2794
DOI 10.1002/art.39817



endothelial cell

TSLP :

- **IL-1ß dependent**
- **Increased by serotonin**



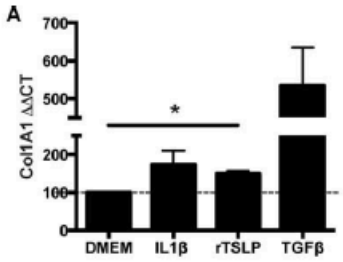
+

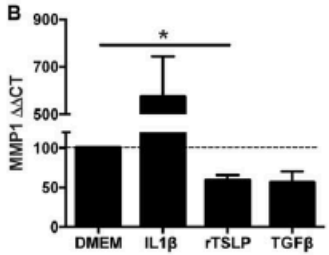
Activated platelets

Activated - Platelets

fibroblast

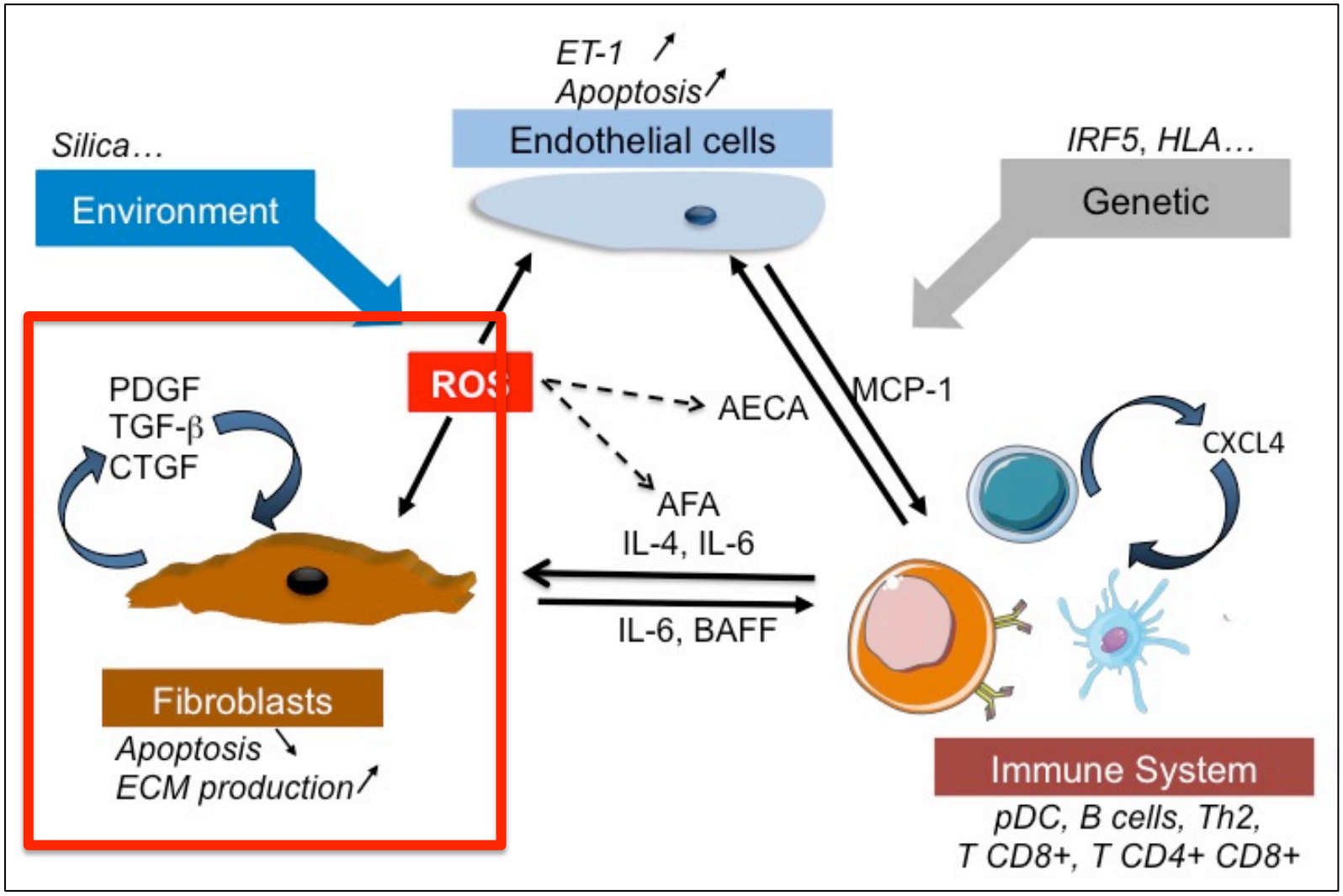
- **Increased collagen 1A1**
- **Decreased collagenase MMP-1**





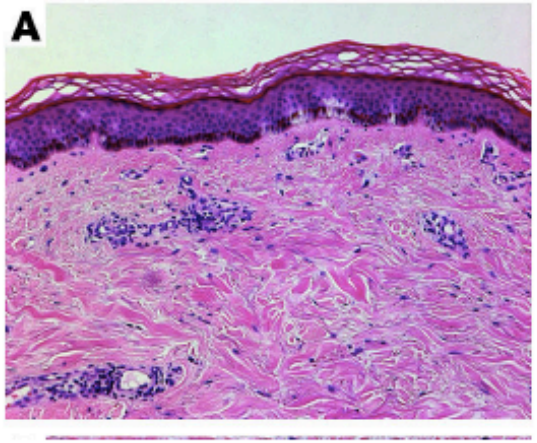
Truchetet *et al.*, *Arthritis Rheumat* 2016

Systemic Sclerosis (SSc): pathophysiology

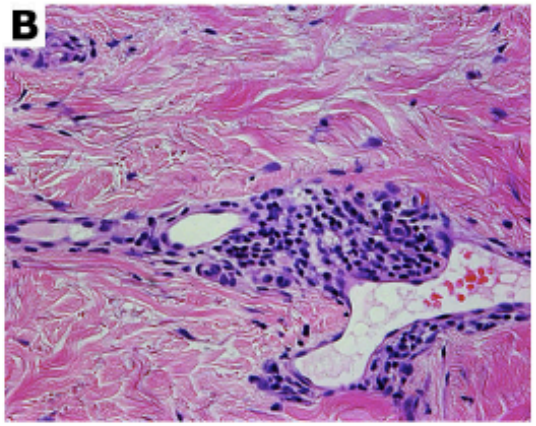


Dumoitier *et al.*, *Presse Médicale* 2014

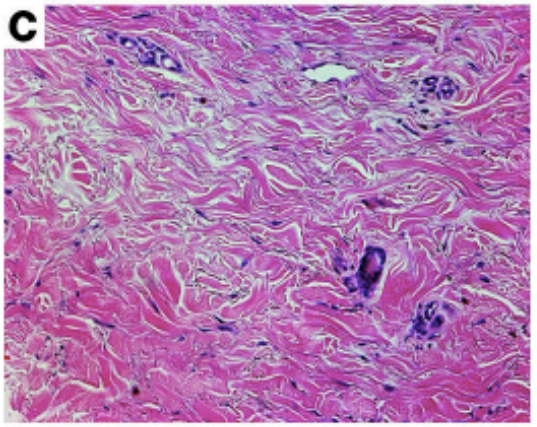
Fibroblast activation => Fibrosis phenomena



(**A**) Early diffuse cutaneous SSc
- Moderate fibrosis
- Inflammatory infiltrates in the dermis and near the dermal-epidermal junction, predominantly around small blood vessels



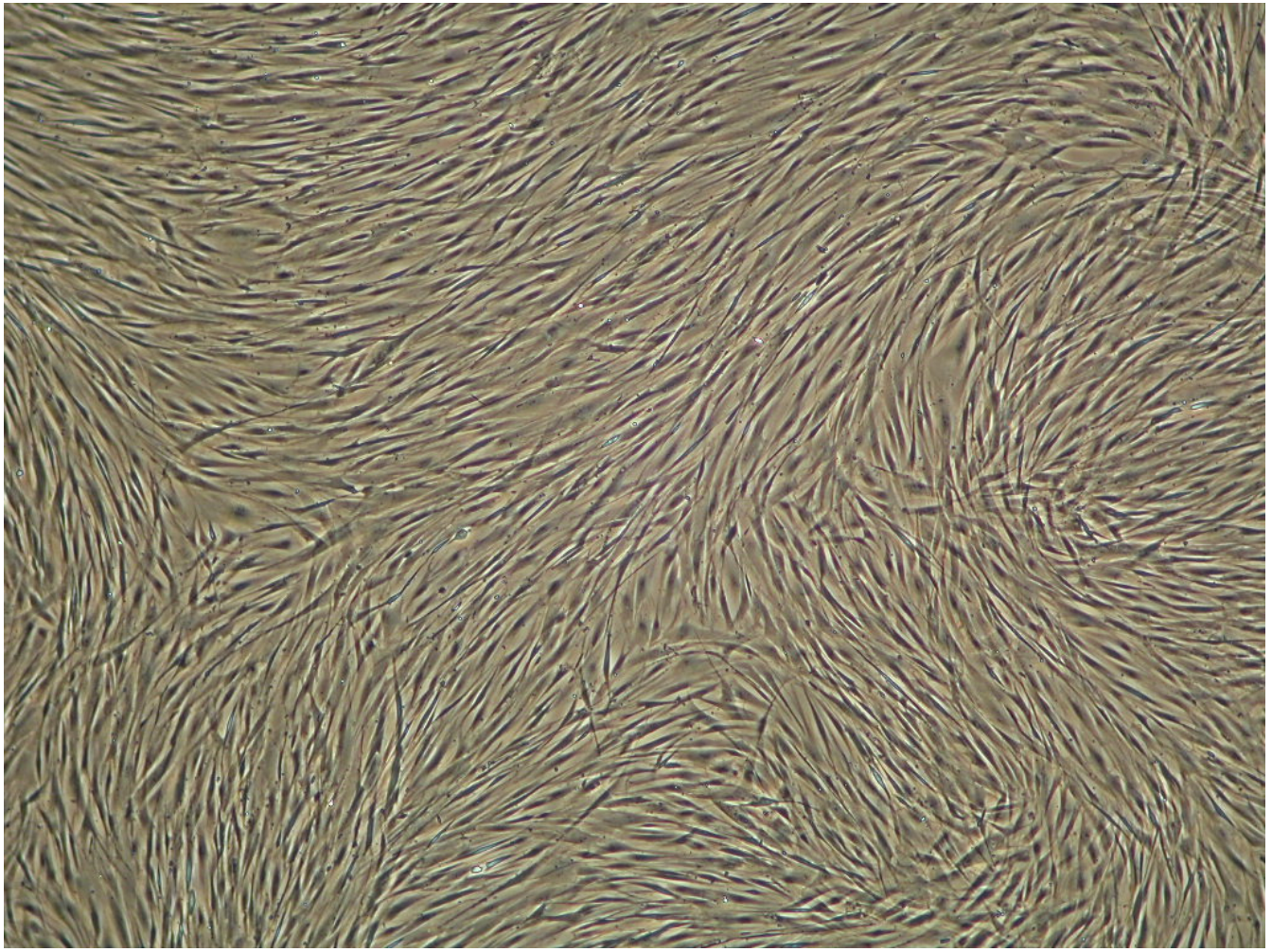
(**B**) Early-stage diffuse disease
- Profound dermal inflammation perivascular mononuclear cellular infiltrate
- Perivascular fibrosis and loss of pericytes and vessel integrity



(**C**) Established fibrosis
- Dermal thickening
- Loss of the microvasculature and dermal structures and the dermis-subcutaneous adipose tissue interface

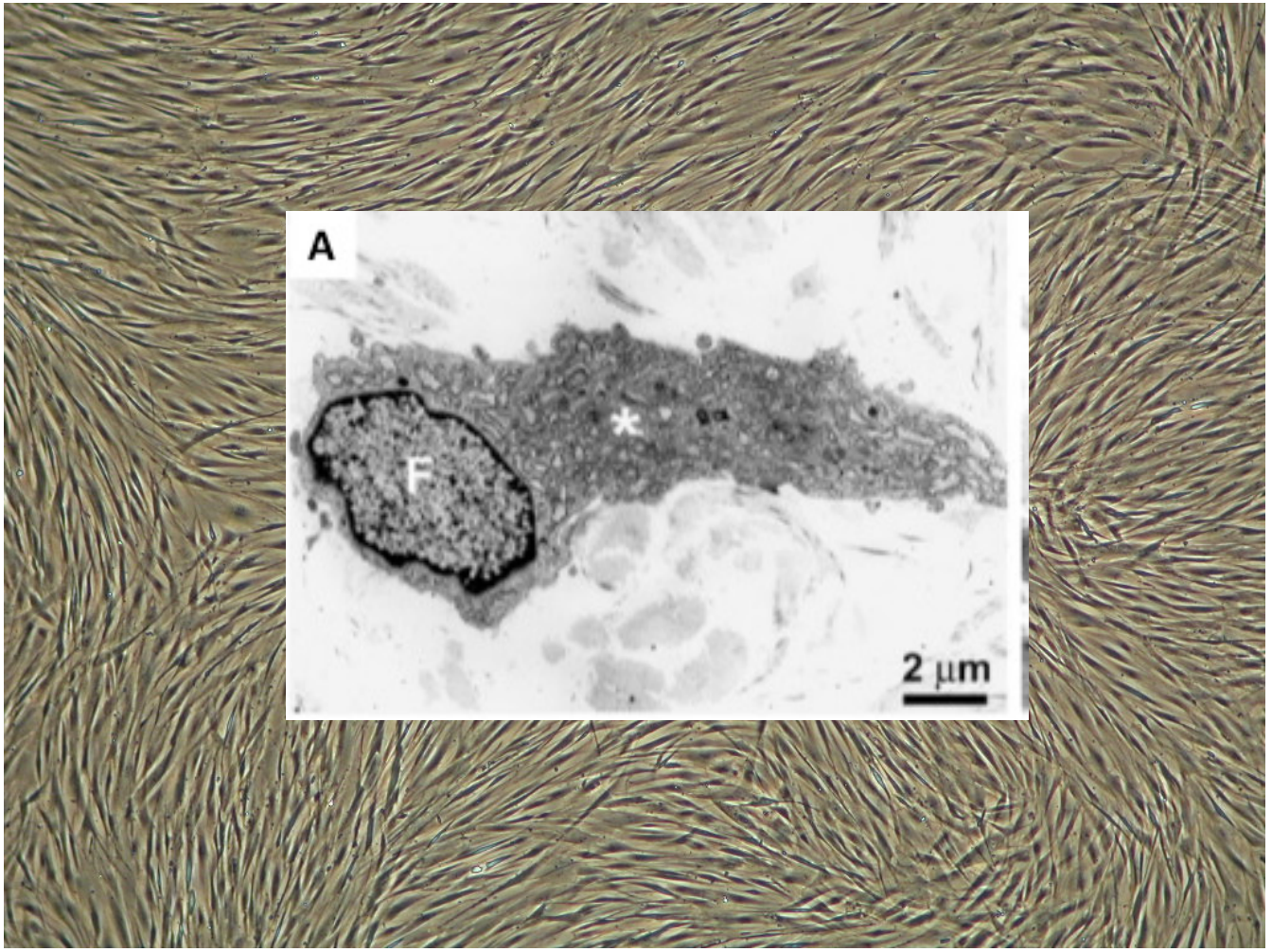
Varga J, Abraham D. *J Clin Invest* 2007; 117:557–67

Fibroblasts



Primary human dermal fibroblasts

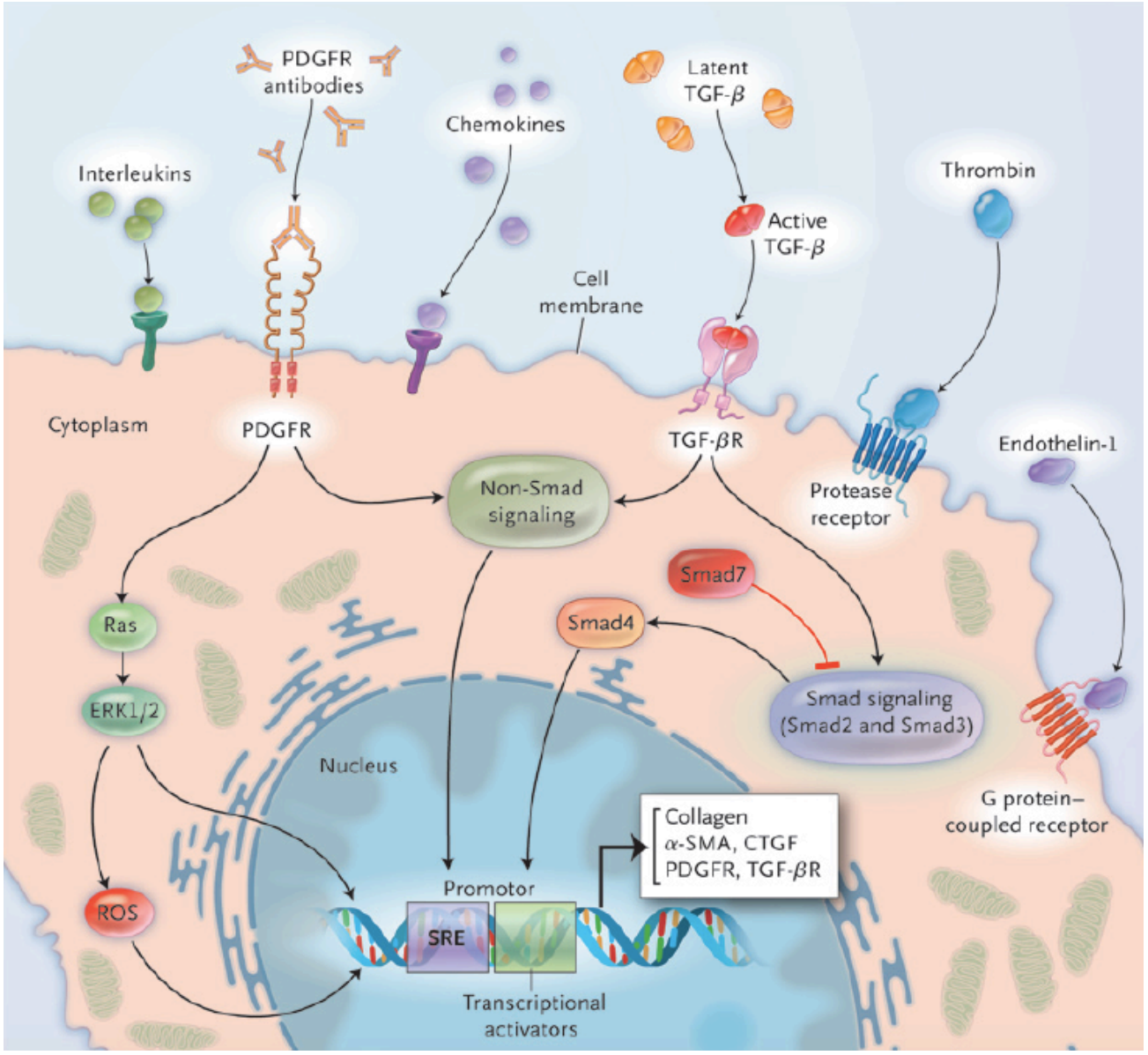
Fibroblasts



Primary human dermal fibroblasts

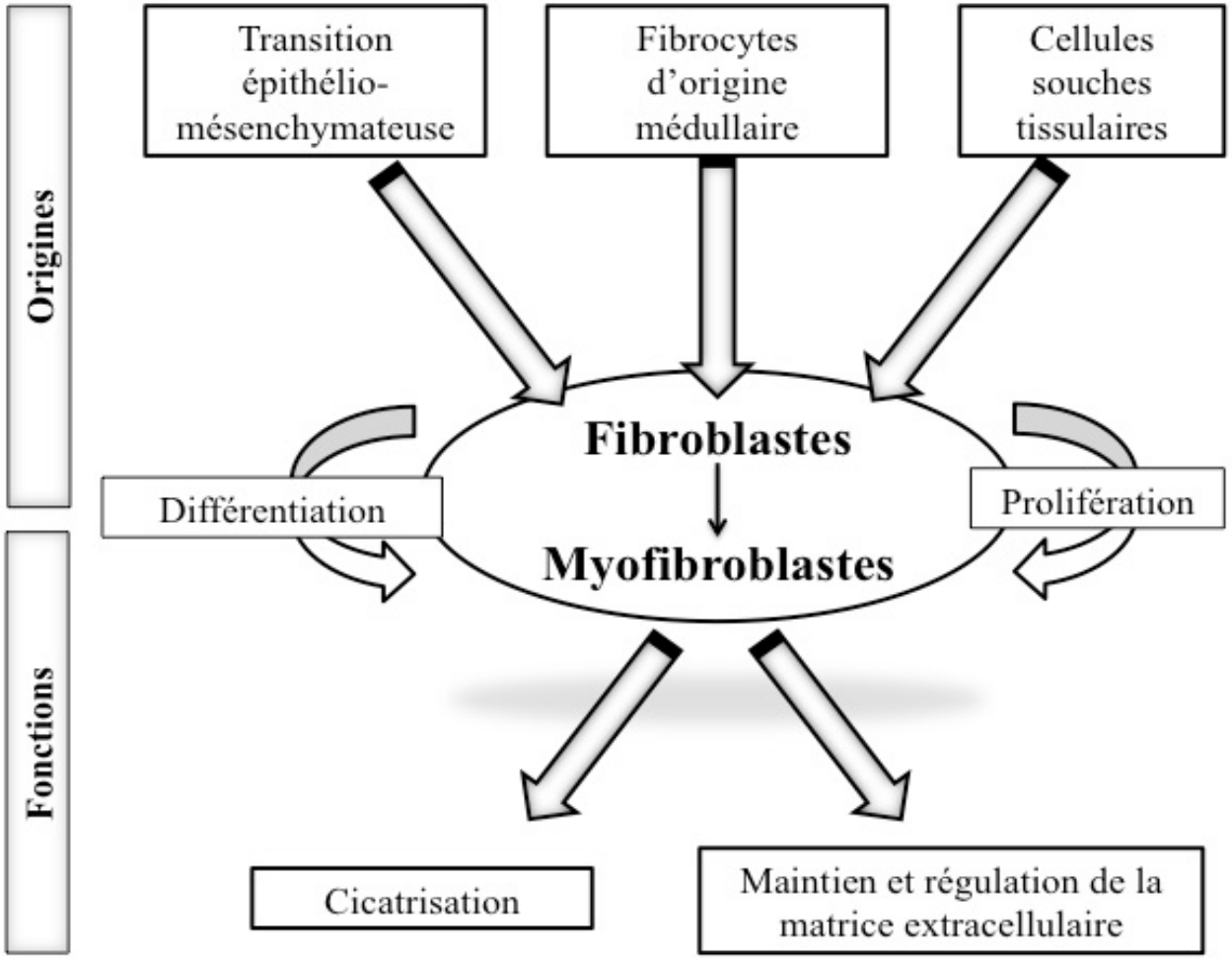
Manetti *et al., J Cell Mol Med* 2013

Fibroblasts activation in SSc



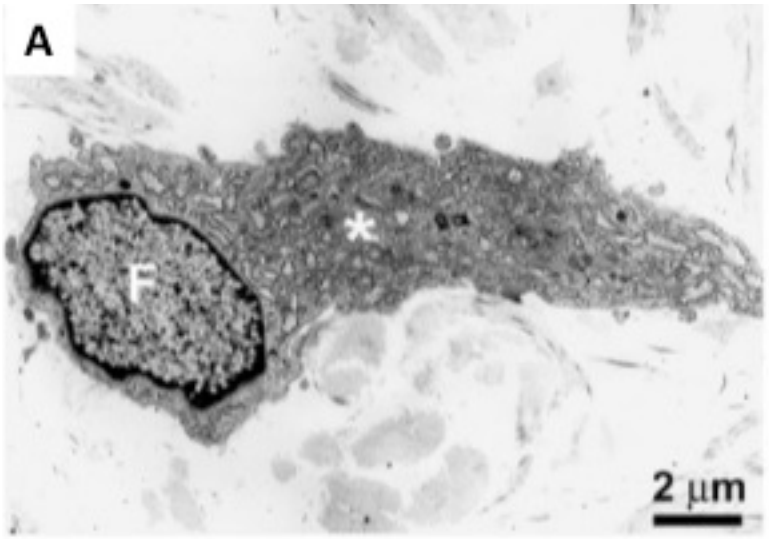
Gabrielli *et al., NEJM* 2009

Fibroblasts: origins and functions

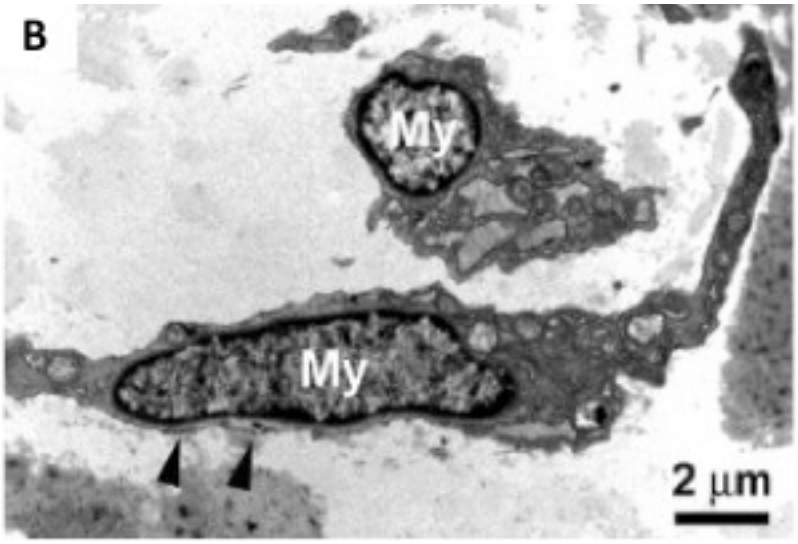


Adapted from McAnulty, *Int J Biochem Cell Biol* 2007

Fibroblasts and Myofibroblasts



Fibroblast



Myofibroblasts

Manetti *et al., J Cell Mol Med* 2013

Activation des fibroblastes

Acquisition d'un phénotype activé en myofibroblastes *(LeRoy, E.C.. J.Clin Invest, 1974; KIRK, J Biol Chem, 1995)*

- α-smooth actin *(Abraham, D.J. Curr. Rheumatol. Rep. 2007)*
- Focal Adhesion Kinase *(Mimura, Y. J. Invest. Dermatol, 2005)*

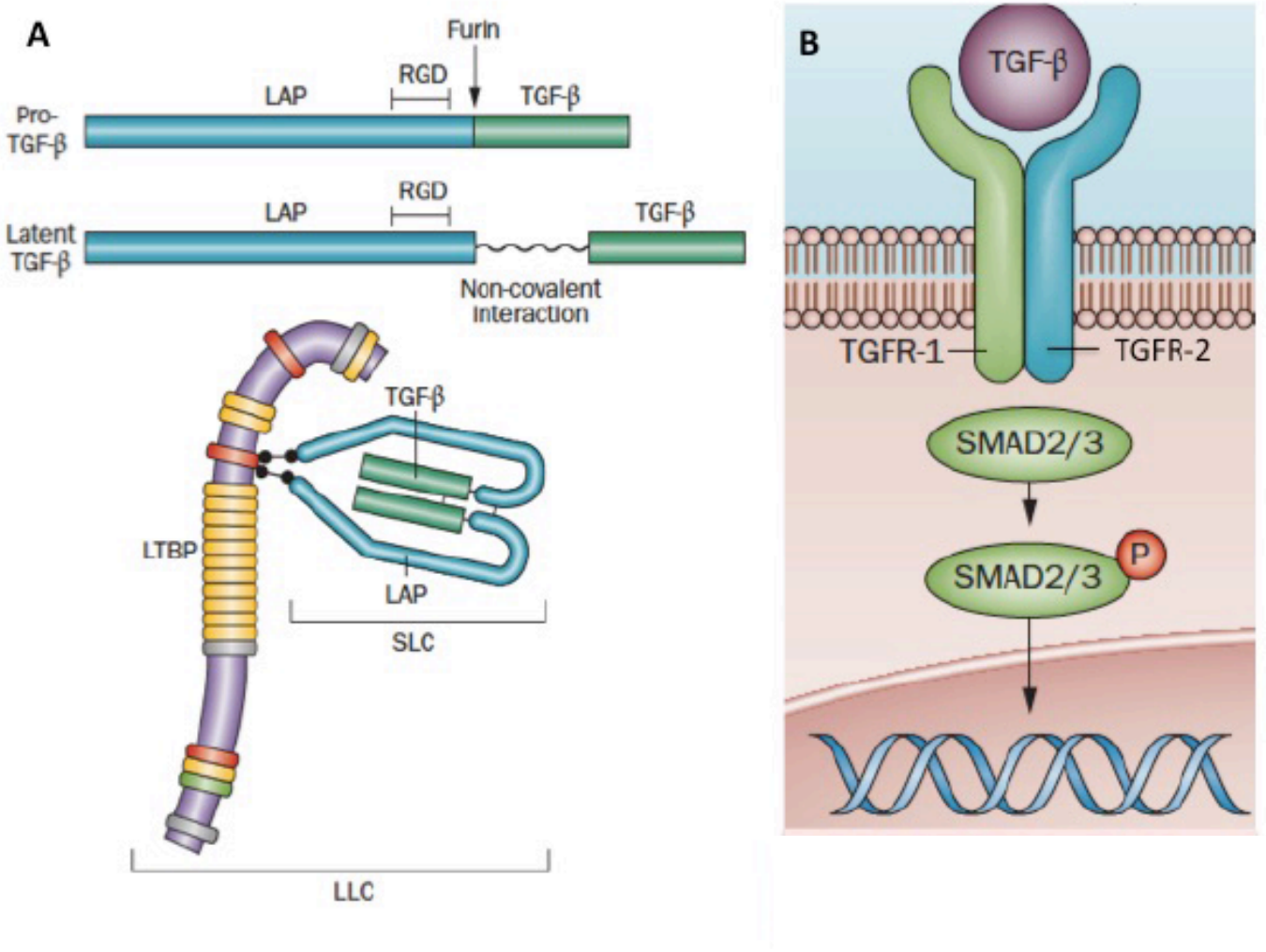
Défaut d'apoptose par Fas/Fas-ligand *(Santiago B., Arthritis Rheum 2001)*

Défaut de synthèse des régulateurs de la MEC (métalloprotéinases) *(VAN DER SLOT, J Biol Chem. 200*

Activation et synthèse excessive de collagène sous le contrôle de

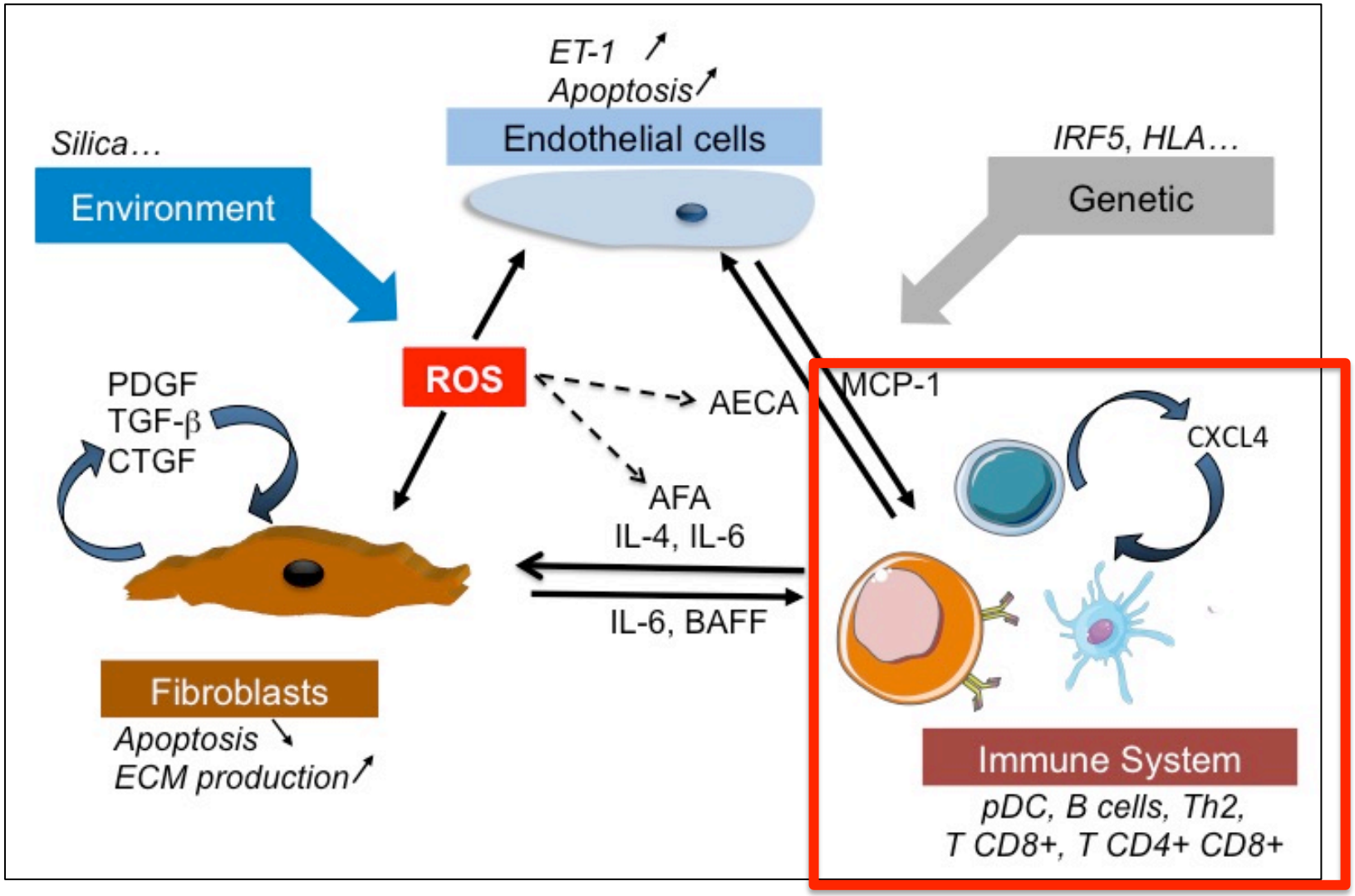
- **IL-4: prolifération** *(POSTLETHWAITE, J Clin Invest, 1992)*
- **Connective Tissue Growth Factor (CTGF)** *(Leask, A., J. Cell Sci. 2006)*
- **Platelet Derived Growth Factor (PDGF)** *(Ludwicka, A., J. Rheum. 1995)*
- **Formes Réactives de l'Oxygène (FRO)** *(Sambo P., Arthritis Rheum.,2001)*
- **Anticorps anti fibroblastes et anti-PDGFR** *(Chizzolini C., Arthritis Rheum 2001, Sevgliati Baroni S., NEJM, 2006)*
- **Transforming Growth Factor-β (TGF-β)** *(Pannu, J., Curr. Opin. Rheumatol. 2004)*

Transforming Growth Factor-ß



Adapted from Lafyatis, *Nat Rev Rheumatol* 2014

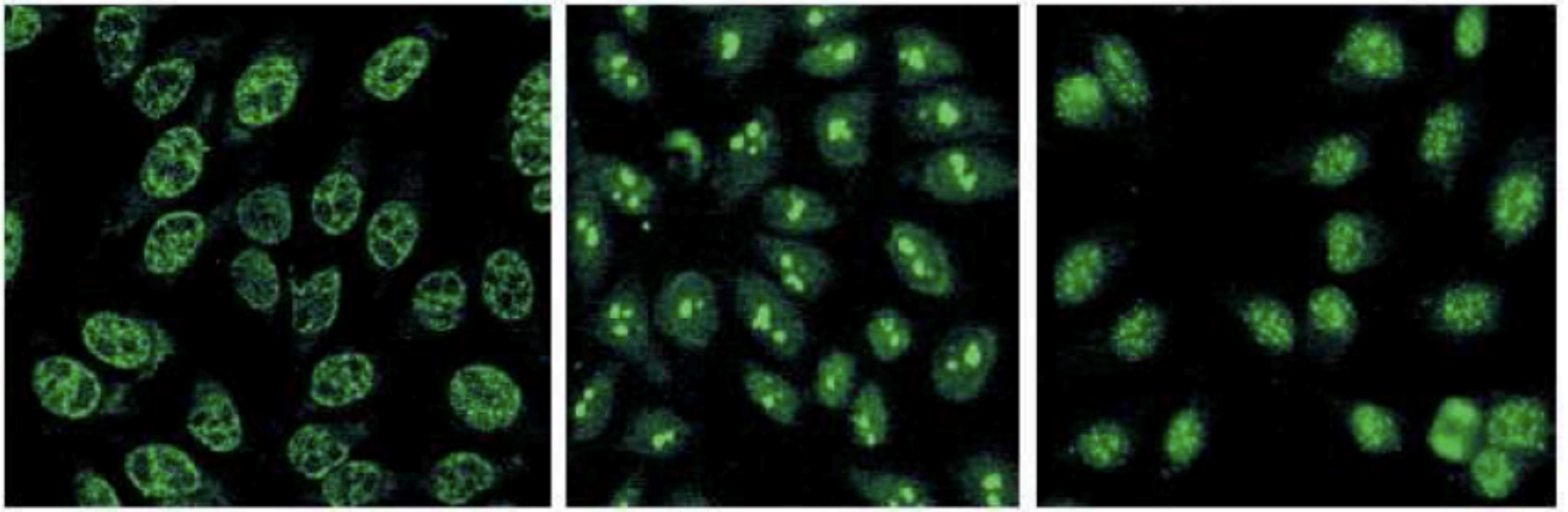
Systemic Sclerosis (SSc): pathophysiology



Dumoitier *et al.*, *Presse Médicale* 2014

Immune system: Autoantibody

A



B

Classic Autoantibodies	Clinical Features	New Autoantibodies	Role
Anti–topoisomerase I	Diffuse cutaneous scleroderma	Anti–endothelial cell	Induce apoptosis of endothelial cells
Anticentromere proteins	Limited cutaneous scleroderma, pulmonary hypertension	Anti–FBN 1	Activate normal human fibroblasts
Anti–RNA polymerase I/II	Diffuse cutaneous scleroderma, renal involvement	Anti–MMP 1 and 3	Prevent degradation of ECM proteins
Antipolymyositis, sclerosis	Polymyositis, calcinosis	Anti-PDGFR	Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS
Antifibrillarin (U3RNP)	Diffuse cutaneous scleroderma, internal-organ involvement	Anti–Nag-2	Induce endothelial-cell apoptosis
Anti-Th/To	Limited cutaneous scleroderma, pulmonary fibrosis		

Gabrielli A, *et al. N Engl J Med* 2009

SSc: origin of autoantibodies

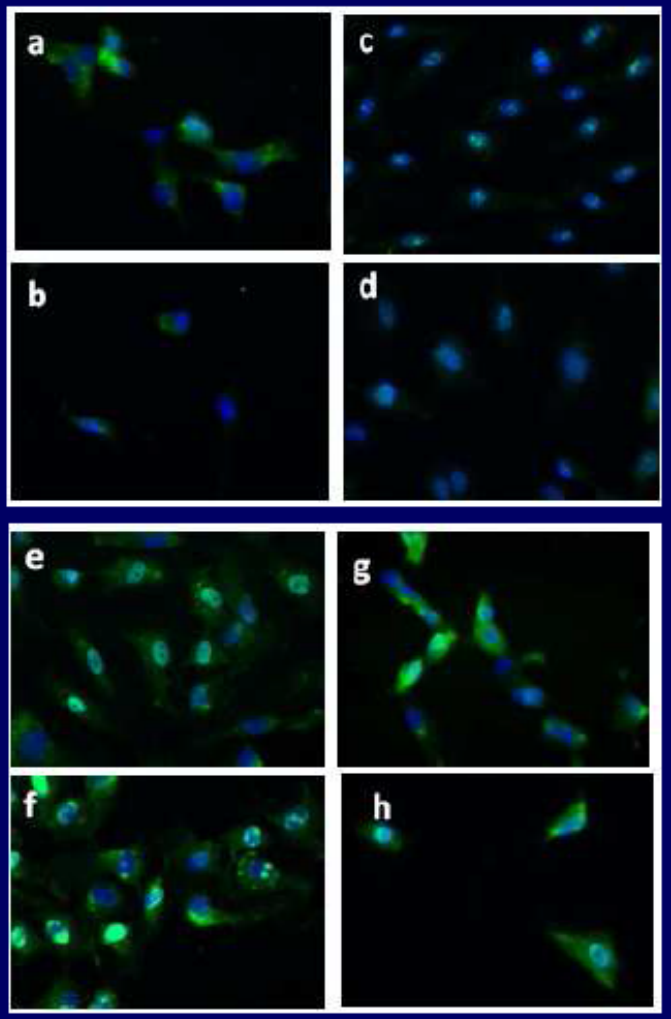
- Molecular mimicry (topo I and CMV)[1]
- Polyclonal B cell activation with excess of IL-4
- Fragmentation of autoantigens by metalloproteinases, favoured by hypoxia[2] and by mercury chloride[3]
- Selective oxidation of DNA topoisomerase 1 induces SSc in the mouse[4]
- A subset of SSc patients shows a "lupus-like" high IFN-α inducible gene expression pattern[5]

1. Lunardi C, *et al. Nat Med* 2000; 6:1183-6.
2. Casciola-Rosen L, *et al. J Exp Med.* 1997; 185:71-9.
3. Arnet F. 1990.
4. Servettaz, *et al. J Immunol* 2009; 182:5855-64..
5. Assassi S, *et al. Arthritis Rheum* 2010; 62:589–98.

Anti-endothelial cell antibodies (AECA) in SSc

- Not disease specific
- Absence of standardization
- Activate EC and induce the expression of adhesion molecules (IL-1 dependent)[1]
- Induce apoptosis in the presence of NK cells[2]
- Cross-reactivity of AECA with a CMV protein[3]
- Target antigens unknown except "scleroderma specific" autoantigens[4,5]

6. Ab: controls; cd: ssc w/o PAH; ef: SSc-PAH; gh: IPAH



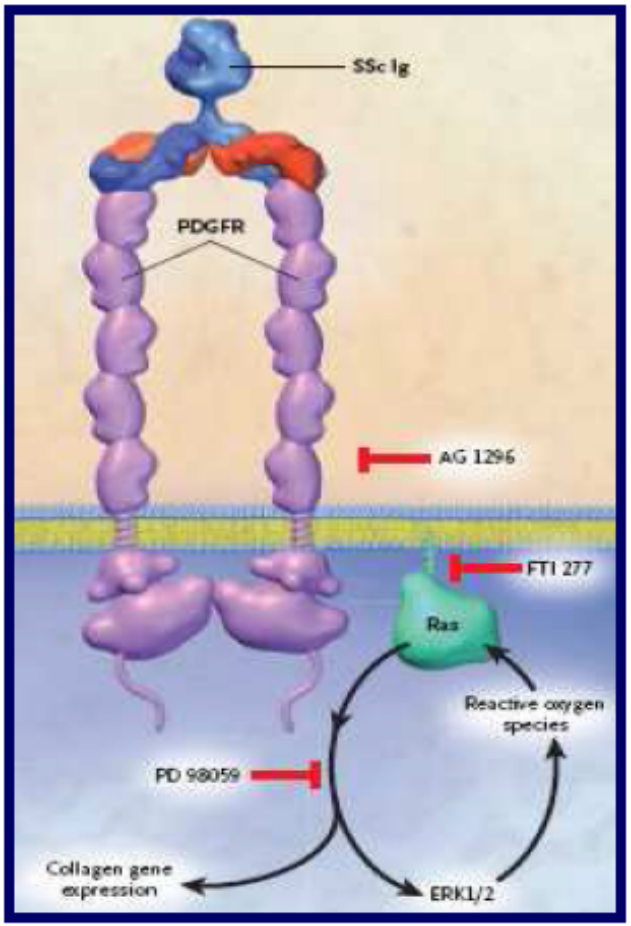
1. Carvalho D. *Arthr Rheum* 1999. 2. Bordron A. *J Clin Invest* 1998.
3. Lunardi C, *et al. Nat Med* 2000. 4. Garcia de la Pena *et al. Clin Immunol* 2004.
5. Servettaz *et al. Clin Immunol* 2006. 6. Dib H, *et al.* Eur Resp J 2011

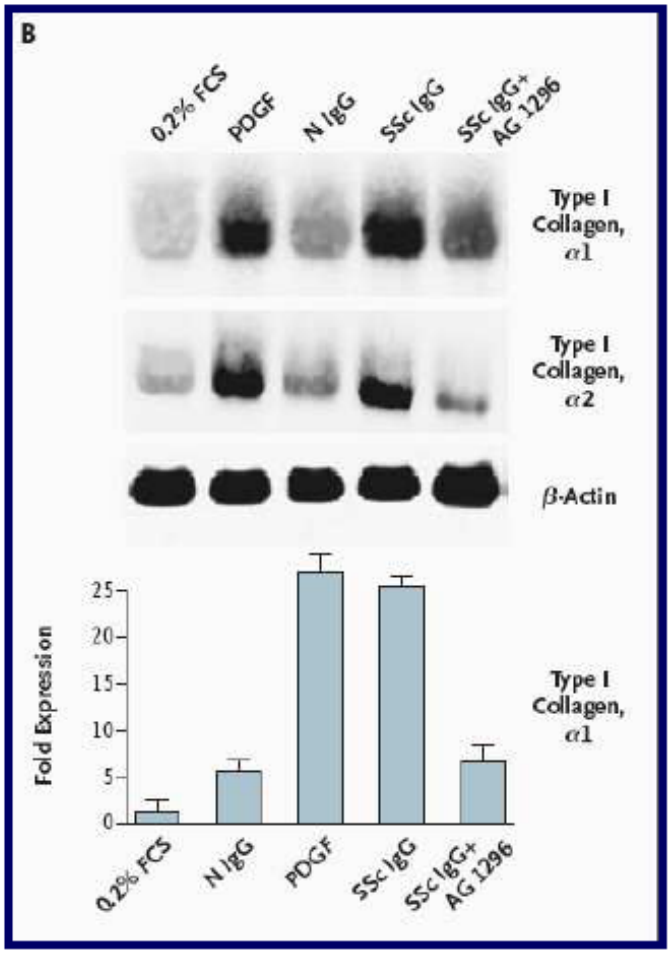
Anti-fibroblast Abs in SSc

- Anti-fibroblast antibodies (AFA) are present in the serum of 20 to 80% of SSc patients[1]
- AFA can activate fibroblasts and induce extracellular matrix proteins synthesis[2]
- Induce a proadhesion fibroblast phenotype by up-regulating ICAM-1 and increase fibroblast synthesis of pro-inflammatory cytokines
- AFA induce fibroblasts to produce profibrotic chemokines, with partial exploitation of TLR4[3]
- Target antigens
  - DNA topoisomerase 1[4]
  - PDGF receptor[5]

1. Brentnall, 1982; Chizzolini, 2002; Alderuccio, 1989; Ronda, 2002.
2. Chizzolini C. *Arthritis Rheum* 2002.
3. Fineschi S. *Arthritis Rheum* 2008.
4. Henault G. *Arthritis Rheum* 2004; Henault G. *Arthritis Rheum* 2006; Tamby MC *et al.* 2008.
5. Baroni S, *et al. NEJM* 2006; Classen, *et al.* 2009; Loizos, *et al.* 2009.

ANTICORPS ANTI-PDGFR





Les IgG sériques stimulent le récepteur de PDGF, qui stabilise RAS et induit ERK1/2

L'induction de ERK1/2 entraine la production de FRO (ROS)

La persistance à long terme de ROS et ERK1/2 entraîne une augmentation de l'expression du gène du collagène

Svegliati Baroni, NEJM, 2006

Elevated levels of cytokines in SSc

- Growth factors
  - TGF-β, CTGF, VEGF, FGF, etc
- Interleukins
  - IL-2, IL-4, IL-6, IL-10, IL-13, etc
- Chemokines
  - MCP-1, IL-8 (CXCL8), TARC, fractalkine, etc
- Other cytokines
  - TNF-α, etc

CTGF = connective tissue growth factor; FGF = fibroblast growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; TARC = thymus and activation-regulated chemokine; TGF = tumour growth factor; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor

Slide courtesy of Kazuhiko Takehara.

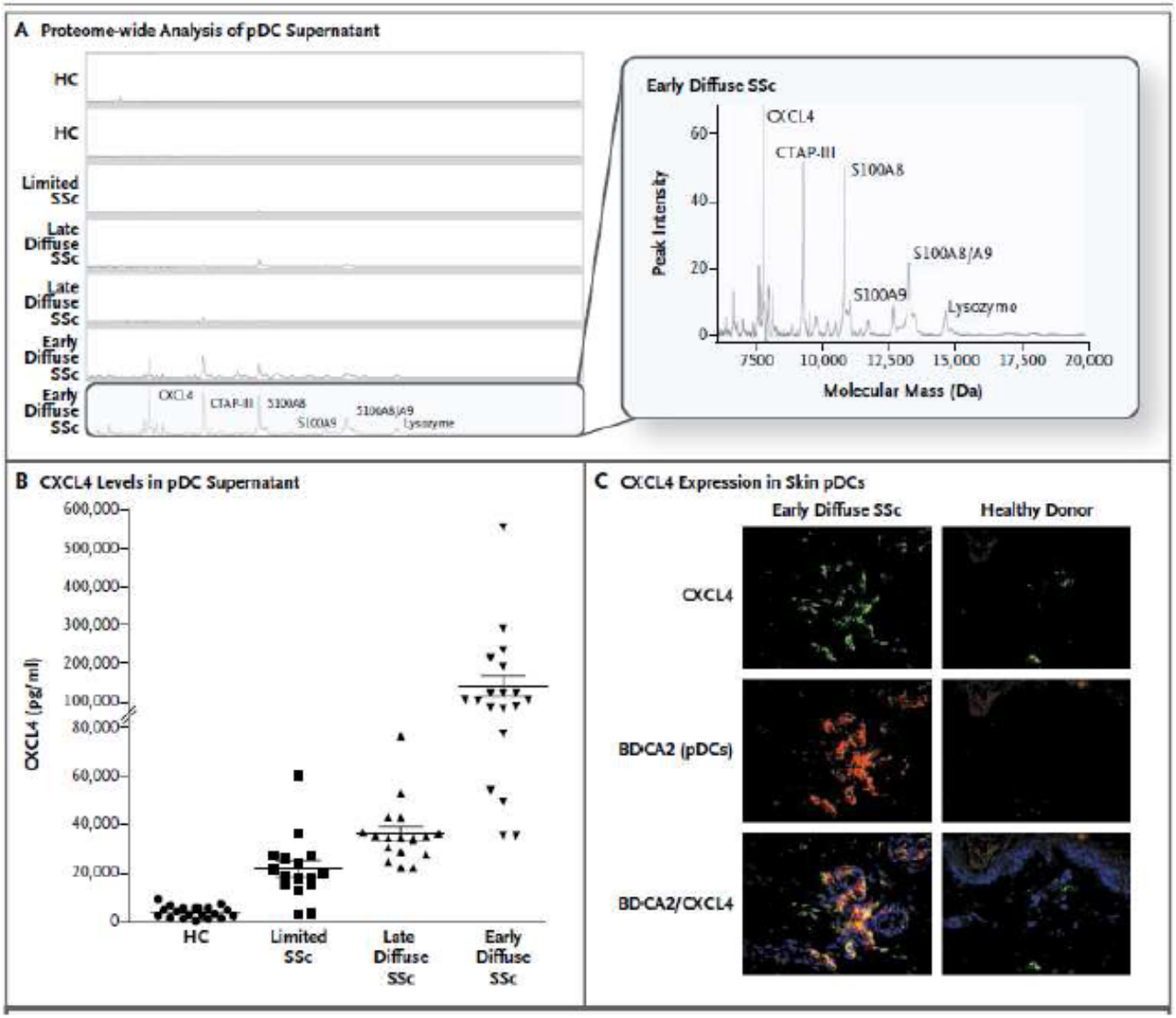
ORIGINAL ARTICLE

Proteome-wide Analysis and CXCL4 as a Biomarker in Systemic Sclerosis

L. van Bon, A.J. Affandi, J. Broen, R.B. Christmann, R.J. Marijnissen, L. Stawski, G.A. Farina, G. Stifano, A.L. Mathes, M. Cossu, M. York, C. Collins, M. Wenink, R. Huijbens, R. Hesselstrand, T. Saxne, M. DiMarzio, D. Wuttge, S.K. Agarwal, J.D. Reveille, S. Assassi, M. Mayes, Y. Deng, J.P.H. Drenth, J. de Graaf, M. den Heijer, C.G.M. Kallenberg, M. Bijl, A. Loof, W.B. van den Berg, L.A.B. Joosten, V. Smith, F. de Keyser, R. Scorza, C. Lunardi, P.L.C.M. van Riel, M. Vonk, W. van Heerde, S. Meller, B. Homey, L. Beretta, M. Roest, M. Trojanowska, R. Lafyatis, and T.R.D.J. Radstake

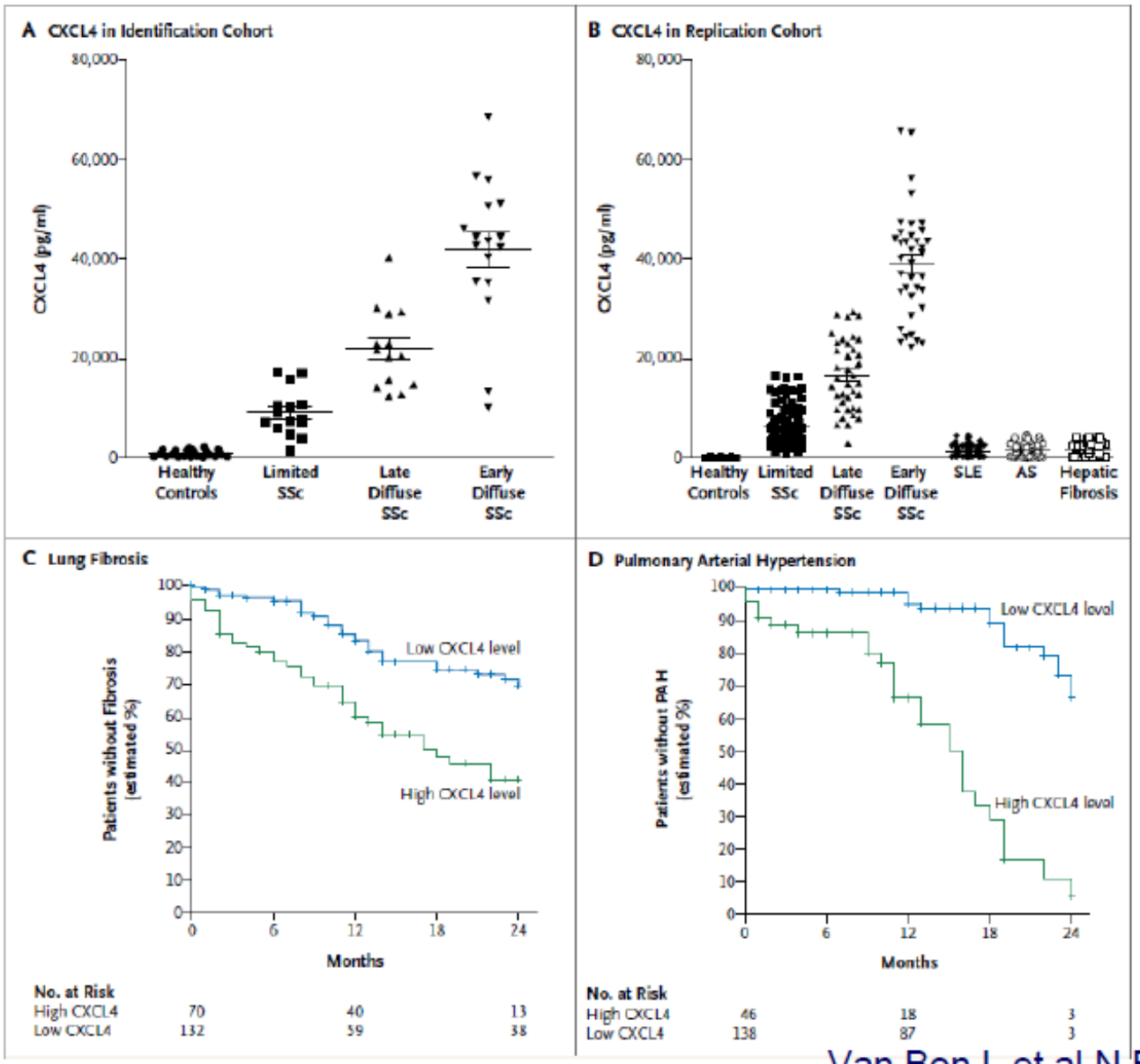
N Engl J Med 2014;370:433-43.

Identification of CXCL4 as the Major Protein Product of Plasmacytoid Dendritic Cells in Systemic Sclerosis.



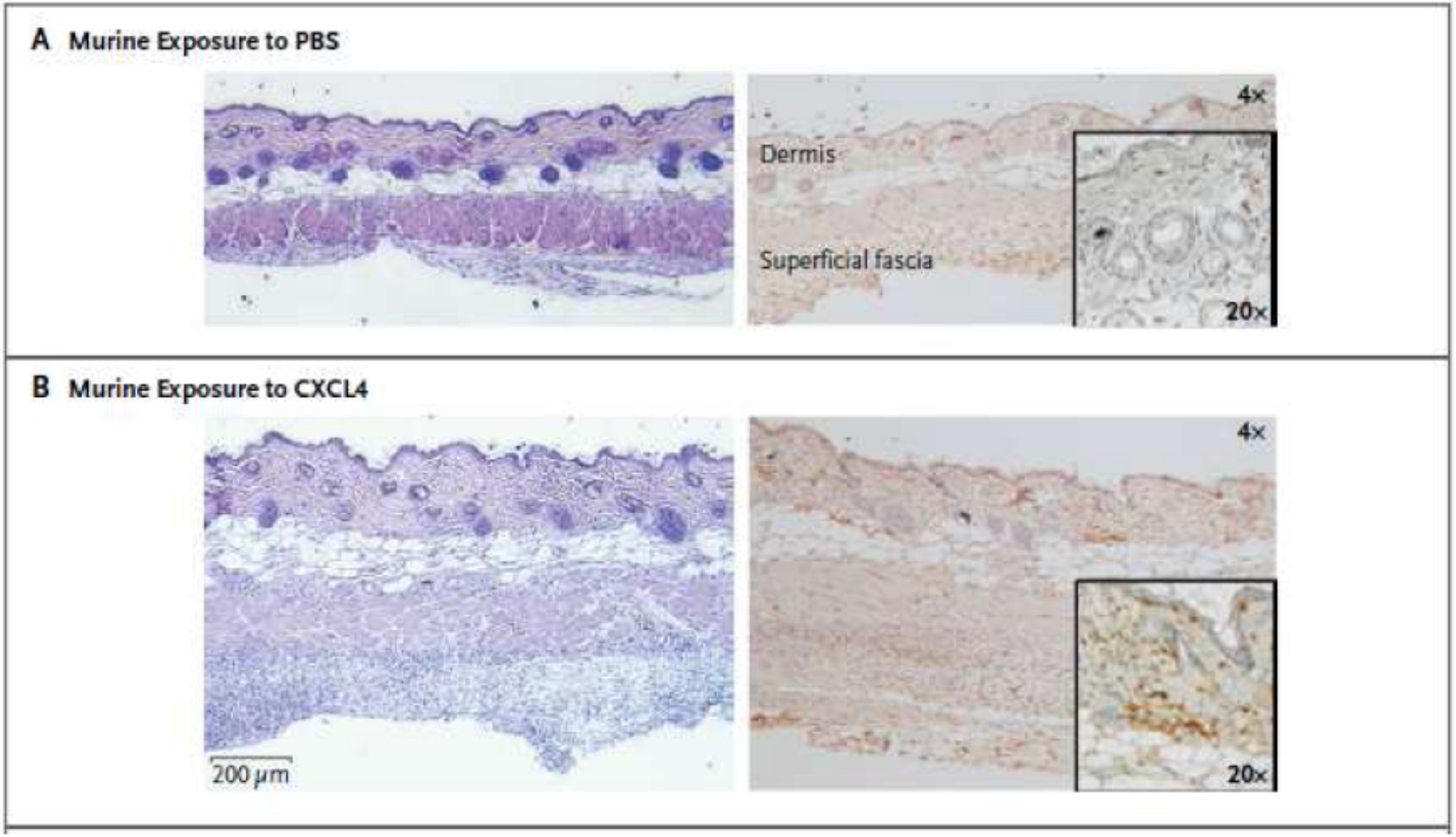
Van Bon L et al N Engl J Med 2014

Increased Levels of Circulating CXCL4 in Systemic Sclerosis and the Association with Lung Fibrosis and PAH



Van Bon L et al N Engl J Med 2014

Inflammatory Skin Changes Mimicking Those in Systemic Sclerosis Induced by CXCL4 In Vivo in Mice.

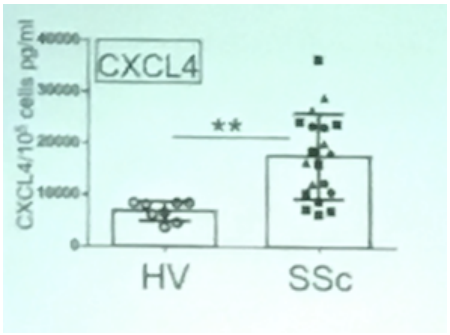


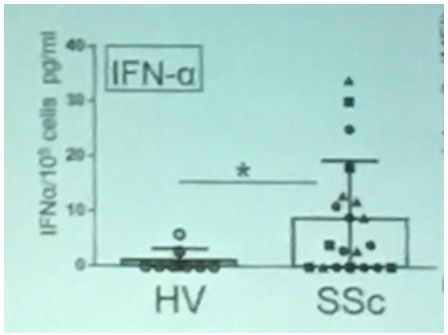
Van Bon L et al N Engl J Med 2014

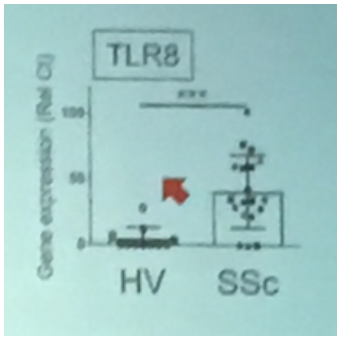
1009 - **Plasmacytoid dendritic cells are activated in systemic sclerosis (SSc) and contribute to the disease by inudcing IFNα and CXCL4**
Marie-Dominique Ah Kioon et al.

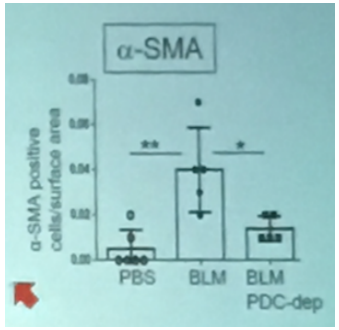
Messages clés

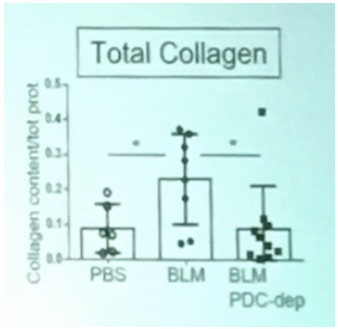
- pDC sont activées et leur suppression améliorent la fibrose
- Elles produisent CXCL4 et IFNα, régulés par PI3Kδ
- Sécrétion dépendante de TLR8
- CXCL4 potentialise la réponse IFNα par les pDC

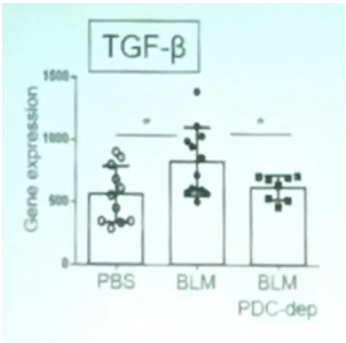








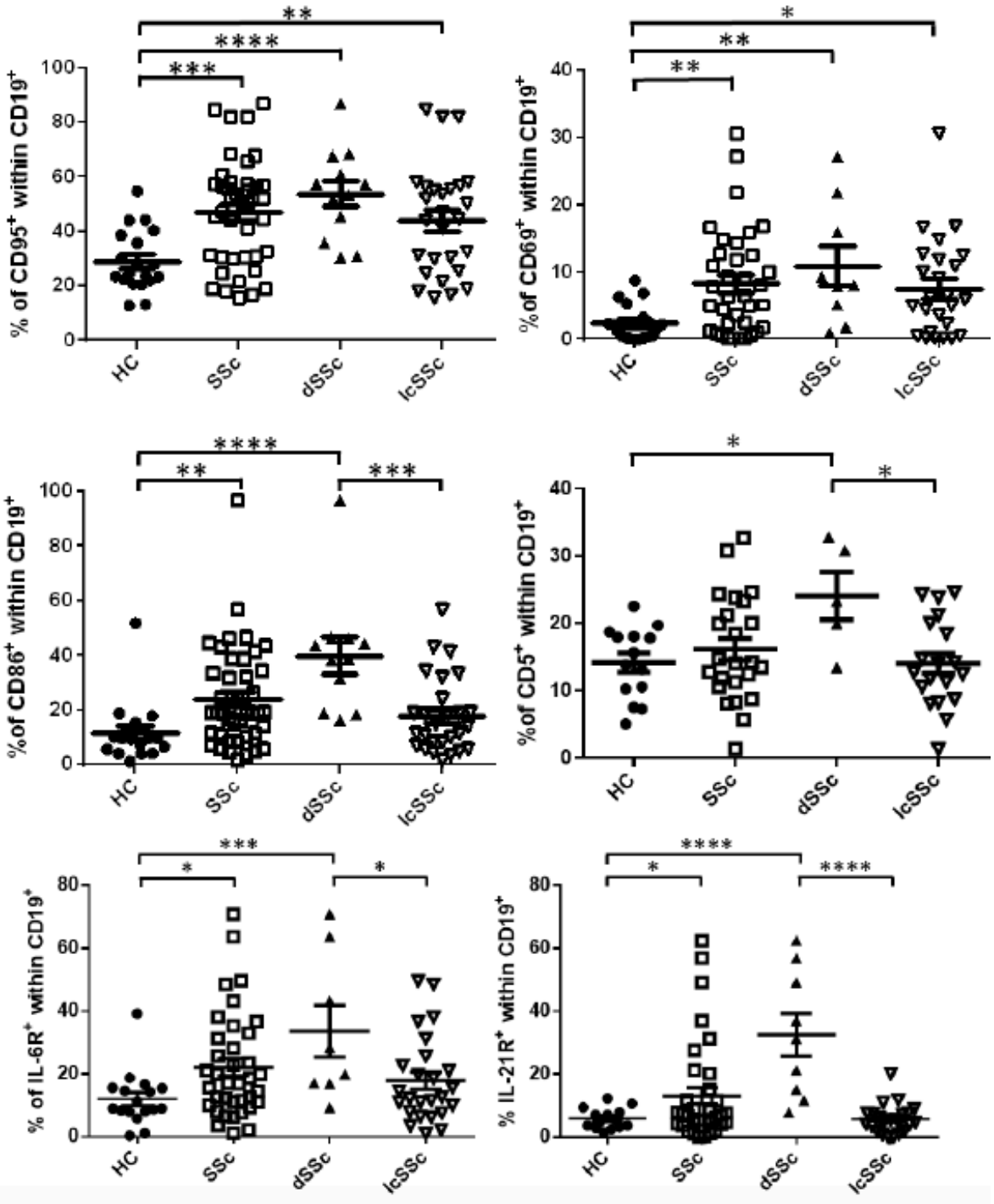




SSc: involvement of B lymphocytes

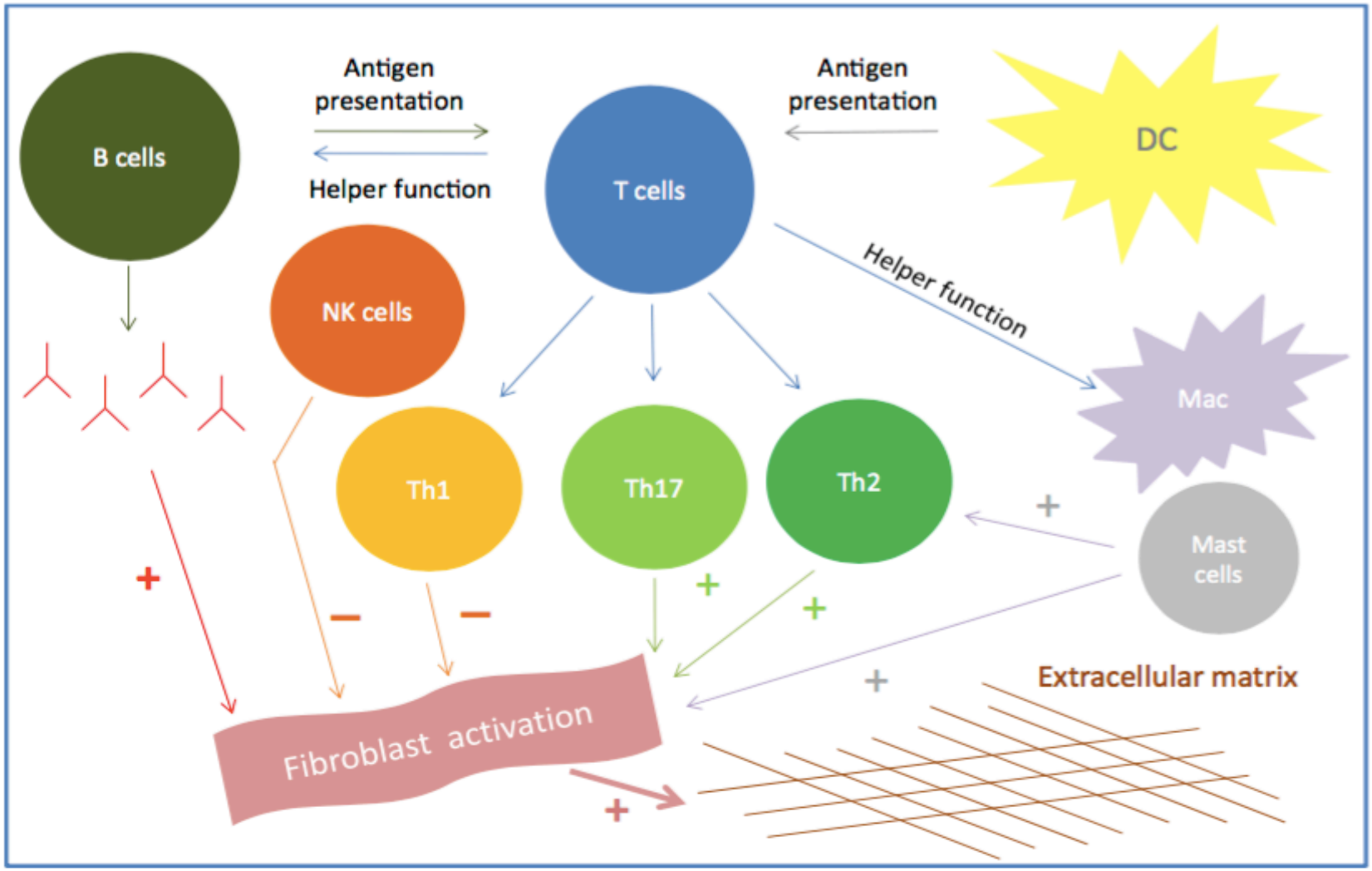
- Abnormal B cell signalling in TSK/+ mice[1]
- Presence of B cells in skin[2] and in lungs from SSc patients[3]
- Increased naive B cells – decreased but activated memory B cells[4]
- Presence of serum autoantibodies and elevated serum levels of cytokines such as IL-6 which correlate with skin fibrosis
- Elevated serum BAFF levels correlate with disease severity[5]
- Preliminary results from pilot studies in SSc patients with rituximab[2,6]

1. Saito *et al., J Clin Invest* 2000;
2. Bosello *et al., Arthritis Res Ther* 2010;
3. Lafyatis *et al., Arthritis Rheum* 2007;
4. Sato *et al., Arthritis Rheum* 2004;
5. Matsushita *et al., Arthritis Rheum* 2006;
6. Lafyatis *et al., Arthritis Rheum* 2009



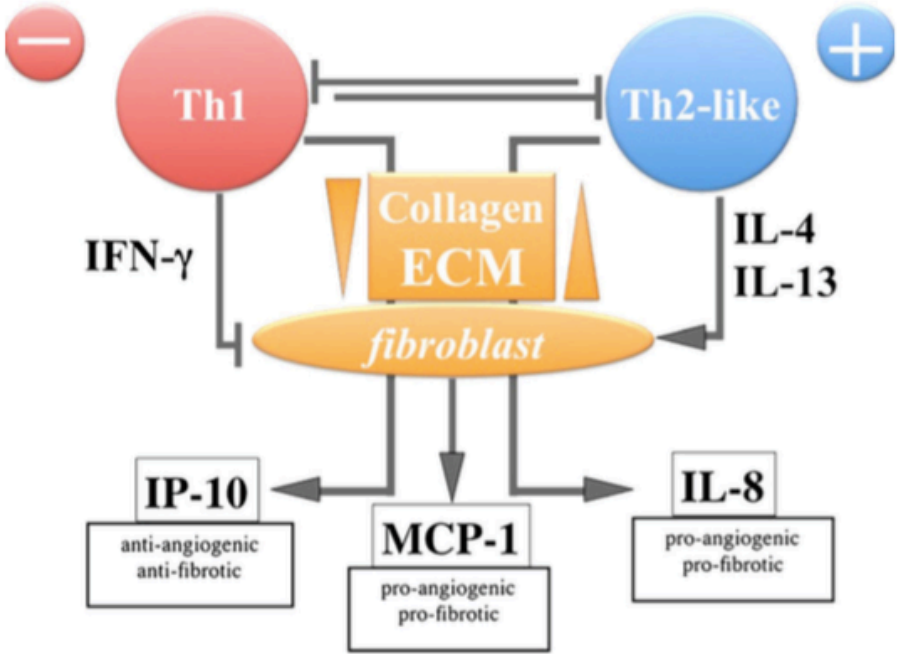
Dumoitier *et al.*, *Arthritis and Rheumatism 2016*

SSc: involvement of T lymphocytes



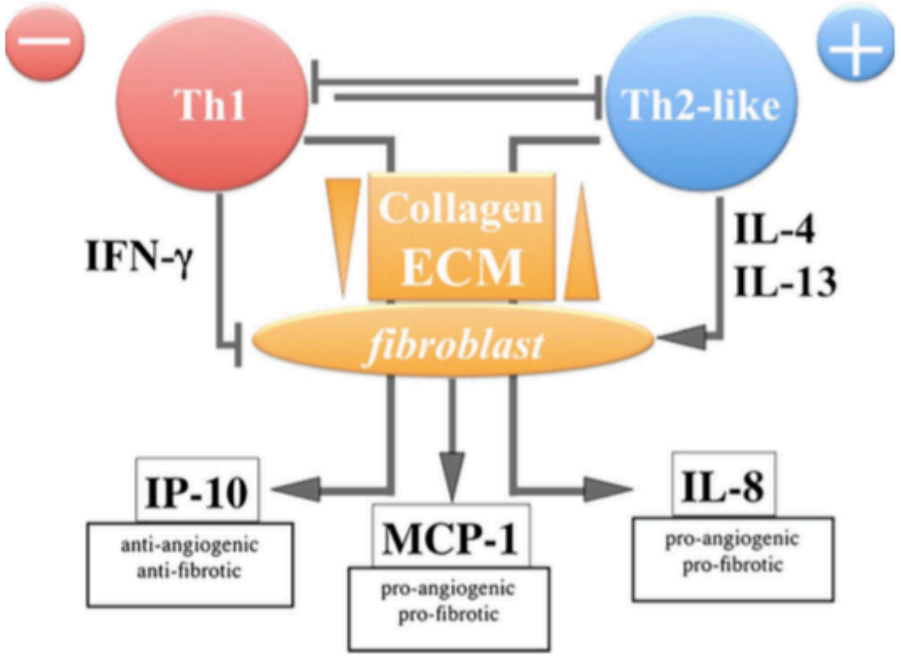
Almeida *et al.*, *CRAI* 2015

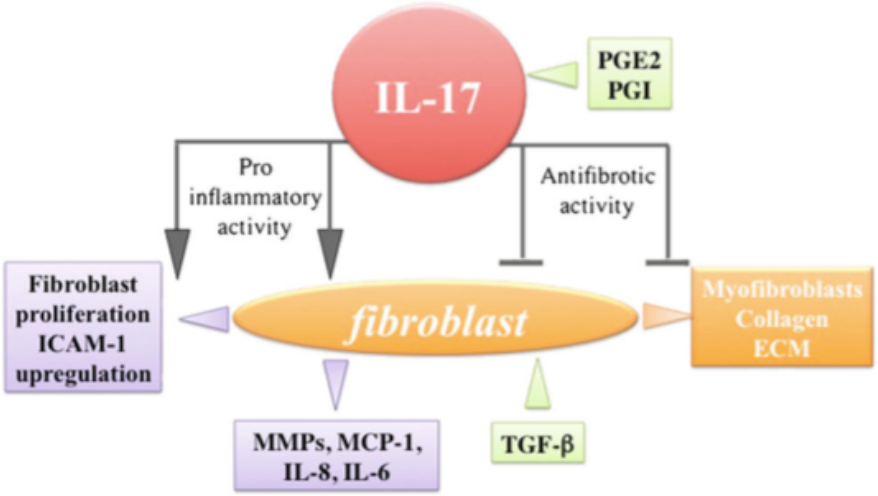
SSc: involvement of T lymphocytes



Chizzolini *et Bouin*, *Semin Immunopathol* 2015

SSc: involvement of T lymphocytes





Chizzolini *et Bouin*, *Semin Immunopathol* 2015

Conclusion

- Beaucoup de progrès dans la physiopathologie de la SSc:
  - Système immunitaire +++
  - Microbiote
  - GWAS
  - Des modèles murins en expansion
- Modèle tri-partite centré sur l'interaction immunité-fibroblastes
- Perspectives:
  - Immunité innée (TLR intégrines cellules mésenchymateuses macrophages)
  - LB et IL-6
  - « Facteurs précoces »
  - Adapter la physiopathologie aux différents phénotypes

Merci pour votre attention!

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