



Rôle physiopathologique des autoanticorps dans la Sclérodermie

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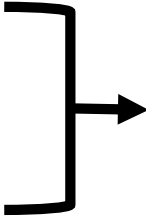
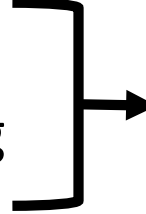
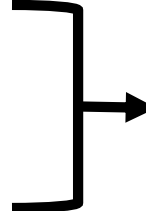
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Conflict of Interest

- Consultant and/or speaker fees from Boehringer Ingelheim, GSK, Astra Zeneca.

Autoantibody (aAb) theoretical functionalities

- Receptor agonist aAb
 - Receptor antagonist aAb
- 
- Affected functions may depend on the cell type(s) expressing the receptor
- aAb directed against structural or functional Ag
- 
- May affect the properties/functions of the targeted Ag
- Immune complex forming aAb
- 
- Will primarily affect the behavior of cells equipped with FcR, particularly FcγR

Cells and aAg recognized by putatively functional aAb in SSc

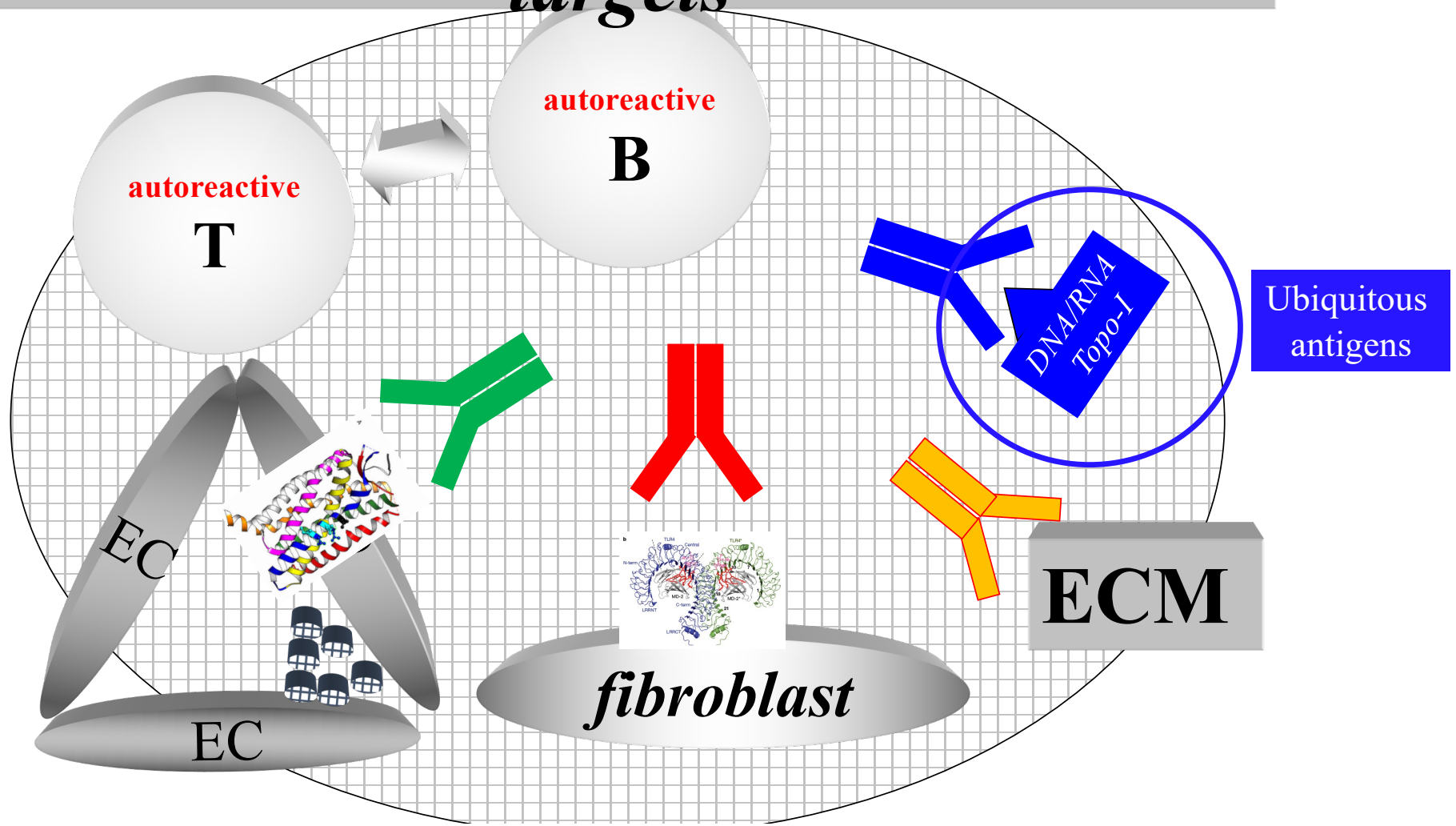
Cell types

- Endothelial cells
- Fibroblasts
- Smooth muscle cells
- Neurons (PNS)
- Lymphocytes
- Monocytes
- Dendritic cells
-

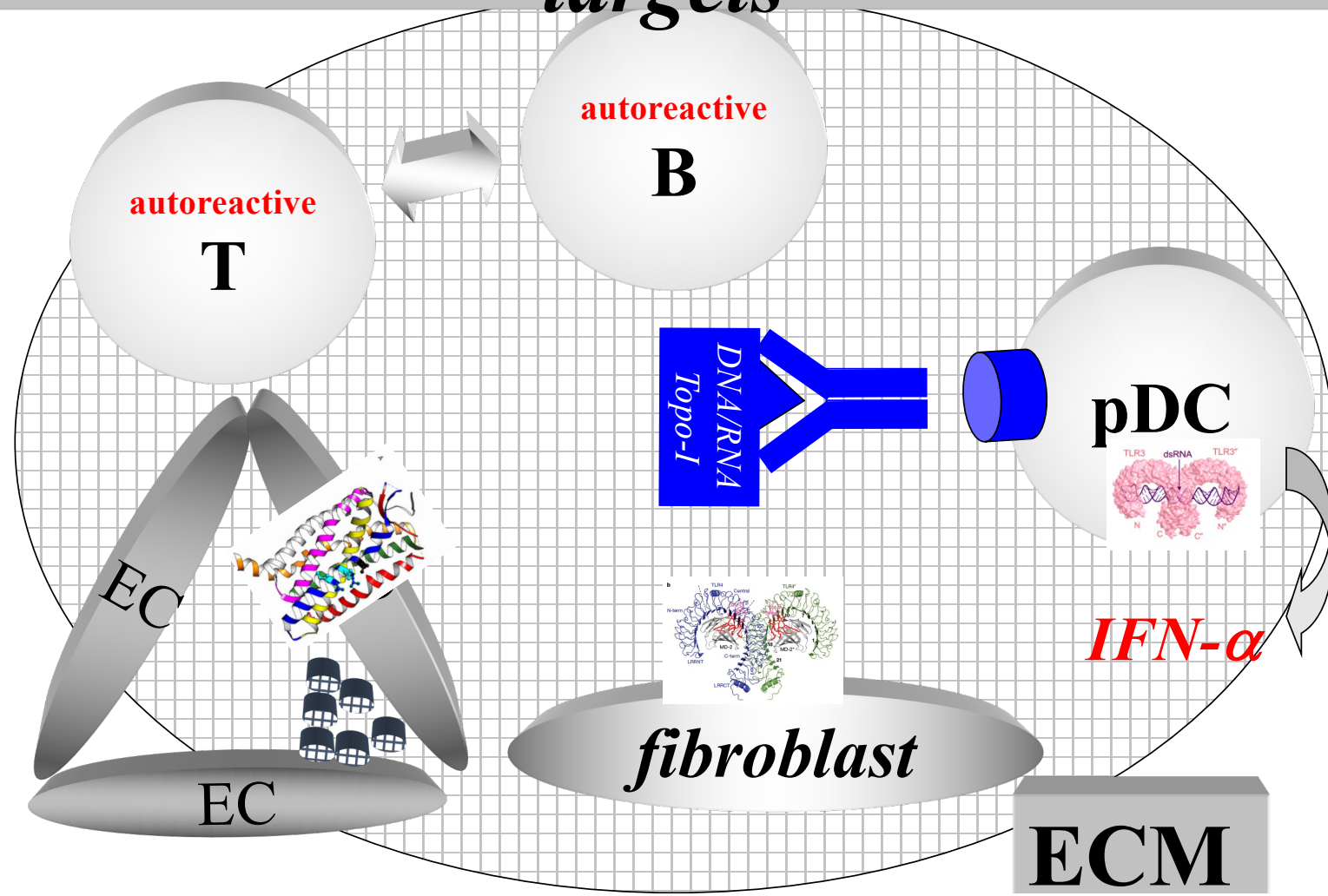
Antigenic structures

- Enzymes
 - MMP1, MMP3
- Fibrillin-1 (ECM)
- Neuronal receptor M3R (Ach)
- R shared by many cell types
 - NAG-2/UL94 (CMV, cross-reactive Ag)
 - AT1R
 - ETAR
 - ICAM
 - TLR4
 - PDGFR β
 - CD22
 - CXCR3, CXCR4
 - Many G-protein coupled receptors (GPCR)
 -

SSc : schematic representation of aAb targets



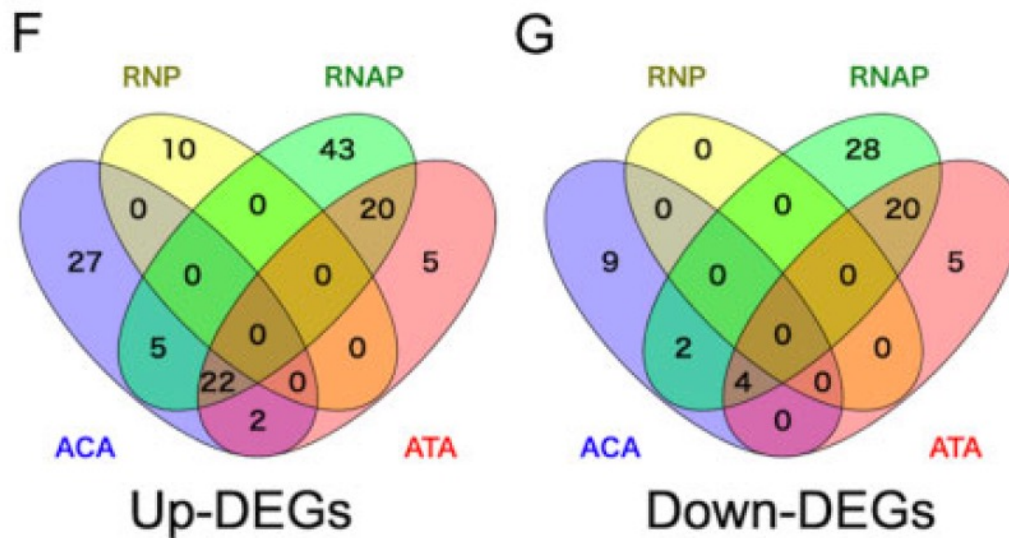
SSc : schematic representation of aAb targets



Association of differentially expressed genes and autoantibody type in patients with systemic sclerosis

Jun Inamo¹ 

Skin gene expression N=63 SSc

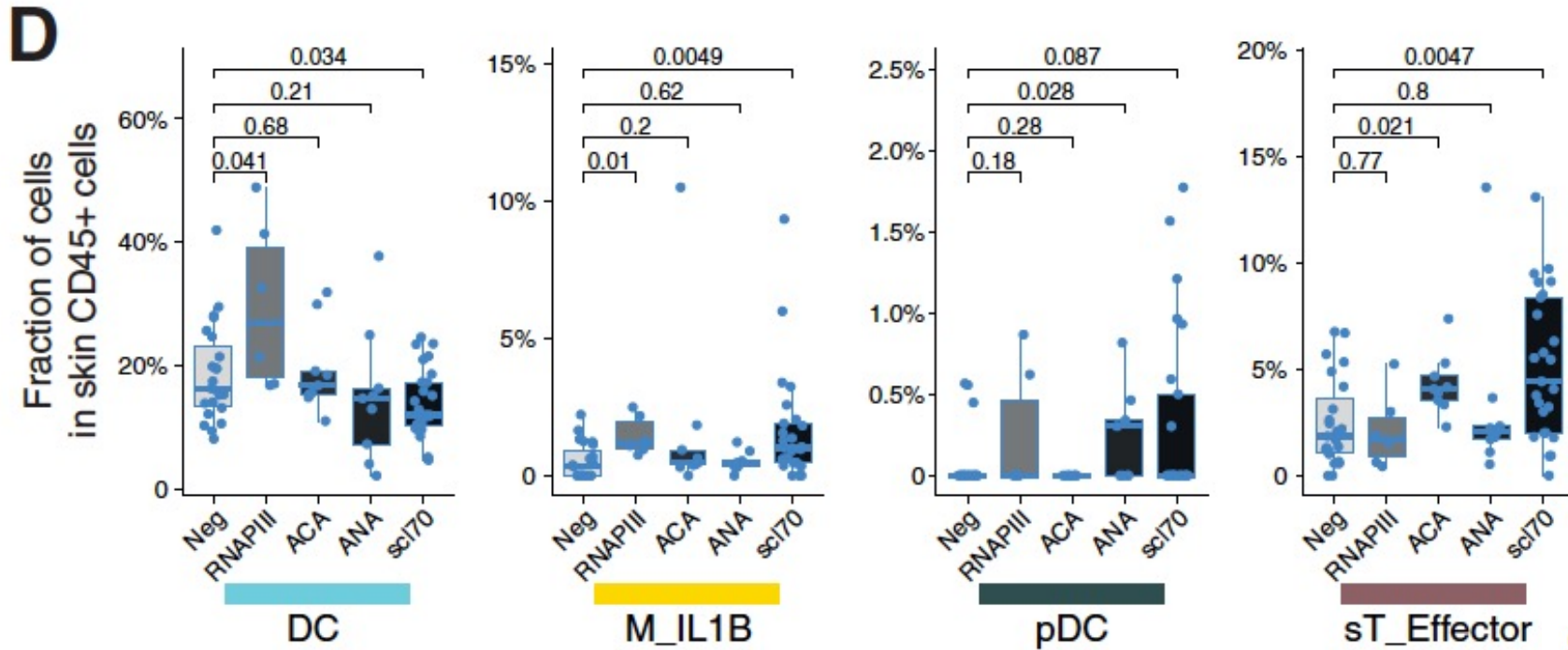
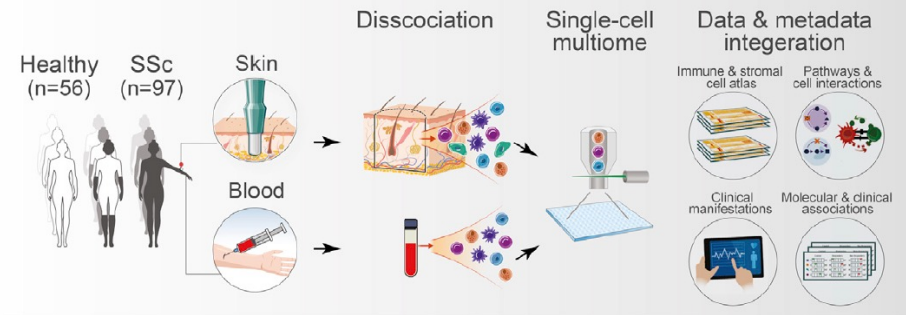


Article

LGR5 expressing skin fibroblasts define a major cellular hub perturbed in scleroderma

Chamutal Gur,^{1,2,14} Shuang-Yin Wang,^{1,14,*} Fadi Sheban,¹ Mor Zada,¹ Baoguo Li,¹ Fadi Kharouf,² Hagit Peleg,² Suhail Amar,² Adam Yalin,¹ Daniel Kirschenbaum,¹ Yolanda Braun-Moscovici,³ Diego Adhemar Jaitin,¹ Tomer meir-salame,⁴ Efrat Hagai,⁴ Bjørt K. Kragesteen,¹ Batia Avni,⁵ Sigal Grisariu,⁵ Chamutal Bornstein,¹ Shir Shlomi-Loubaton,¹ Eyal David,¹ Rony Shreberk-Hassidim,⁶ Vered Molho-Pessach,⁶ Dalit Amar,⁷ Tomer Tzur,⁷ Rottem Kuint,⁸ Moshe Gross,⁹ Oren Barboy,¹ Adi Moshe,¹ Liat Fellus-Alyagor,¹⁰ Dana Hirsch,¹⁰ Yoseph Addadi,¹¹ Shlomit Erenfeld,⁵ Moshe Biton,¹² Tehila Tzemach,² Anat Elazary,² Yaakov Naparstek,² Reut Tzemach,^{1,13} Assaf Weiner,^{1,15} Amir Giladi,^{1,15} Alexandra Balbir-Gurman,^{3,15} and Ido Amit^{1,15,16,17,*}

Molecular dissection of Systemic Sclerosis (SSc)



Three stories

- Antagonistic aAb= anti muscarinic (M3) achetylcholine receptors
- Agonist aAb = anti-PDGF-R
- Agonist aAb = anti G-protein coupled receptors

Ab anti-Muscarinic acetylcholine receptor M3 and their role in the GIT dysfunction in SSc

Antagonistic aAb

- 1963: Peristaltic dysfunction and oesophageal smooth muscle atrophy precedes increased visceral collagen deposition and fibrosis
- 1973: Decreased cholinergic nerve input as a major cause of lower esophageal sphincter incompetence
- 1994: Antimyenteric neuronal antibodies in scleroderma (19/ 41; IFA on rat intestine neurons)
- 1999: **Passive transfer of purified IgG** from an SSc patient with high titers of anti-neuronal antibodies inhibited myenteric electrical activity in rats' intestines



Ab anti-Muscarinic acetylcholine receptor M3 (M3R) and their role in the GIT dysfunction in SSc

- 2002: IgG from 7/9 SSc patients specifically inhibited the response of M3R to carbachol. The presence of these antibodies correlated with the patients' GI dysfunction
- 2003: Anti-idiotypic antibodies neutralize autoantibodies that inhibit cholinergic neurotransmission
- 2009: M3R autoantibody in patients with systemic sclerosis: contribution to **GIT dysmotility** (EIA; 9/14 (64%) with vs 3/62 (5%) w/o symptoms)

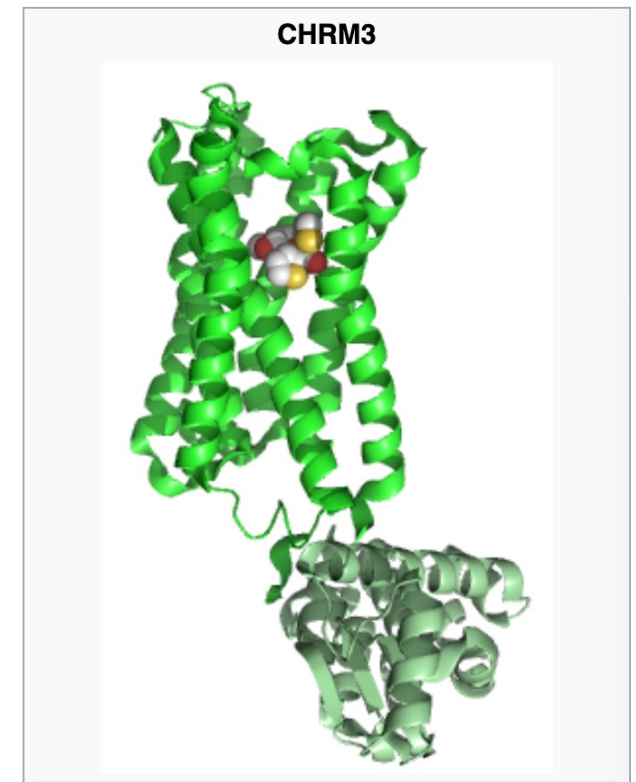
Antagonistic aAb



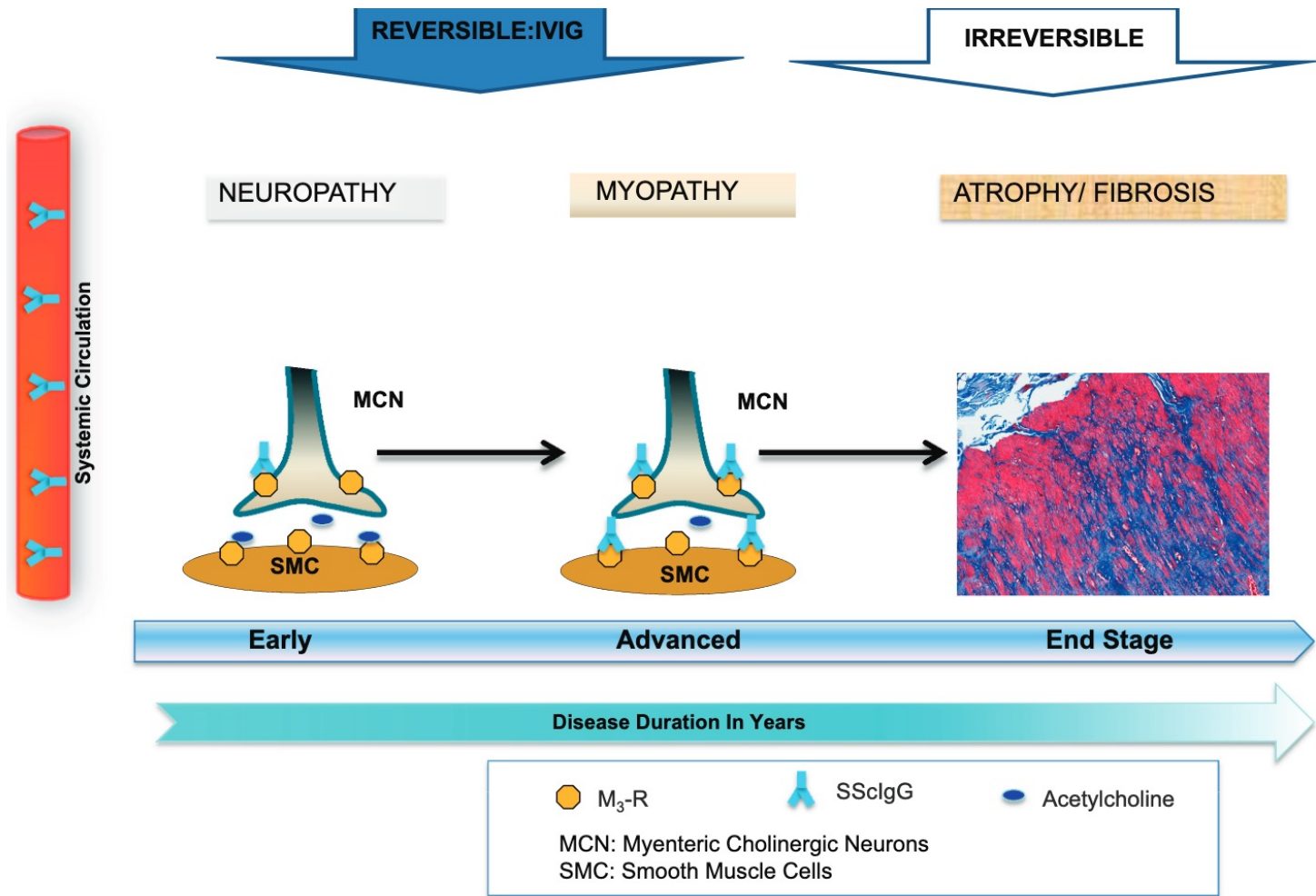
Ab anti-Muscarinic acetylcholine receptor M3 and their role in the GIT dysfunction in SSc

Antagonistic aAb

- 2009^{*}: SSc IgG inhibit the M3R in internal **anal sphincter** smooth muscle cells. (n=7)
- 2012^{*}: Epitope in the second extracellular loop of the M3R (n=6)
- 2014: A novel method for the **detection of functionally active aAb** to M3R. Inhibitory aAb **could not be detected in any of 47 SSc patients**, but were present 42.5% of SS and 14.5% of patients with early onset MG
- 2016^{*}: Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIG (n=10, longitudinal)



Anti AChM3R Ab in SSc GIT dysfunction: Proposed model



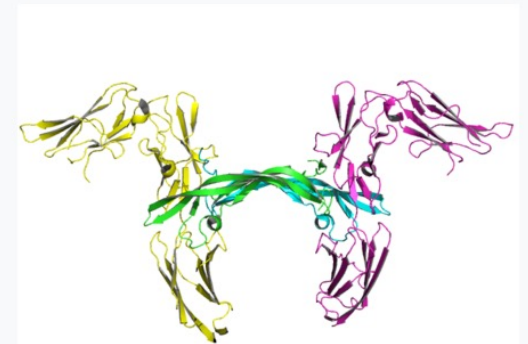
*Kumar S. et al. Am J Physiol Gastrointest Liver Physiol 310: G1052–G1060, 2016

aAb anti-PDGF receptor and their role in SSc

- 2006*: Stimulatory aAb to the PDGFR in SSc (mouse embryonic fibroblasts transfected with PDGFR α), 100% of specificity and sensitivity (SSc=46, HD=75)
- 2008: No differences in levels of PDGFR aAb in SSc patients versus controls as tested by ELISA
- 2009: Lack of evidence of stimulatory aAb to PDGFR (porcine aortic endothelial cells stably expressing human PDGFR α)
- 2009: No difference in stimulatory aAb to PDGFR among SSc and HC (32D mouse cell line transfected with human PDGFR α and PDGFR β)

Agonistic aAb
(with exceptions)

Platelet-derived growth factor receptor

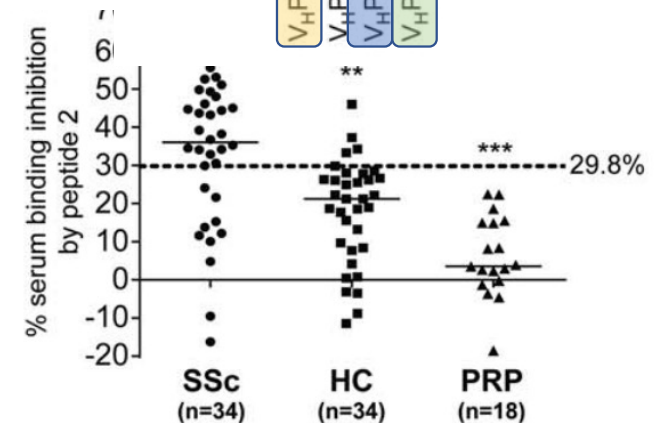
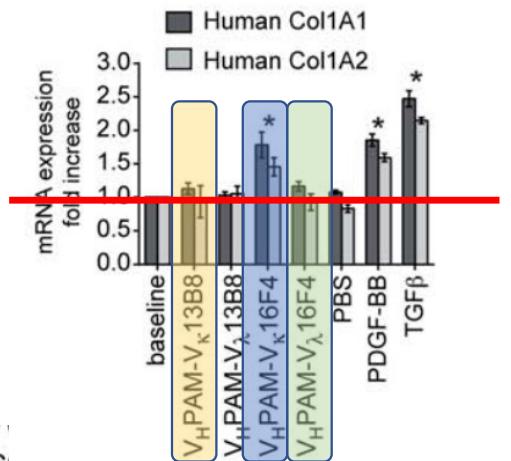
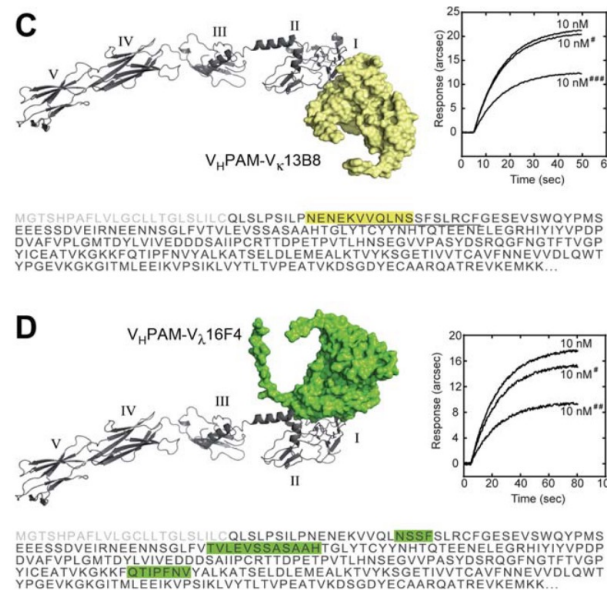
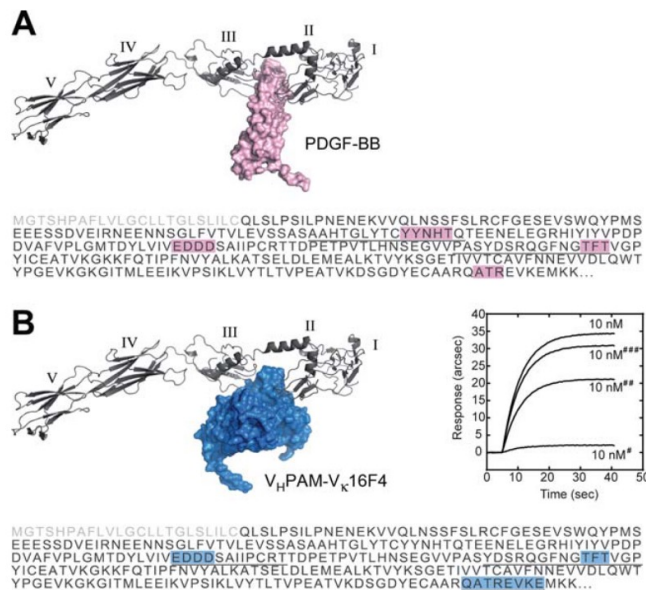


Ribbon image of two molecules of human PDGF receptor beta (yellow and magenta) in complex with dimeric PDGF-B (cyan and green).^[1]

aAb anti-PDGF receptor and their role in SSc

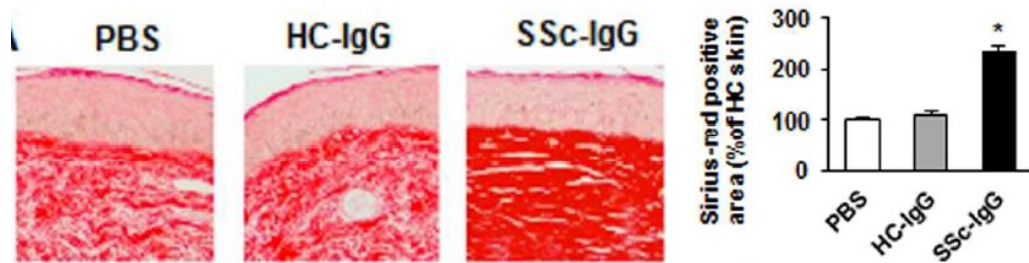
- 2015*: Epitope specificity determines pathogenicity and detectability of aAb PDGFR α (human mAb generated from a single donor)

Agonistic aAb
(detailed analysis)



aAb anti-PDGFR and their role in SSc

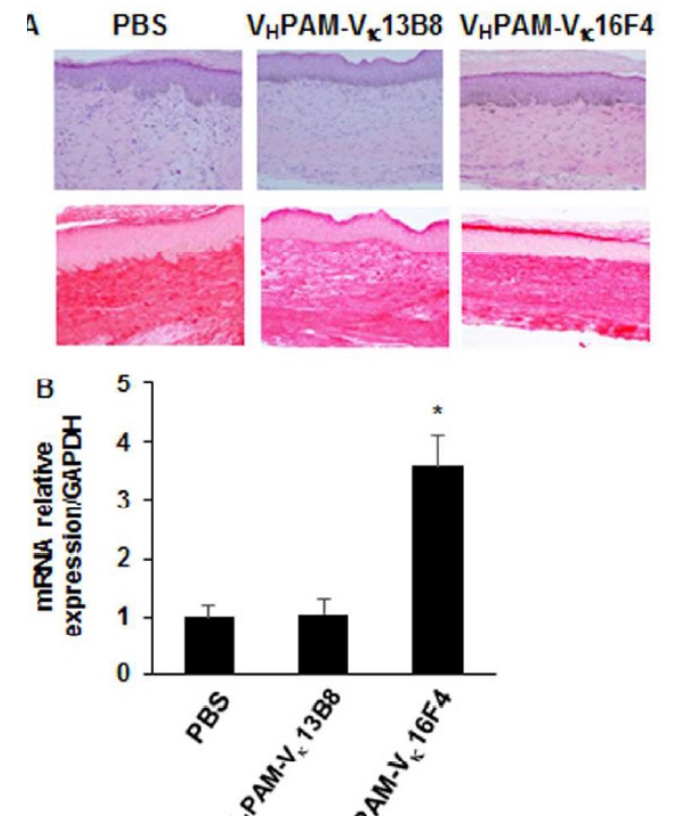
- 2016*: Induction of scleroderma fibrosis in skin-humanized mice by administration of anti-platelet-derived growth factor receptor agonistic autoantibodies.



Skin generated with HD keratinocytes and fibroblasts

Lucchetti MM et al. ARTHRITIS & RHEUMATOLOGY
2016; 68: 2263-73.

Agonistic aAb



aAb anti-PDGF receptor and their role in SSc

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stimulatory Autoantibodies to the PDGF Receptor in Systemic Sclerosis

Silvia Svegliati Baroni, Ph.D., Mariarosaria Santillo, Ph.D., Federica Bevilacqua, M.D., Michele Luchetti, M.D., Tatiana Spadoni, B.Sc., Matteo Mancini, B.Sc., Paolo Fraticelli, M.D., Paola Sambo, M.D., Ada Funaro, Ph.D., Andrius Kazlauskas, Ph.D., Enrico V. Avvedimento, M.D., Ph.D., and Armando Gabrielli, M.D.

N ENGL J MED 354:25 WWW.NEJM.ORG JUNE 22, 2006

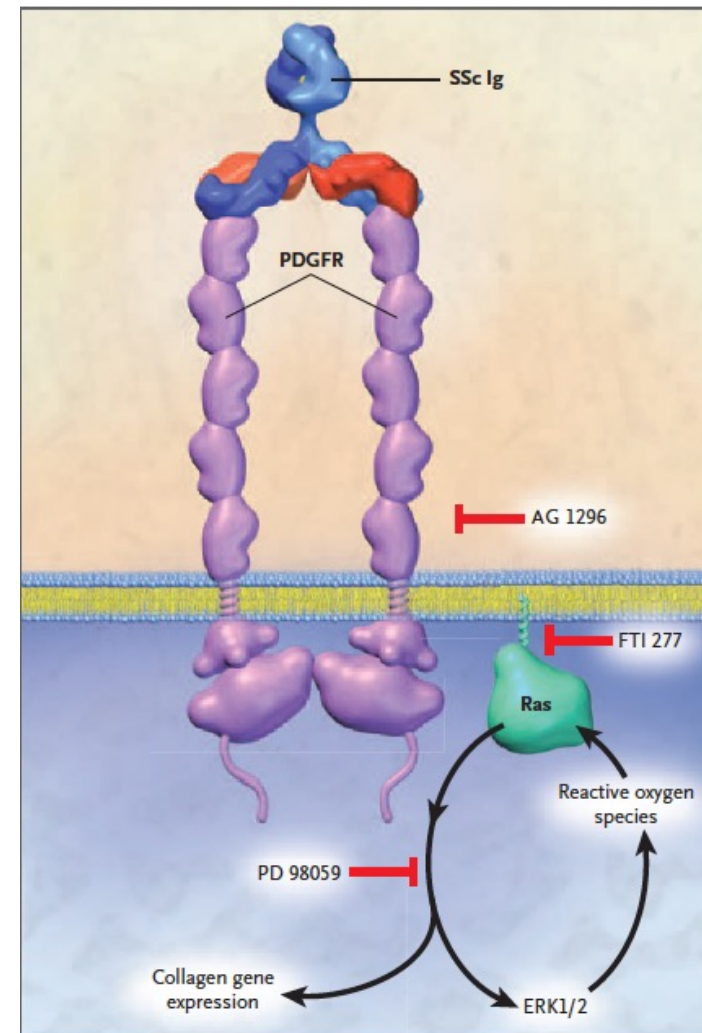
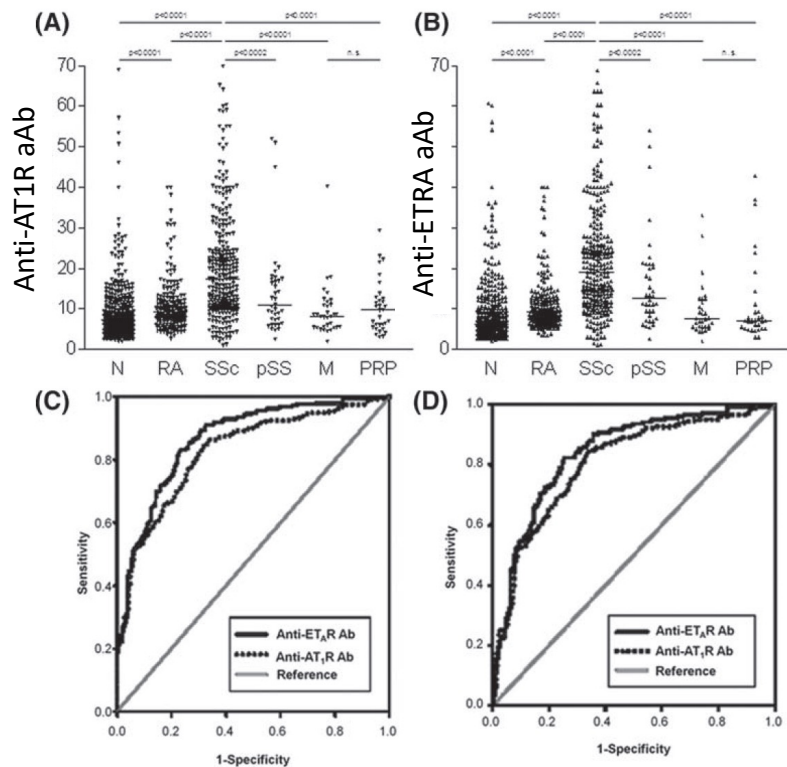


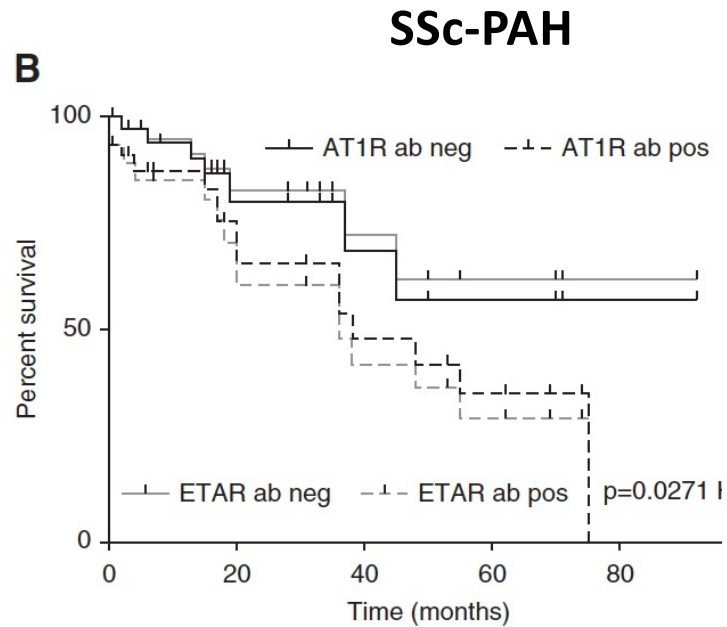
Figure 5. Schematic Diagram of a Possible Cascade Triggered by Sclerodermal Autoantibodies against PDGFR.

The sclerodermal antibodies stimulate PDGFR,¹⁹ which in turn stabilizes Ras and induces ERK1/2. Induction of ERK1/2 increases levels of reactive oxygen species. The long-term persistence of reactive oxygen species and ERK1/2 ultimately results in the stimulation of collagen-gene expression.

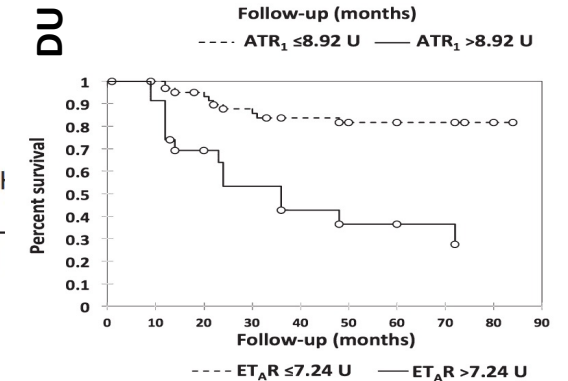
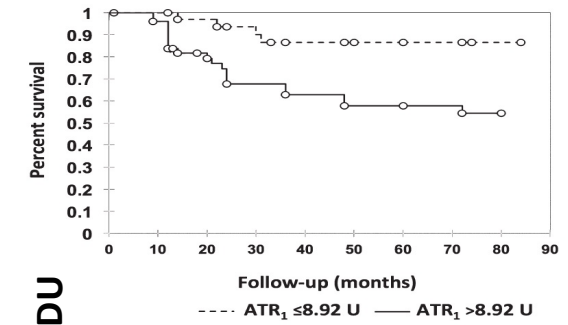
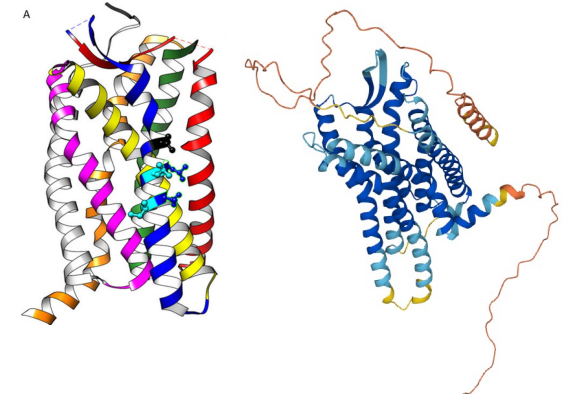
Anti-AT1R & ETRA aAb in SSc



Ann Rheum Dis 2011;70:530–536.
doi:10.1136/ard.2010.135772

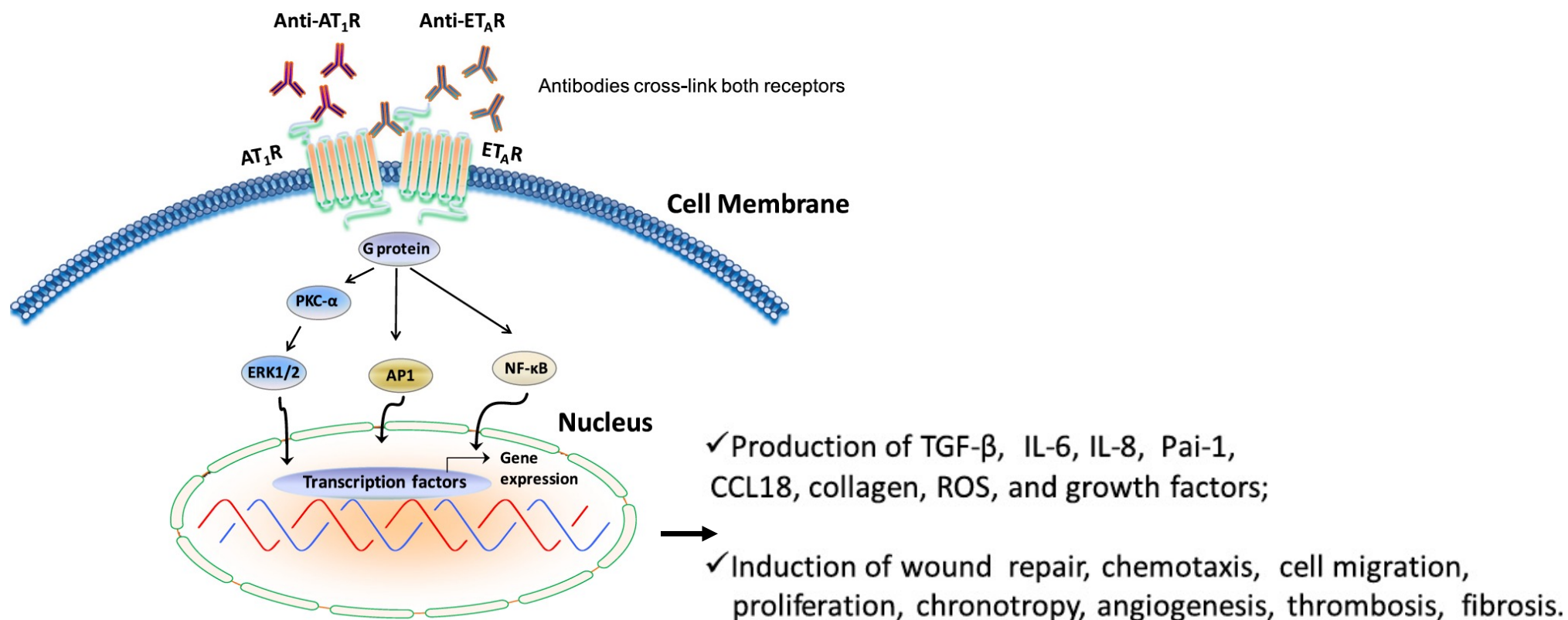


Am J Respir Crit Care Med Vol 190,
pp 808–817, 2014

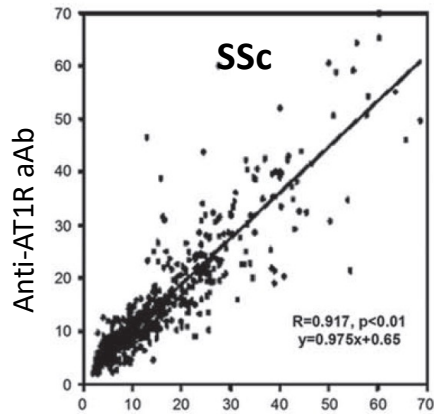


J Rheumatol 2015;42:1801–7
doi:10.3899/jrheum.150061

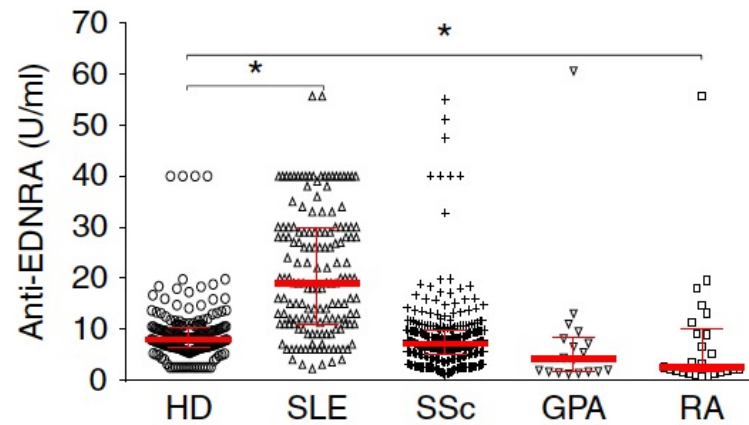
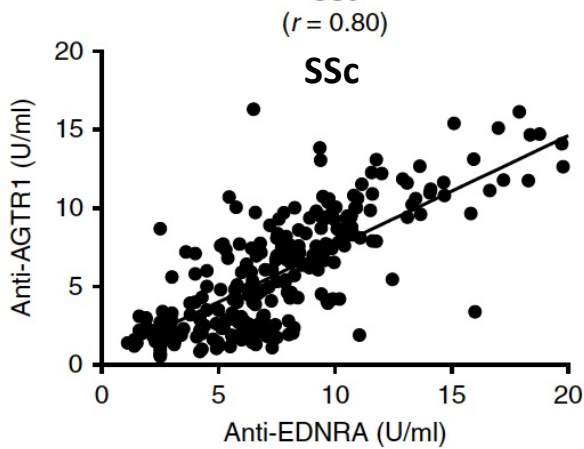
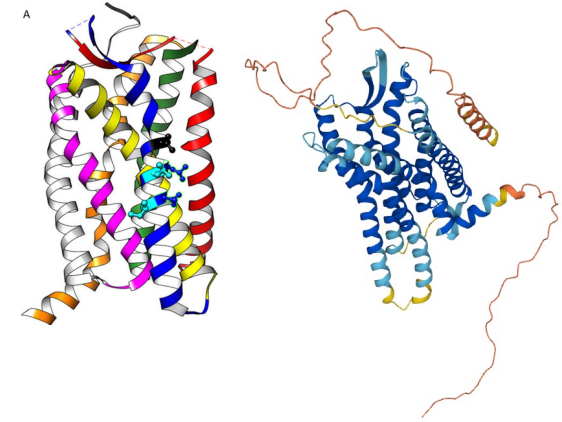
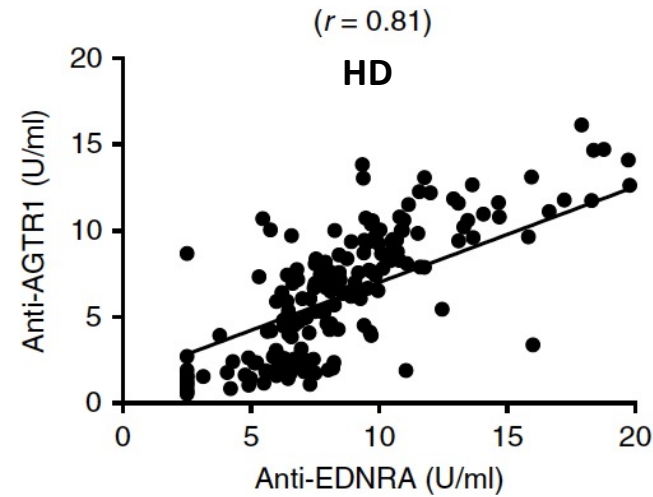
Cellular and systemic events induced by stimulating anti-AT1R and anti-ETAR autoantibodies



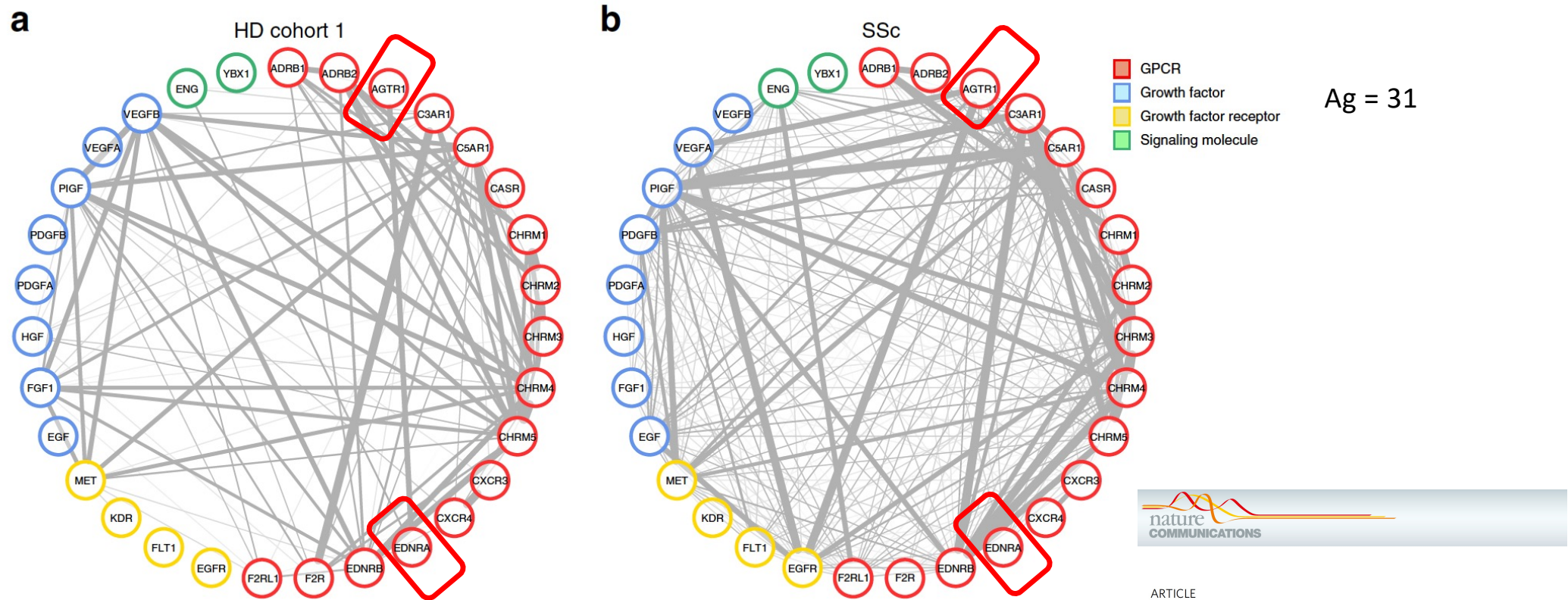
Anti-AT1R & ETRA aAb in HD & SSc



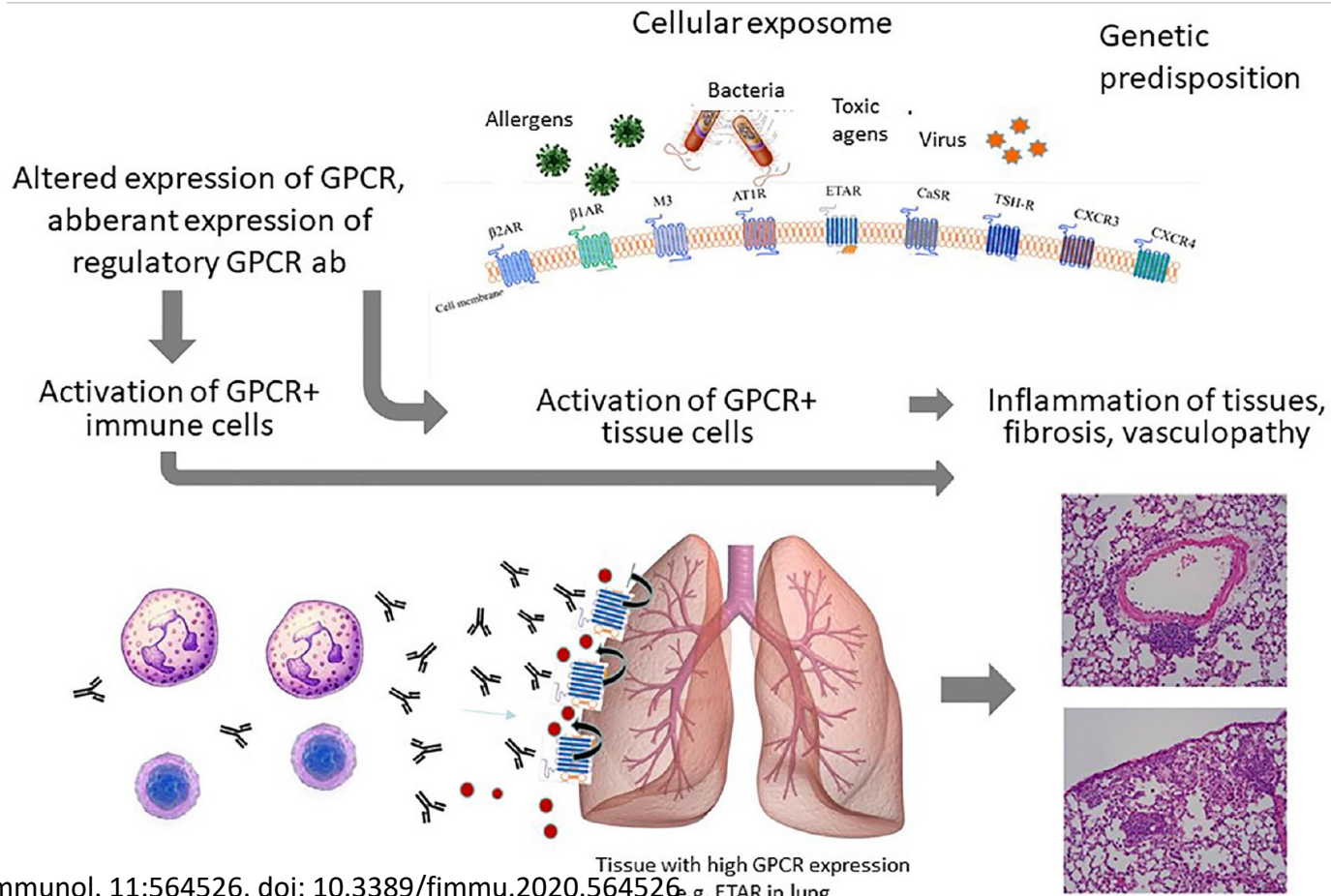
ARD, 2011;70:530–536.



aAb networks distinguish health and disease



The chronic cellular **exposome** leads to an altered GPCR and GPCR aAb signature.



Putative functional pathogenic aAb in SSc: *Take home messages*

- aAb with multiple distinct specificities have been described in SSc
- Distinct functional assays have document aAb specific activities relevant to SSc pathogenesis
- These aAb are often/uniquely studied within a single laboratory
- Lack of standardized and commonly shared assays limit the universal acceptance of the data
- The boundaries between pathogenic aAb and “natural” Ab may be difficult to establish. Dysregulated networks of aAb may better represent their complexity

An abstract painting featuring swirling colors of blue, yellow, orange, and purple. The background is filled with various textures, including brushstrokes and fragments of handwritten text in black ink. The overall composition is dynamic and expressive.

Merci pour l'attention

M3R (Ach) literature

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AT1R, ETRA literature

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Criteria to postulate an autoimmune origin

- ***Passive transfer*** of the disease symptoms or pathology to animals by ***serum*** or ***antibodies*** from ***patients***
- ***Reproduction of cellular damage or dysfunction*** in *ex vivo* models using patients' sera or immunoglobulin
- Development of the essential features of the disease following ***immunization*** of animals with the ***putative target antigen***
- ***Passive transfer*** of the pathology to non-immunized animals with ***antibodies or lymphocytes of immunized animals***

Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today 1993;14:426–30