Παθογένεια Ρευματοειδούς Αρθρίτιδας

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ
ΝΟΣΟΚΟΜΕΙΟ ΗΡΑΚΛΕΙΟΥ

Π. Σιδηρόπουλος
Ρευματολογία, Κλινική Ανοσολογία, Αλλεργιολογία
Ιατρική Σχολή, Παν. Κρήτης
www.rheumatology-uoc.gr
sidiropp@uoc.gr

ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

References

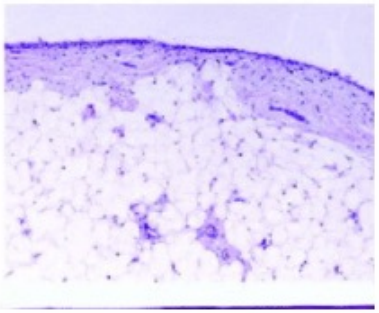
- Nat Immunol. 2021 Jan;22(1):10-18
- Sci Transl Med. 2016 Mar 23;8(331):331ra38
- Immunity. 2016, 45, 903–916
- Cell Metabolism. 2019, 30, 1–16
- Nat Immunol. 2019 Jul;20(7):928-942
- Nat Rev Immunol. 2017 Jan;17(1):60-75.

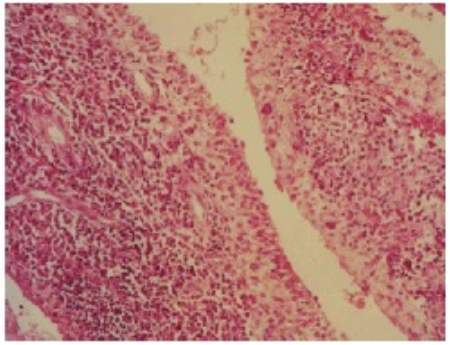
Outline

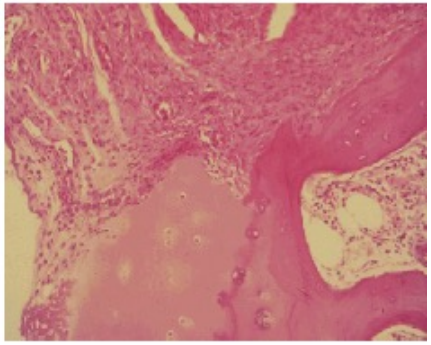
- Autoimmunity development in RA
  - Genes
  - Environment
  - Autoimmunity
  - Citrullination
- Synovial targeting
  - CD4
  - Fibroblasts
  - Macrophages/monocytes

Rheumatoid arthritis target tissue of inflammation: Synovium

Normal





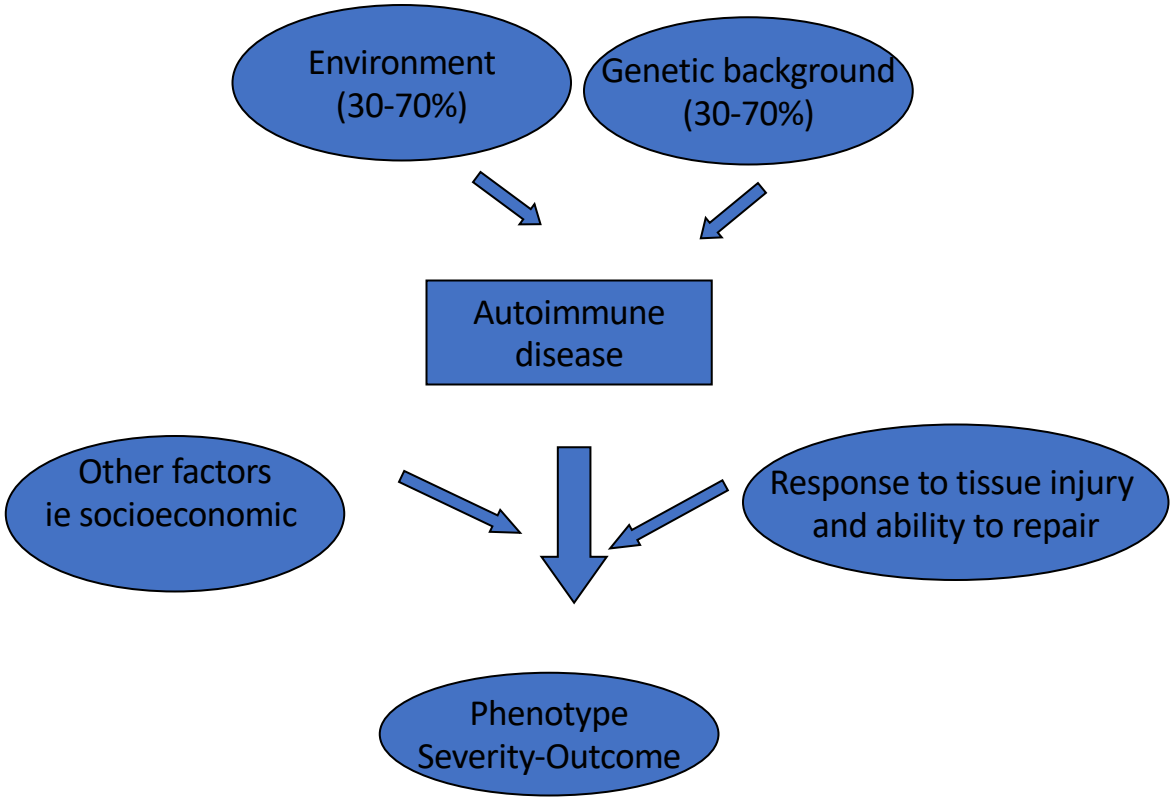


Pathophysiological process:

Tissue hyperplasia
Inflammatory cell infiltration
Angiogenesis
Bone distruction

The cause of autoimmune disease is generally unknown.

Tissue damage pathogenesis is complex but rather well characterized

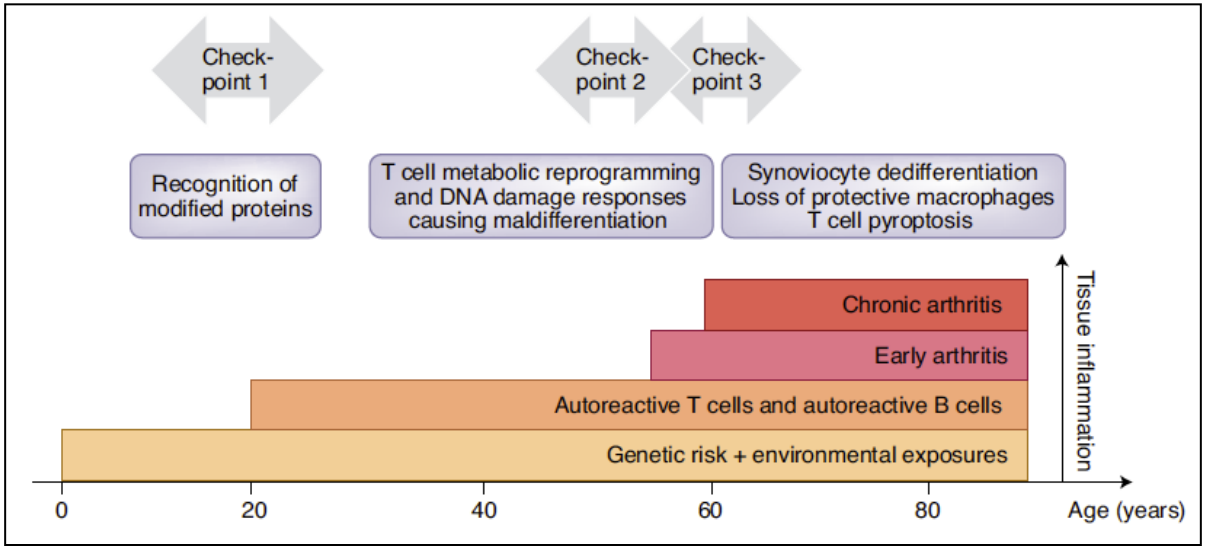


General concept for RA pathogenesis

"RA is an almost lifelong process in with distinct phases:

- ✓ **disease risk:** genetically predisposed individuals lose self-tolerance, produce autoantibodies.
- ✓ **asymptomatic autoimmunity:** characterized by prototypic autoantibodies reactive against post-translationally modified proteins, often citrullinated antigens.
- ✓ **symptomatic synovitis:** Acute joint inflammation transitions

into chronic, destructive synovitis. Tissue responds with a maladaptive wound healing response (pannus), which by itself has destructive features and will lead to irreversible tissue injury"



Nat Immunol. 2021 Jan;22(1):10-18

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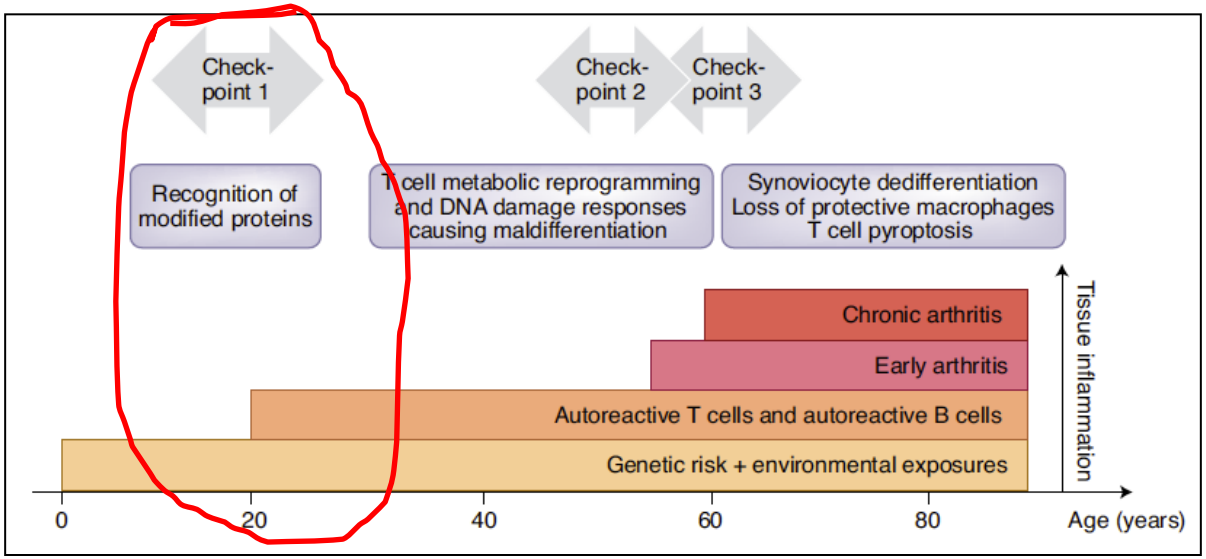
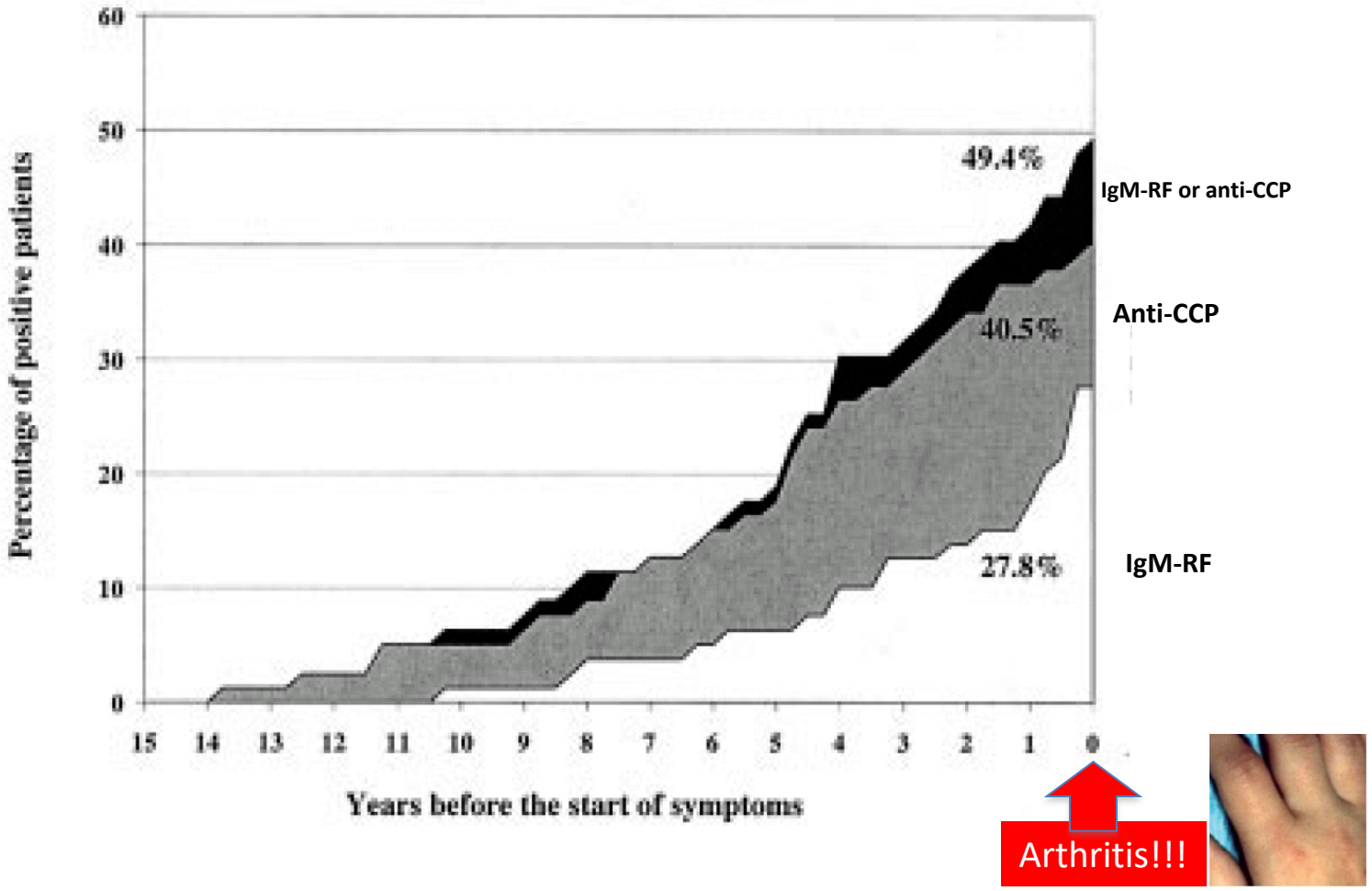


Nat Immunol. 2021 Jan;22(1):10-18

Autoimmunity in RA starts long before symptoms:

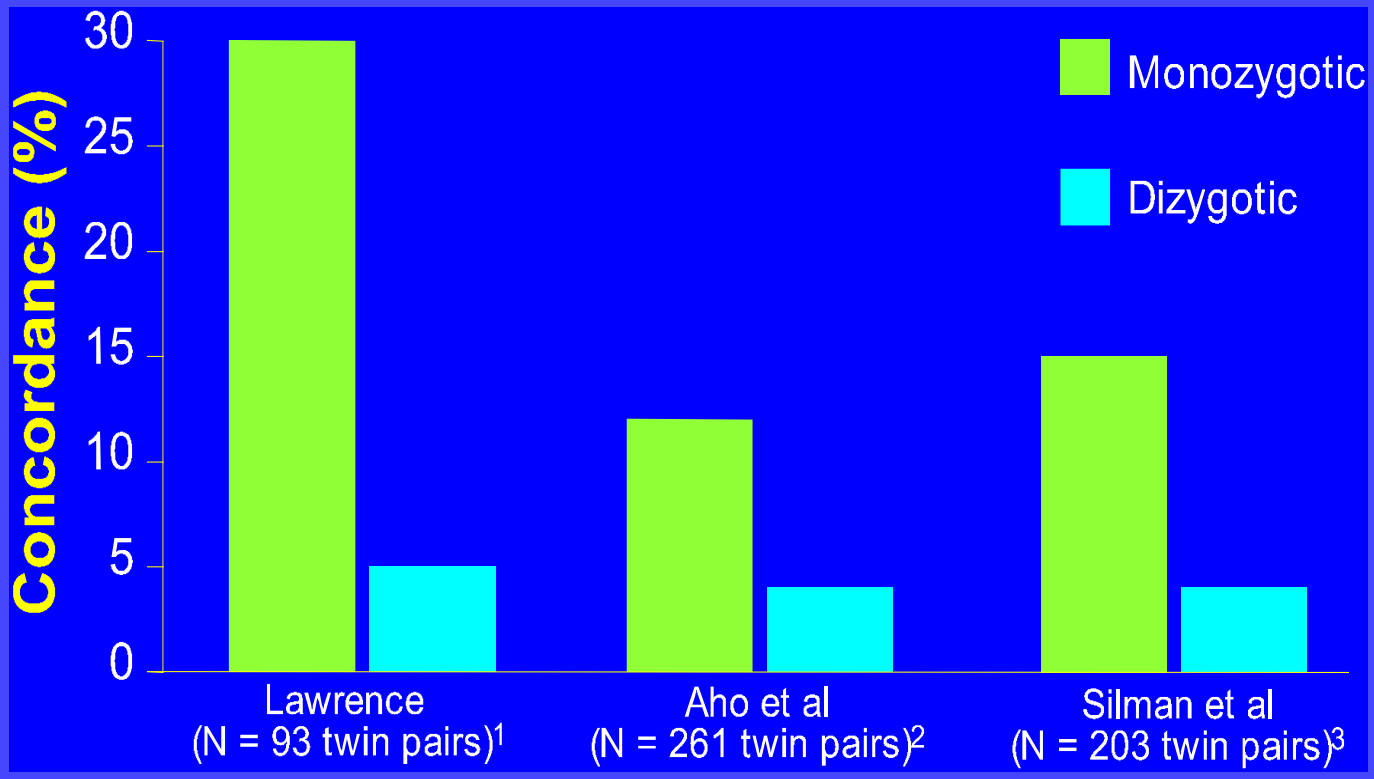
ACPA (anti citrullinated peptide antibodies) and RFs (Rheumatoid factors) decades before symptoms



Nielen M et al, A&R50; 2004, 380

Twin Studies in Rheumatoid Arthritis:

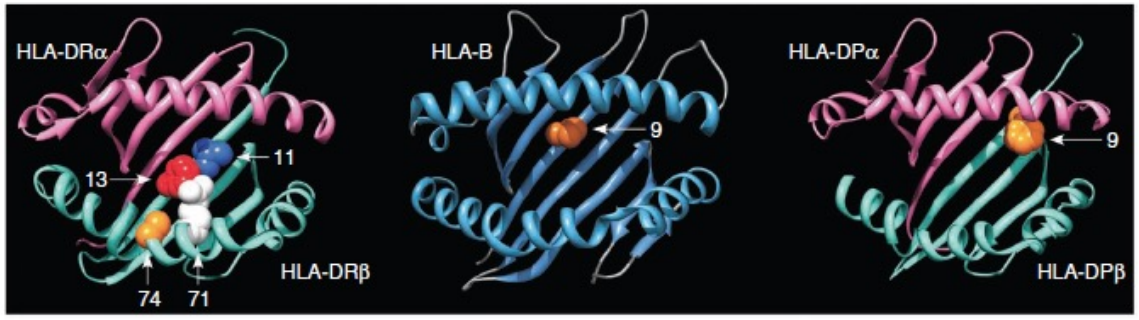
Increased incidence in twins and in families with affected members



1. Lawrence JS. *Ann Rheum Dis.* 1970;28:357-379.
2. Aho K et al. *J Rheumatol.* 1986;13:899-902.
3. Silman AJ et al. *Br J Rheumatol.* 1993;32:903-907.

Genetic risk for RA:
Major contribution of HLA-DR

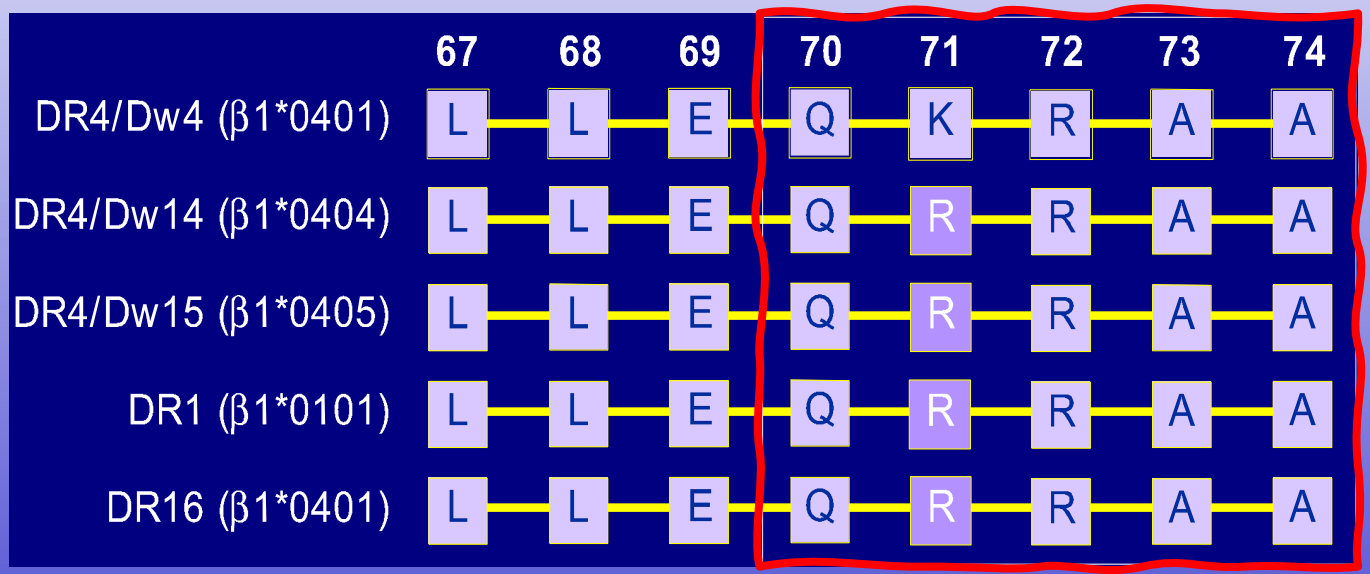
- Studies in twins ➔genetic contribution to RA accounts **for ~60%** of the variation in liability to disease.
- The most important genetic risk : class **MHC class II** region (HLA-DR).
- MHC contribute **18–37%** of the total genetic susceptibility to RA, increasing disease liability **4–6-fold**.
- For **ACPA +ve RA: HLA-DRβ1** and two additional amino acid positions in **HLA-B** and **HLA-DP** in conferring risk to anti-CCP–positive rheumatoid arthritis.
  - These variants account for **12.7%** of the phenotypic variance of seropositive RA risk
  - common validated alleles outside the MHC explain **~4%** of this variance



Nat Rev Rheumatol. 2012 Oct;8(10):573-86
Nat Genet. 2012 Jan 29;44(3):291-6

Shared Epitope Hypothesis

Alleles Associated with Rheumatoid Arthritis



Lipsky PE. In: *Harrison's Principles of Internal Medicine.* 1994:1648-1655.

Shared epitope hypothesis

All *HLADRB1* alleles associated with RA risk encode a conserved sequence of 5 amino acids (positions 70–74) that surrounds the **peptide-binding pocket** of the antigen-presenting molecule.

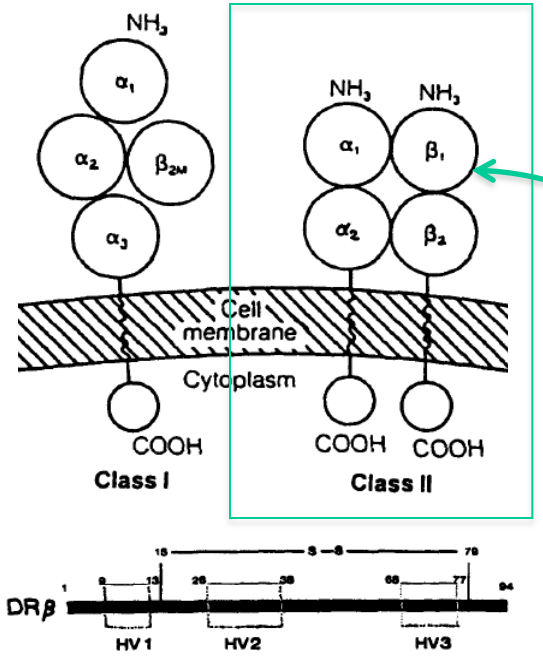


Figure 2. Top, Schematic diagram comparing the structural features of class II molecules at the cell surface with those of class I molecules. Bottom, The first domain, which contains regions of variability that alternate with invariant regions.

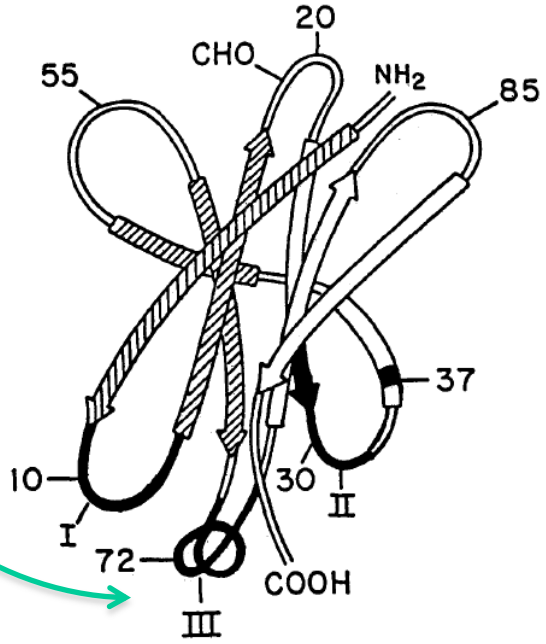


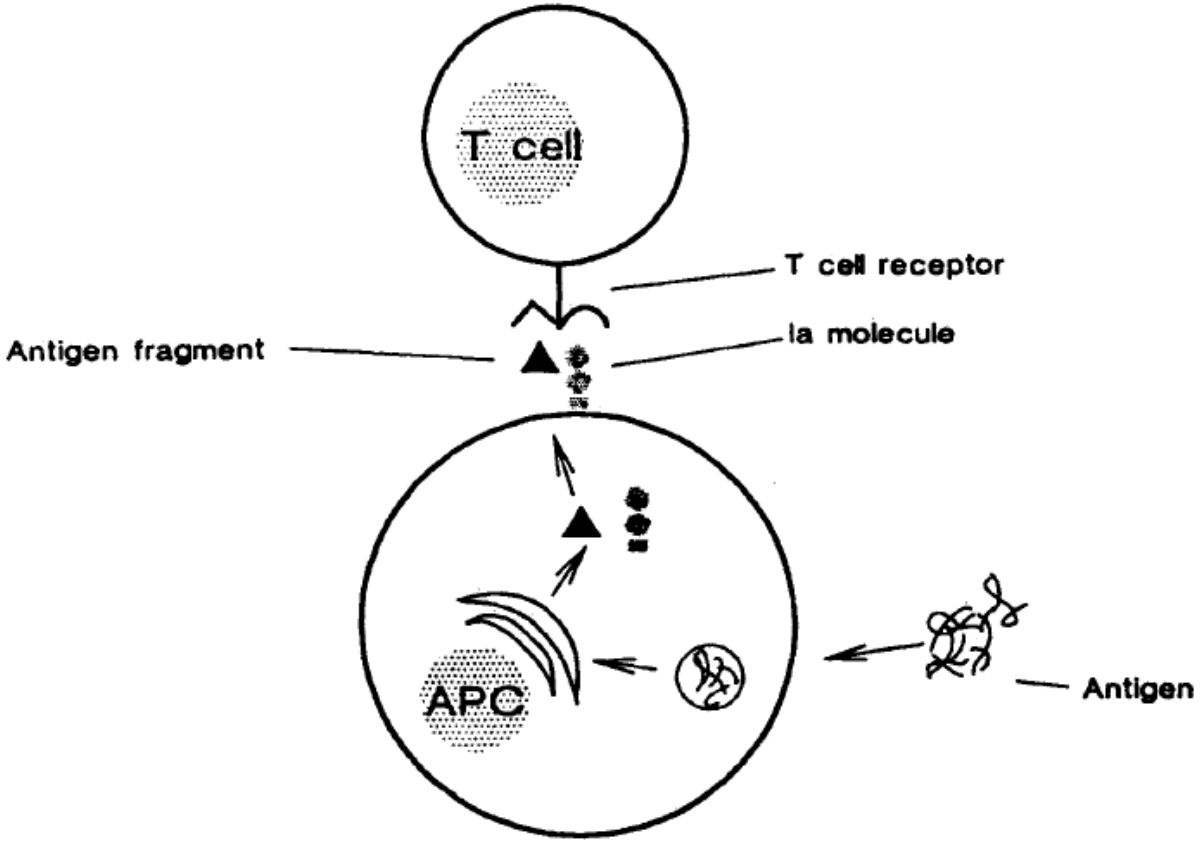
Figure 4. The predicted 3-dimensional structure of a class II β chain. Note that the third hypervariable region around position 70 is predicted to contain a region of α helical structure. It is this region which differs among the DR4 subtypes. Adapted from the *Scandinavian Journal of Immunology* (Norcross and Kanehisa [4]), copyright 1985, and used with the permission of Blackwell Scientific Publications.

Arthritis and Rheumatism, 1987, Vol. 30, No. 11

Shared epitope hypothesis

The presence of this shared epitope suggests that the molecules containing it might:

- ✓ bind the **same antigen**, induce altered T-cell–antigen presenting cell interactions,
- ✓ and/or shape the T-cell repertoire participating in broader adaptive immune responses.



Arthritis and Rheumatism, 1987, Vol. 30, No. 11

RA related Genes ➔ autoimmunity

Τα HLA-DRB1 αλληλόμορφα σχετίζονται ΜΟΝΟ με ACPA θετική νόσο!

Genetic association to autoimmunity

Shared Epitope alleles (HLA-DRB1) are associated with development of anti-CCP (and RFs) antibodies and thus only to seropositive

Table 1. Distribution of SE and anti-CCP positivity*

		Dutch EAC RA patients			
		Anti-CCP positive (n = 195)		Anti-CCP negative (n = 213)	
SE	Dutch controls (n = 423), no. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
+/+	26 (6)	49 (25)	11.79 (6.58–21.13)	16 (8)	1.38 (0.71–2.67)
+/−	153 (36)	107 (55)	4.37 (2.88–6.65)	88 (41)	1.29 (0.91–1.82)
−/−	244 (58)	39 (20)	1.0	109 (51)	1.0

* The following alleles were classified as shared epitope (SE) positive: DRB1*0101, *0102, *0104, *0401, *0404, *0405, *0408, *0413, *0416, *1001, and *1402 (4). EAC = Early Arthritis Clinic; RA = rheumatoid arthritis; CCP = cyclic citrullinated peptide; OR = odds ratio; 95% CI = 95% confidence interval.

AR, Vol. 52, No. 11, 2005, pp 3433–3438

Mechanism of the shared epitope / ACPA-association:

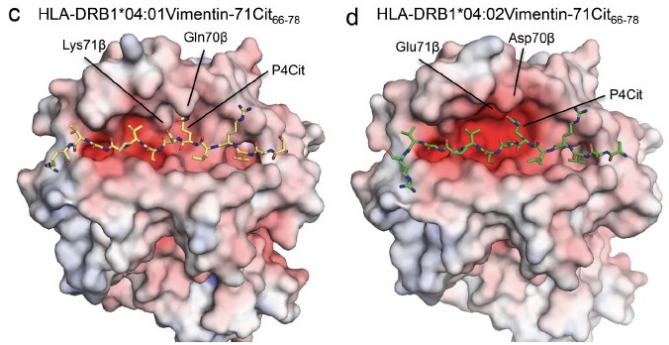
DR-B1 alleles bind more avidly citrulline-containing peptides

- It is partly attributable to the finding **that citrulline-containing peptides bind more avidly than unmodified molecules to the binding pocket of DRB1** molecules that contain the epitope, with subsequent activation of CD4+ T cells.

J. Immunol. 171, 538–541 (2003).

- The shared epitope also seems to function as an **immunostimulatory** ligand that polarizes T-cell differentiation towards type 17 T helper (TH17) cells, which are associated with autoimmunity.

J. Immunol. 185, 1927–1934 (2010).



J. Exp. Med. 2013 Vol. 210 No. 12 2569

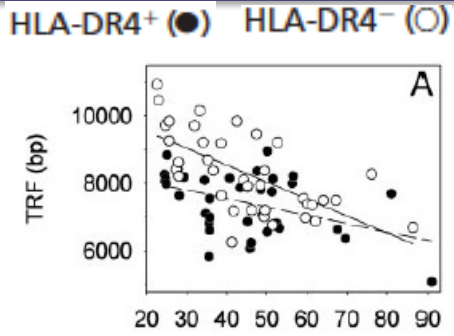
Genes ➔ T cell function: HLA-DR4+ & T cell dysfunction

HLA-DRB1 alleles are associated to T-cell senescence

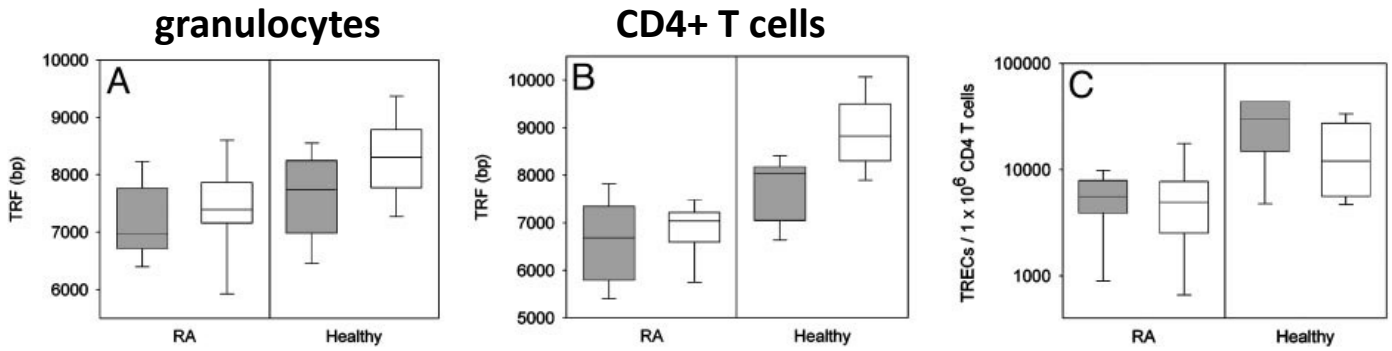
Premature telomeric loss in rheumatoid arthritis is genetically determined and involves both myeloid and lymphoid cell lineages

Stefan O. Schönland[†], Consuelo Lopez[†‡], Thomas Widmann[†‡], Julia Zimmer[†], Ewa Bryl[†], Jörg J. Goronzy[†§], and Cornelia M. Weyand[†§¶]

HLA-DR4 Affects Telomeric Length in CD4 T Cells



Premature telomeric erosion in lymphocytes and granulocytes and decreased frequencies of TREC T cells in patients with RA.



HLA-DR4- (white) and HLA-DR4+ (gray)

PNAS 2003 Nov 11;100(23):13471-6.

RA - Genetic susceptibility of non-HLA genes

MHC: makes up 12.7% of total genetic variance

Non-MHC: makes up ~4% of total genetic variance

Table 1. Candidate Genes with Single-Nucleotide Polymorphisms (SNPs) Linked to Rheumatoid Arthritis and Their Potential Function in Pathogenesis.*

Candidate Gene and Pathway	SNP Locus	Function Relevant to Pathogenesis
T-cell activation		
HLA-DRB1†	6p21	HLA DRB1 allele (also known as the shared epitope) involved in MHC molecule–based antigen presentation and responsible for self-peptide selection and T-cell repertoire; first discovered and still by far the strongest genetic link to rheumatoid arthritis
PTPN22	1p13.2	Lymphocyte-specific nonreceptor tyrosine phosphatase involved in regulation of activation threshold of lymphocytes; second genetic link described in rheumatoid arthritis
AFF3	2q11.2	Transcription factor for lymphoid development
CD28	2q33.2	Costimulatory molecule for T-cell activation
CD40	20q13.12	Costimulatory molecule that enhances interactions between T and B cells and increases auto-antibody production
CTLA4	2q33.2	Costimulation suppressor that regulates interactions between T cells and antigen-presenting cells
IL2RA	10p15.1	High-affinity receptor for interleukin-2 on lymphocyte subsets
IL2	4q27	Cytokine that regulates activation of T cells, particularly regulatory T cells
IL-21	4q27	Cytokine that regulates differentiation of T cells, particularly Th17, and activation of B cells
PRKCQ	10p15.1	Member of the protein kinase C family that regulates T-cell and macrophage activation
STAT4	2q32.3	Transducer of cytokine signals that regulate proliferation, survival, and differentiation of lymphocytes
TAGAP	6q25.3	Rho-GTPase enzyme involved in T-cell activation

N Engl J Med 2011;365:2205

RA - Genetic susceptibility of non-HLA genes

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Candidate Gene and Pathway	SNP Locus	Function Relevant to Pathogenesis
NF-κB pathway		
REL	2p16.1	Proto-oncogene member of the NF-κB family that regulates leukocyte activation and survival
TNFAIP3	6q23.3	Signaling protein and negative regulator of TNF-α–induced NF-κB activation
TRAF1	9q33.1	Regulator of TNF-α–receptor superfamily signaling (e.g., to NF-κB and JNK)
Other pathways		
BLK	8p23.1	B-lymphoid tyrosine kinase involved in B-cell receptor signaling and B-cell development
CCL21	9q13.3	Chemokine implicated in germinal-center formation
FCGR2A	1q23.2	Low-affinity IgG Fc receptor that regulates macrophage and neutrophil activation and immune-complex clearance
PADI4	1p36.2	Enzyme that converts arginine to citrulline, creating autoantigens in rheumatoid arthritis
PRDM1	6q21	Protein that acts as a repressor of β-interferon gene expression
TNFRSF14	1p36.32	TNF-α–receptor superfamily member with proinflammatory activity

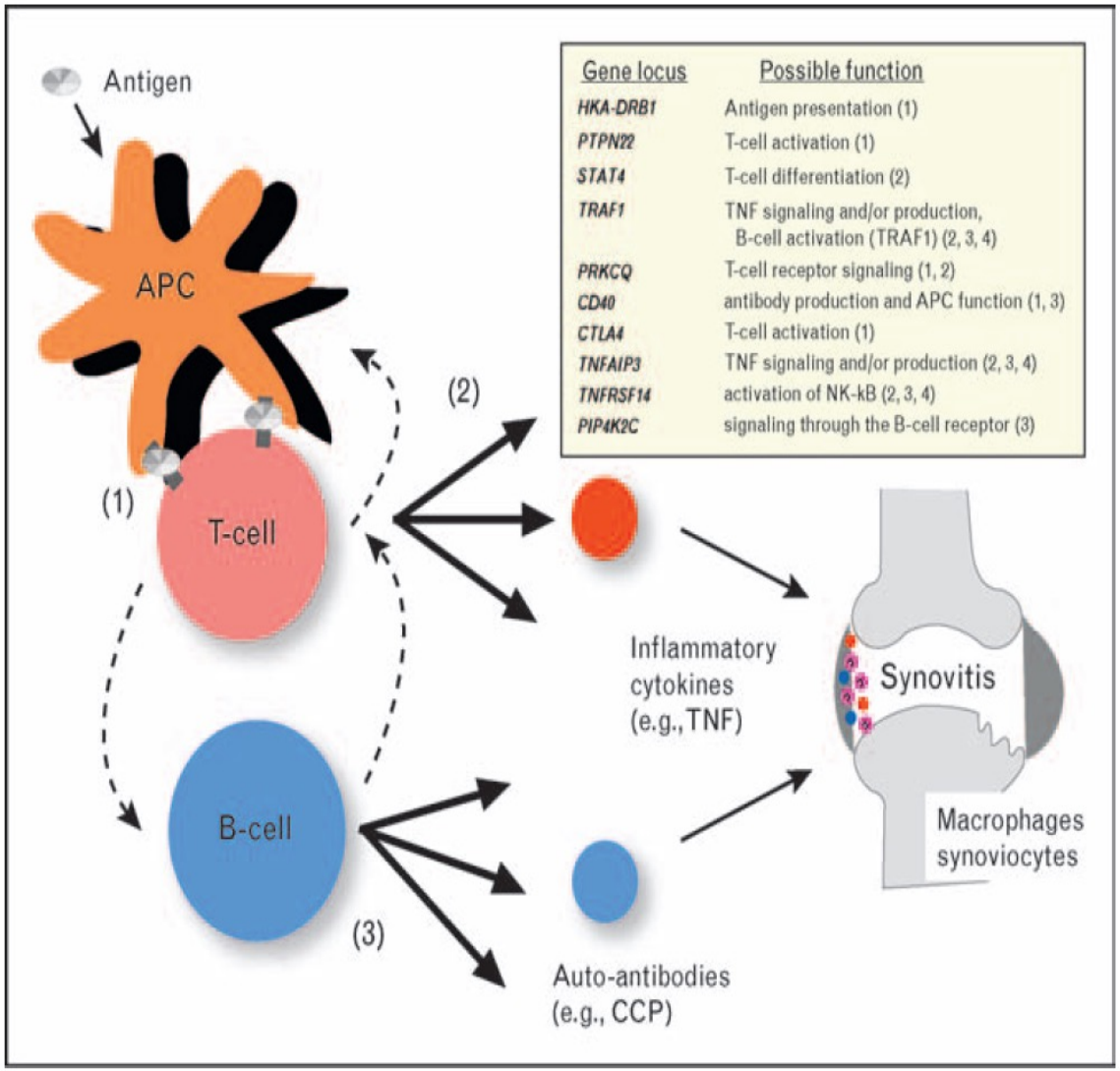
Complex interactions:
Gene–gene interactions that increase disease risk, as described between *HLA-DRB1* and *PTPN22,* exemplify the complexity of the net risk conferred by any given gene

Genetics /Autoimmunity / Clinical correlations:
The above genetic background, mainly for ACPA + patieents

N Engl J Med 2011;365:2205

Genes & RA pathogenesis

Function	Genes
Antigen presentation	*DRB1,CD40*
T-cell activation/ differentiation	*PTPN22, STAT4, CTLA4, TNFAIP3*
Ab production	*TRAF1, CD40, TNFAIP3, PIP4K2C*
Inflammation	*TRAF1, TNFAIP3*



Plenge (2009), Cur Op Rheum

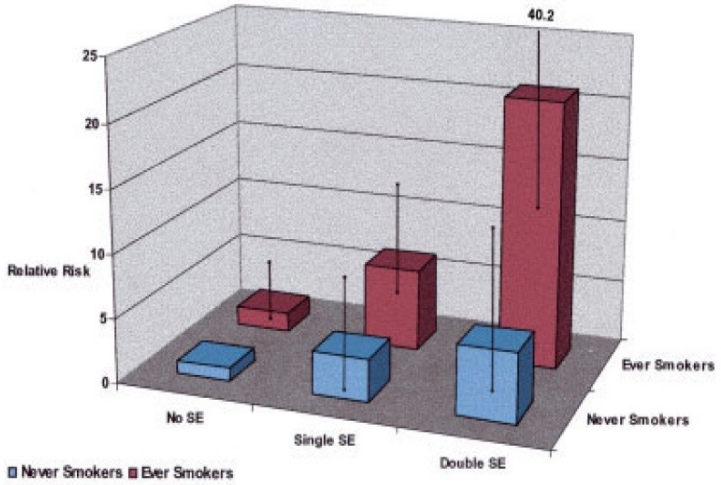
Environment and gene interaction in autoimmunity/ disease development

Environment and gene interaction in autoimmunity/ disease development

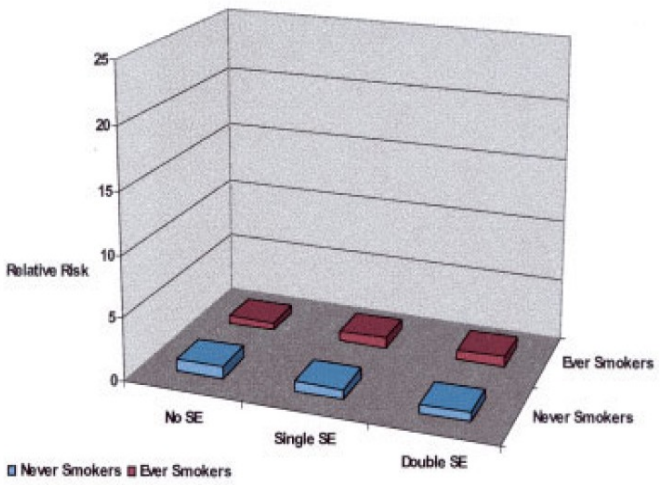
Smoking *increased the risk of* ***developing ACPA*** *only in HLA-SE RA carriers*

Relative risk of developing rheumatoid arthritis (RA) in subjects exposed to different combinations of smoking and HLA–DR shared epitope (SE) genes

The Epidemiological Investigation of Rheumatoid Arthritis [EIRA] study



ACPA positive



ACPA negative

A&R 54(1), 2006, pp 38–46

Context dependent mechanisms

If not in the joints where autoimmunity starts?

Context dependent mechanisms

If not in the joints where autoimmunity starts?

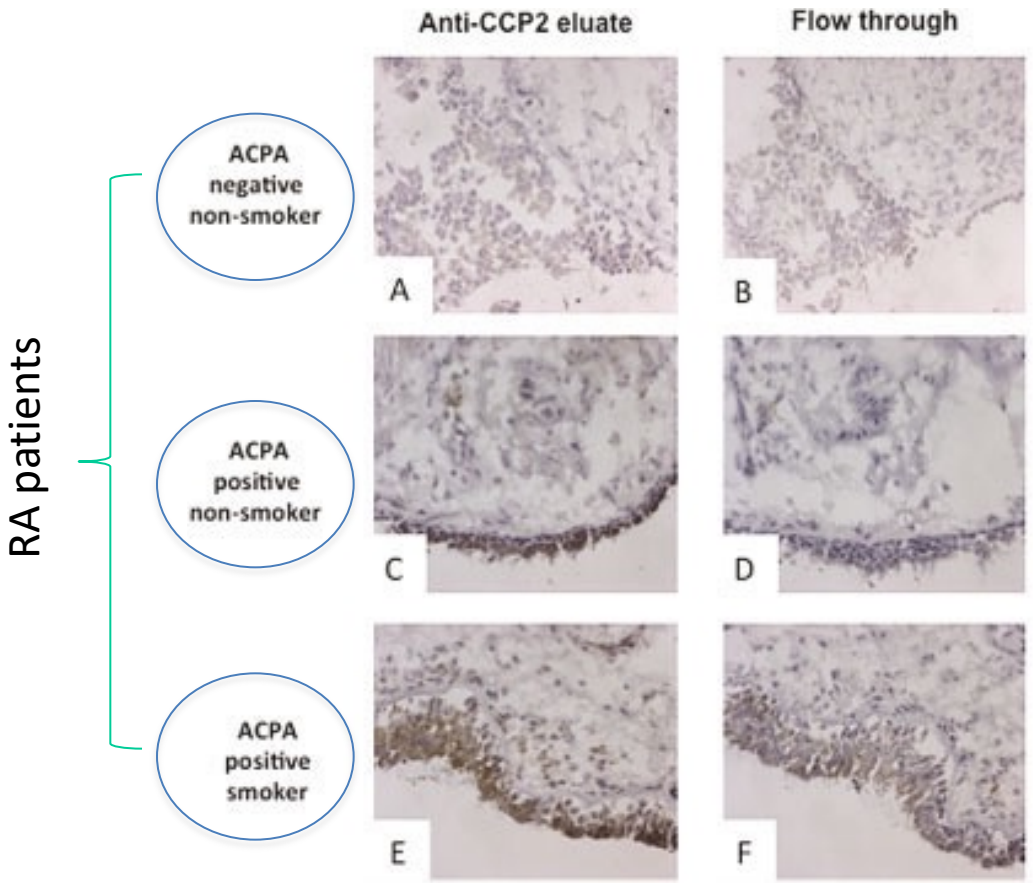
- **Mucosal tissue sites** and **neutrophil extracellular traps** may provide relevant contextual signals through which **citrullinated antigens** gain immunogenicity, supporting that early steps of tolerance loss may occur in the lung and the gut.

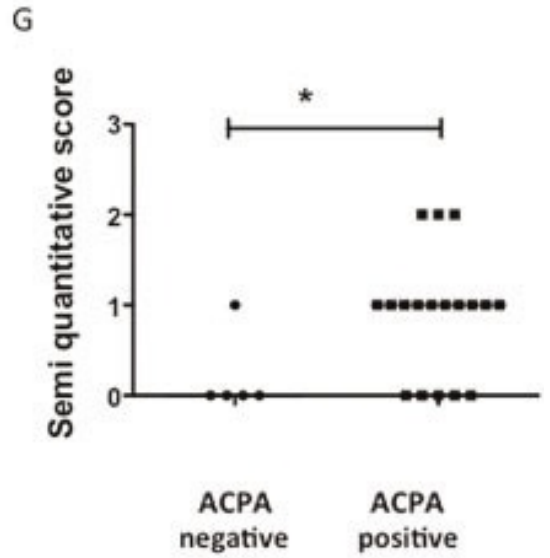
- Nevertheless, how tolerance to the modified peptides is broken remains unclear, and a common denominator is not clear

Context dependent mechanisms

Lung as the site of citrullination and initial ACPA development

Early, untreated ACPA +ve RA exhibit higher levels of expression of the citrullinated protein in large bronchial biopsy tissue.



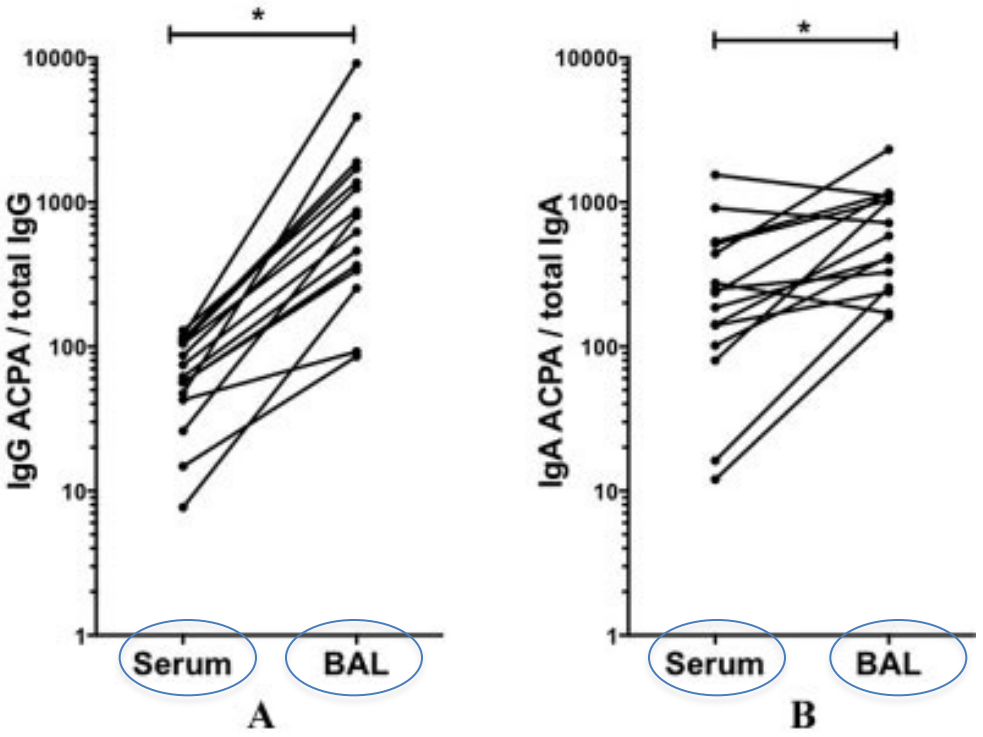


Reynisdottir. A&R 66 January 2014, pp 31

Context dependent mechanisms

Lung as the site of citrullination and initial ACPA development

Enrichment of ACPAs in the lungs vs serum of ACPA-positive patients with early, untreated RA



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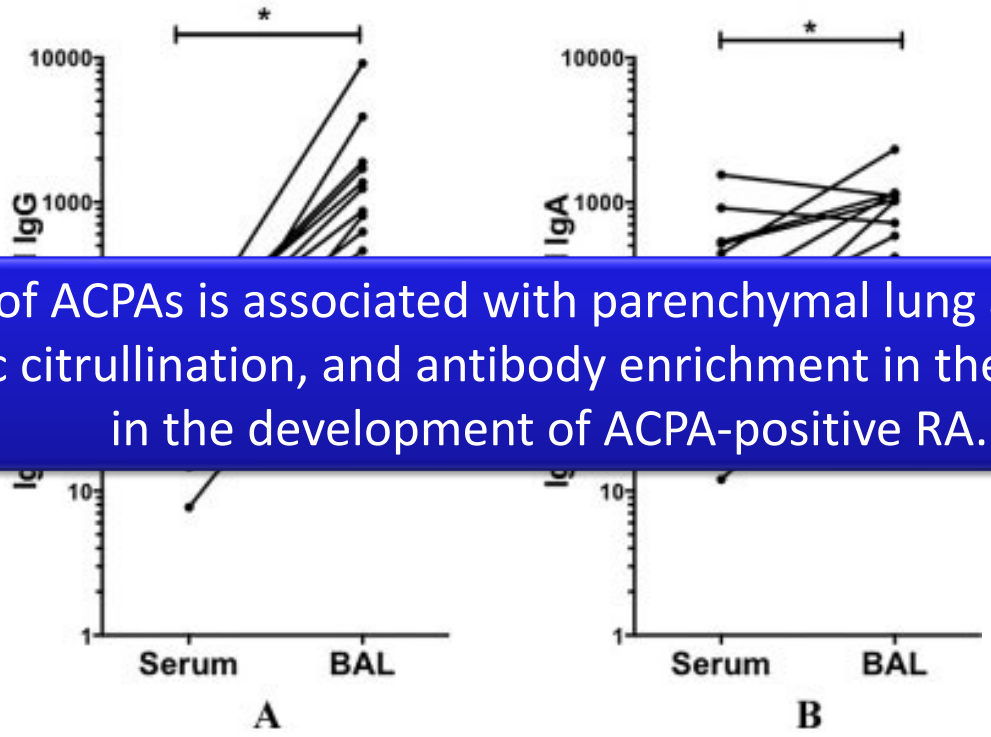


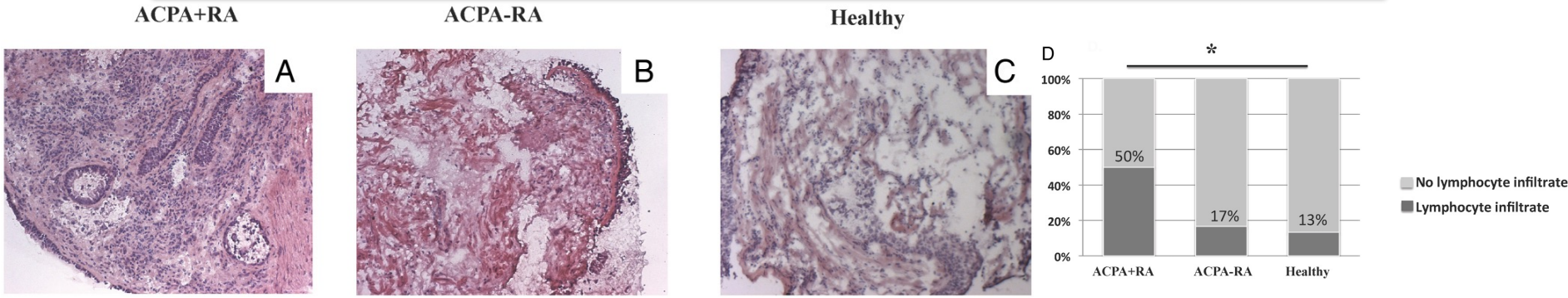
The presence of ACPAs is associated with parenchymal lung abnormalities, site-specific citrullination, and antibody enrichment in the lungs early in the development of ACPA-positive RA.

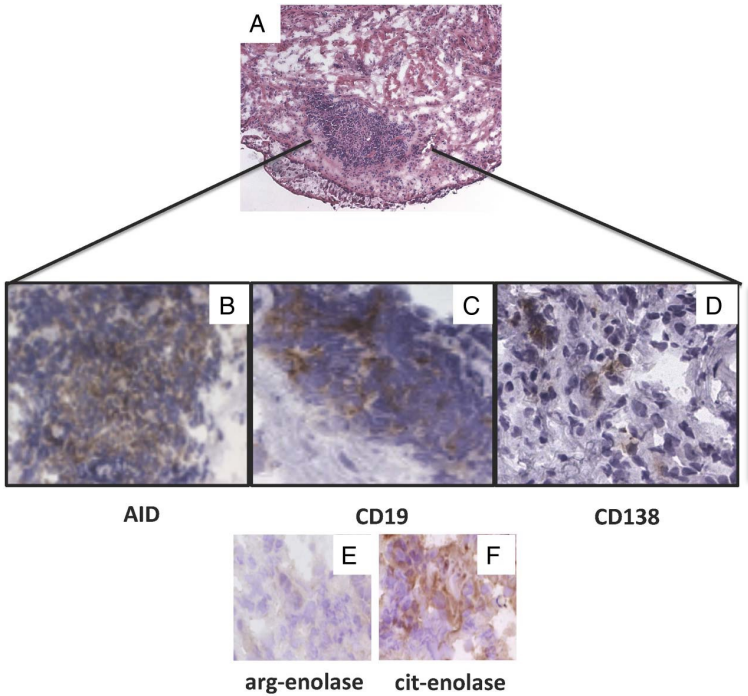
Reynisdottir. A&R 66 January 2014, pp 31

Context dependent mechanisms

Immune activation in BAL and bronchial biopsies of patients with early untreated ACPA-positive RA

Lymphocytic infiltration in the bronchial biopsies of patients with ACPA-positive untreated early rheumatoid arthritis





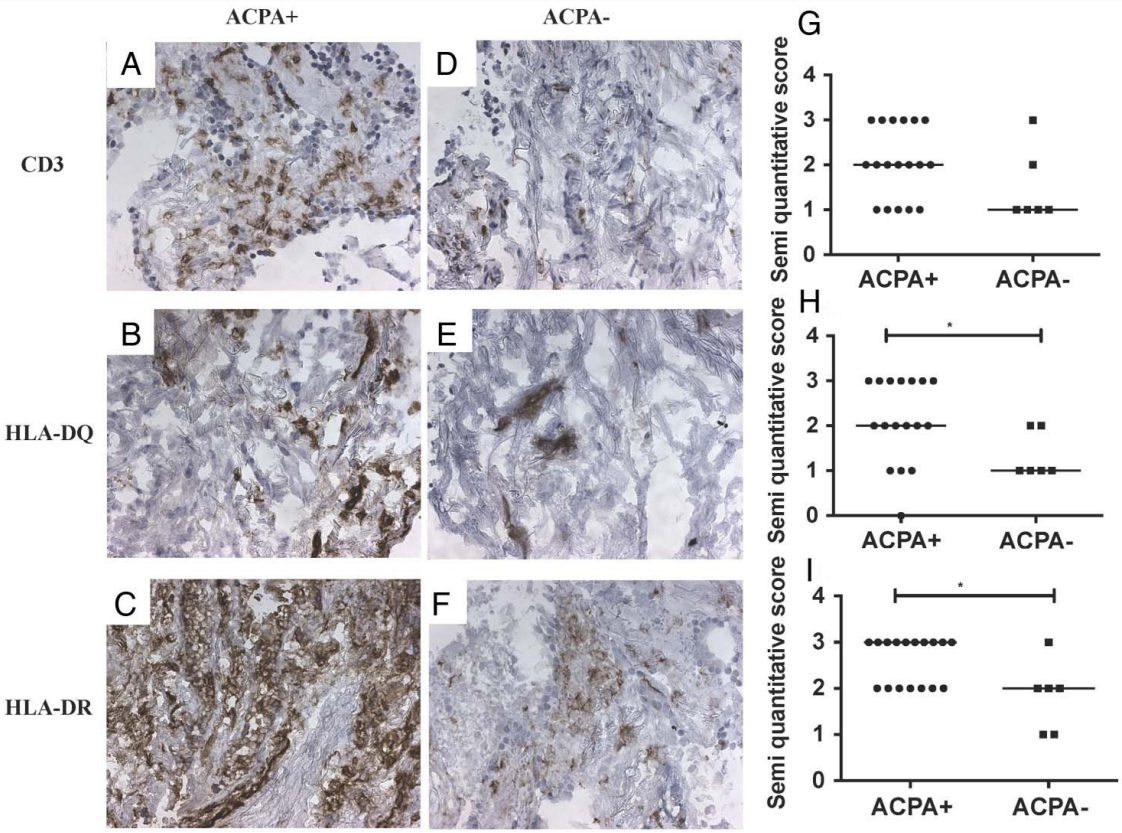
Germinal centre-like structures are present in bronchial biopsies

Reynisdottir. Ann Rheum Dis 2016;75:1722

Context dependent mechanisms

Immune activation in BAL and bronchial biopsies of patients with early untreated ACPA-positive RA

Immune activation are present in bronchial biopsies of patients with ACPA-positive untreated early RA

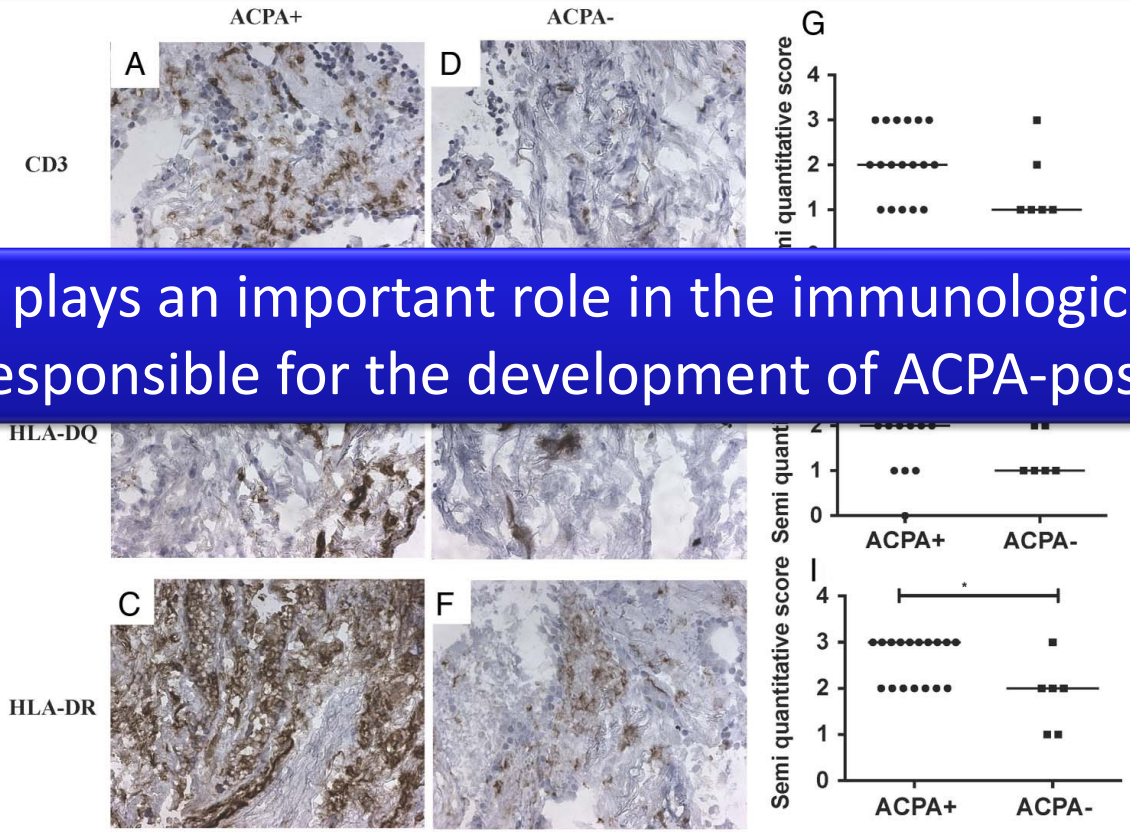


Reynisdottir. Ann Rheum Dis 2016;75:1722

Context dependent mechanisms

Immune activation in BAL and bronchial biopsies of patients with early untreated ACPA-positive RA

Immune activation are present in bronchial biopsies of patients with ACPA-positive untreated early RA

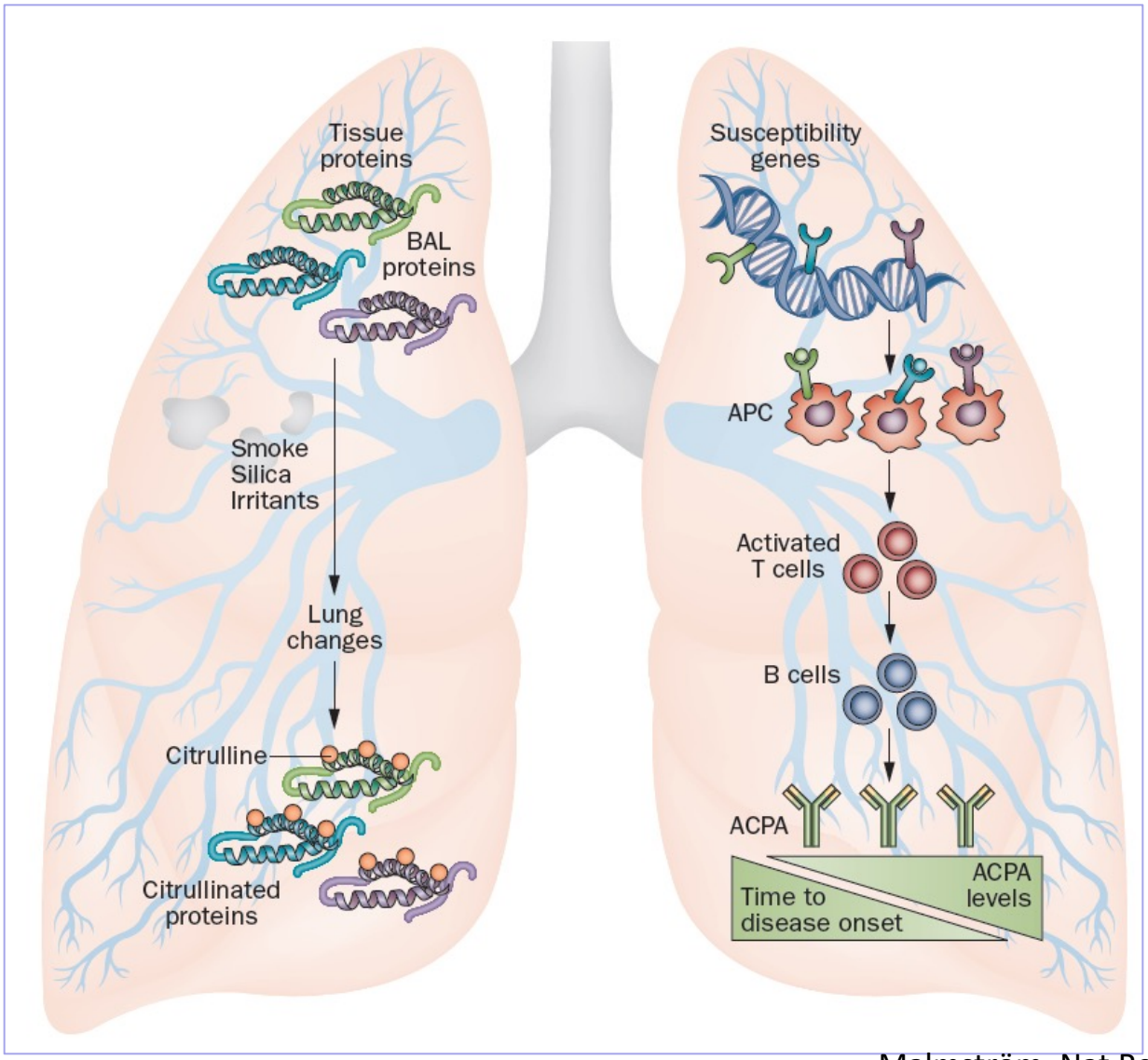


Lung plays an important role in the immunological reactions responsible for the development of ACPA-positive RA

Reynisdottir. Ann Rheum Dis 2016;75:1722

Context dependent mechanisms

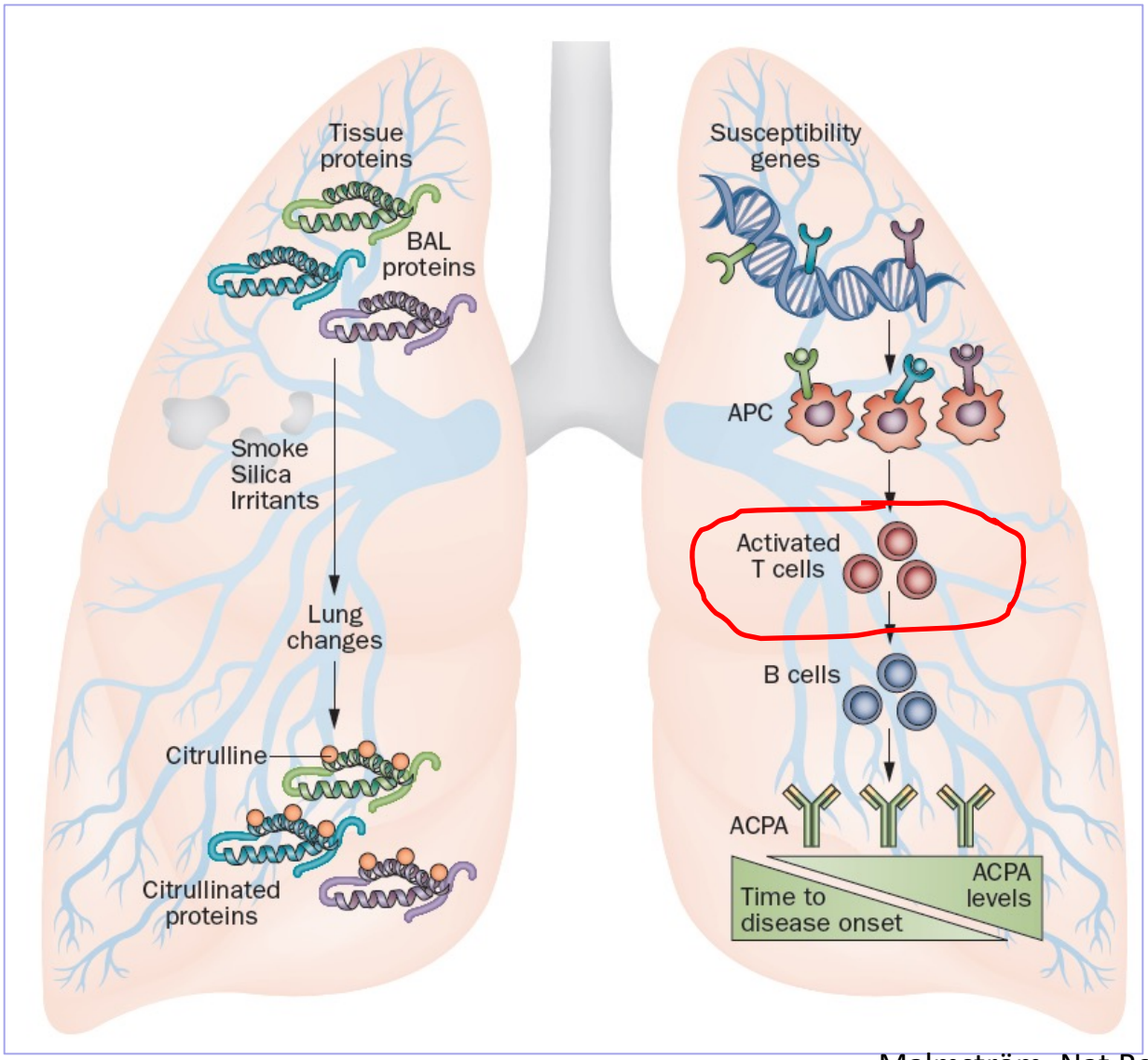
Initiation of RA-associated immunity against citrullinated proteins in the lungs.



Malmström, Nat Rev Rheumatol. 2014:645

Context dependent mechanisms

Initiation of RA-associated immunity against citrullinated proteins in the lungs.

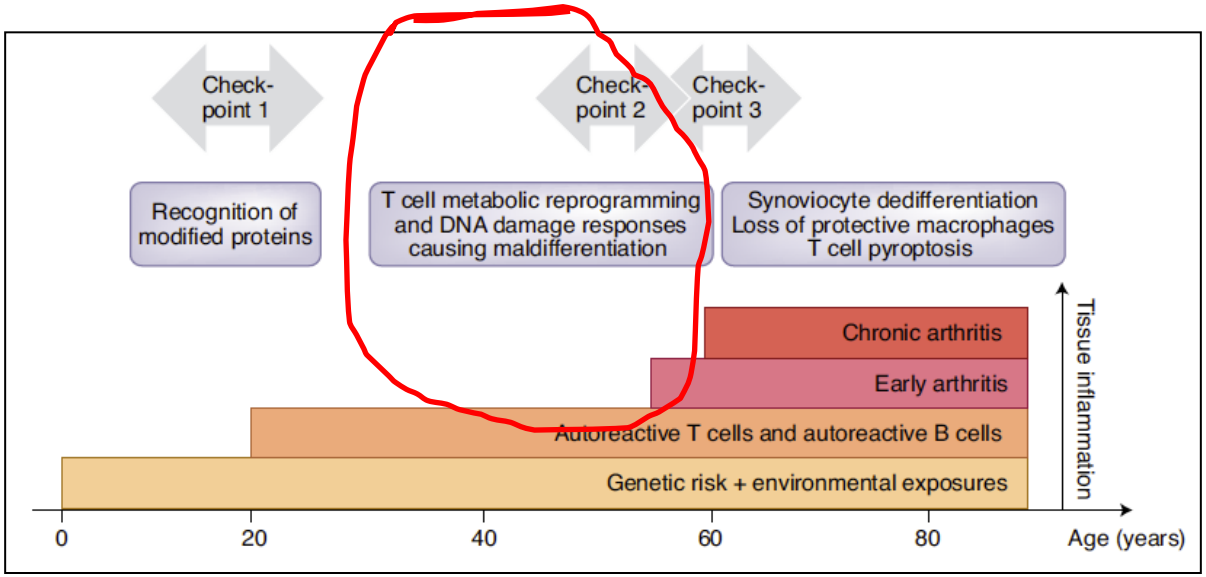


Malmström, Nat Rev Rheumatol. 2014:645

General concept for RA pathogenesis

"RA is an almost lifelong process in with distinct phases:

- ✓ **disease risk:** genetically predisposed individuals lose self-tolerance, produce autoantibodies.
- ✓ **asymptomatic autoimmunity:** characterized by prototypic autoantibodies reactive against post-translationally modified proteins, often citrullinated antigens.
- ✓ **symptomatic synovitis:** Acute joint inflammation transitions into chronic, destructive synovitis. Tissue responds with a maladaptive wound healing response (pannus), which by itself has destructive features and will lead to irreversible tissue injury"



Nat Immunol. 2021 Jan;22(1):10-18

Immune factors contributing to synovial localization of inflammation

"The onset of synovial inflammation, is closely linked to cell-intrinsic defects in CD4+ T cells and is functionally caused by a mis-differentiation step during the conversion of naive resting CD4+ T cells into memory and effector T cells"

- ✓ **CD3+ T** cells are present in most **early synovitis** cases and the **histologic phenotype** of synovial biopsy samples **predicts** disease persistence and severity.

  Ann. Rheum. Dis. 78, 761–772 (2019). Cell Rep. 28,2455–2470.e5 (2019)

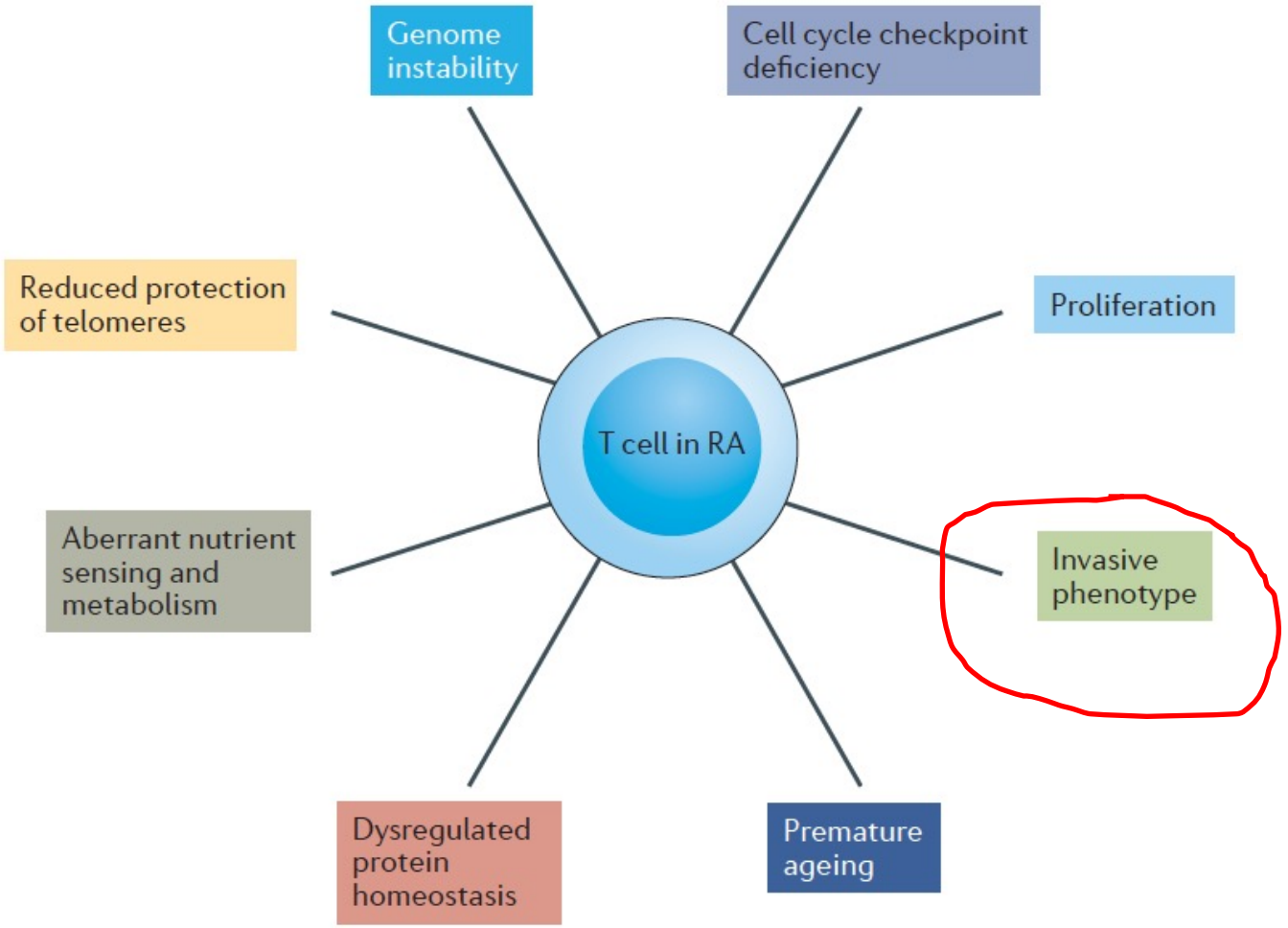
- ✓ **Decreased frequency of naïve CD4+ T** cells is the strongest predictor for the progression from **ACPA positivity to synovitis**.

  Sci. Rep. 10, 3669 (2020)

- ✓ **Differential methylation** patterns of naïve CD4+ T cells characterize the **earliest stages** of joint inflammation in patients who were drug naïve

  Clin. Epigenetics 12,54 (2020)

Hallmarks of T cells in rheumatoid arthritis



Nat Rev Rheumatol. 2017 May;13(5):291-301

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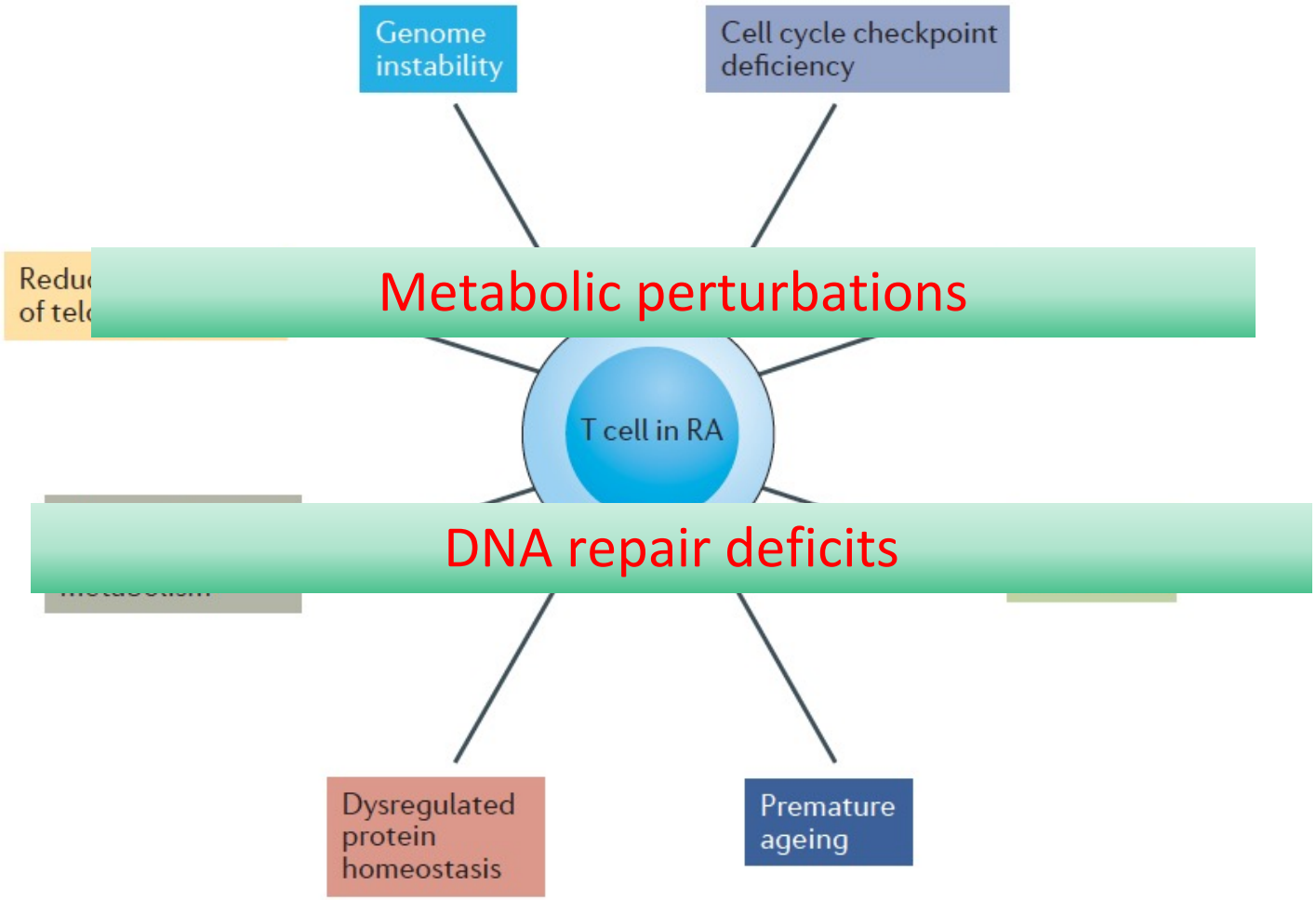

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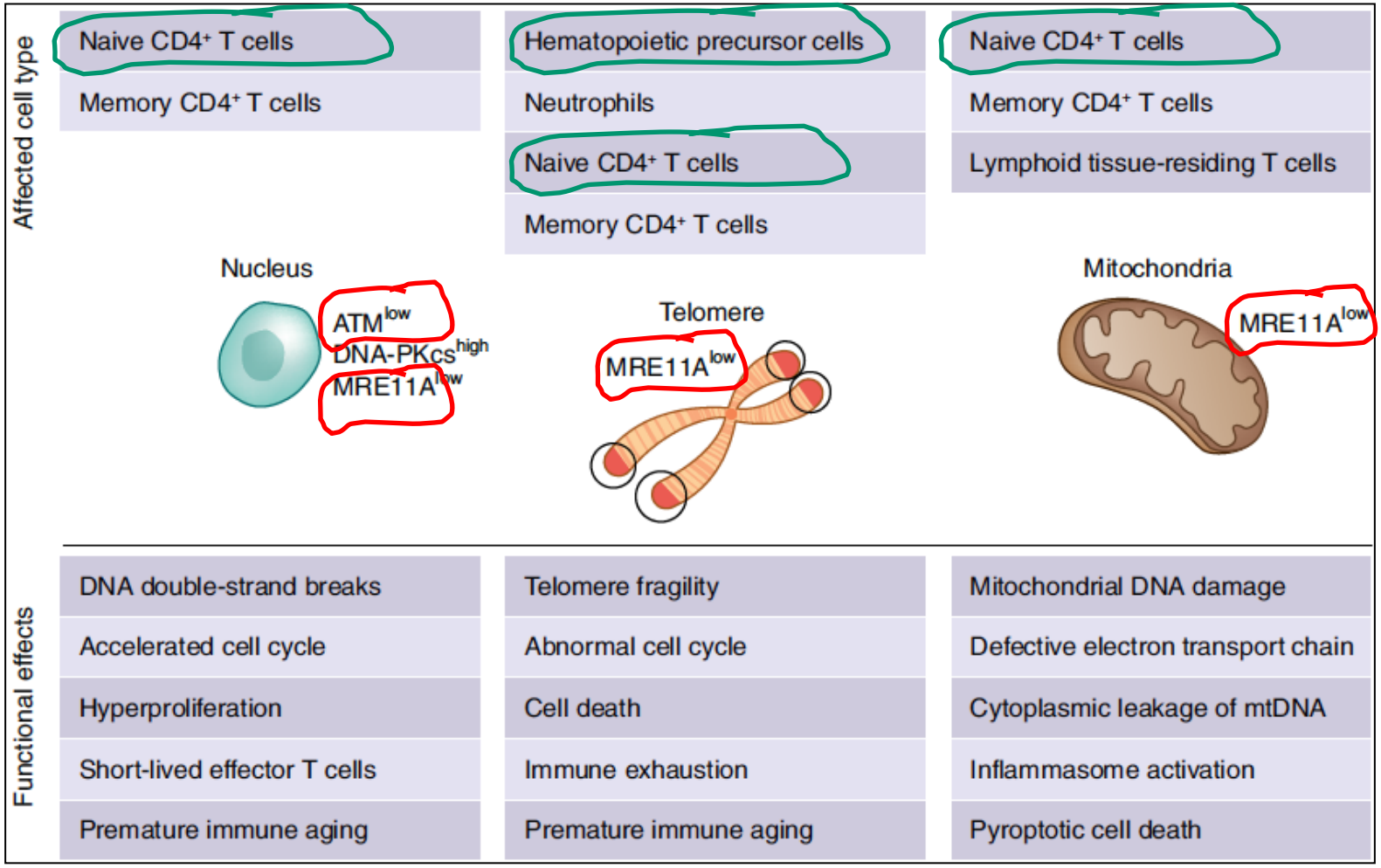
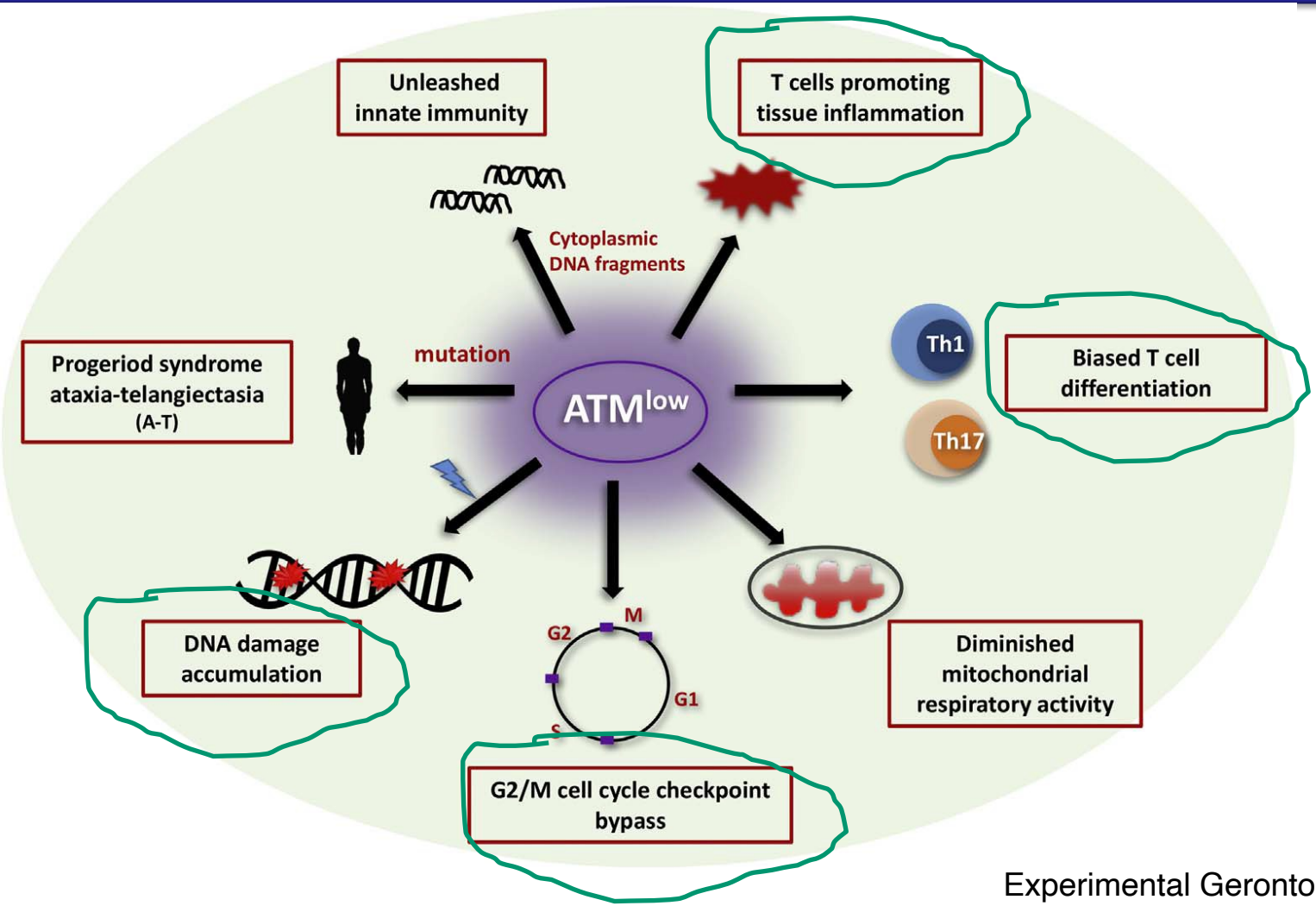
DNA repair deficits in rheumatoid arthritis



Nat Immunol. 2021 Jan;22(1):10-18

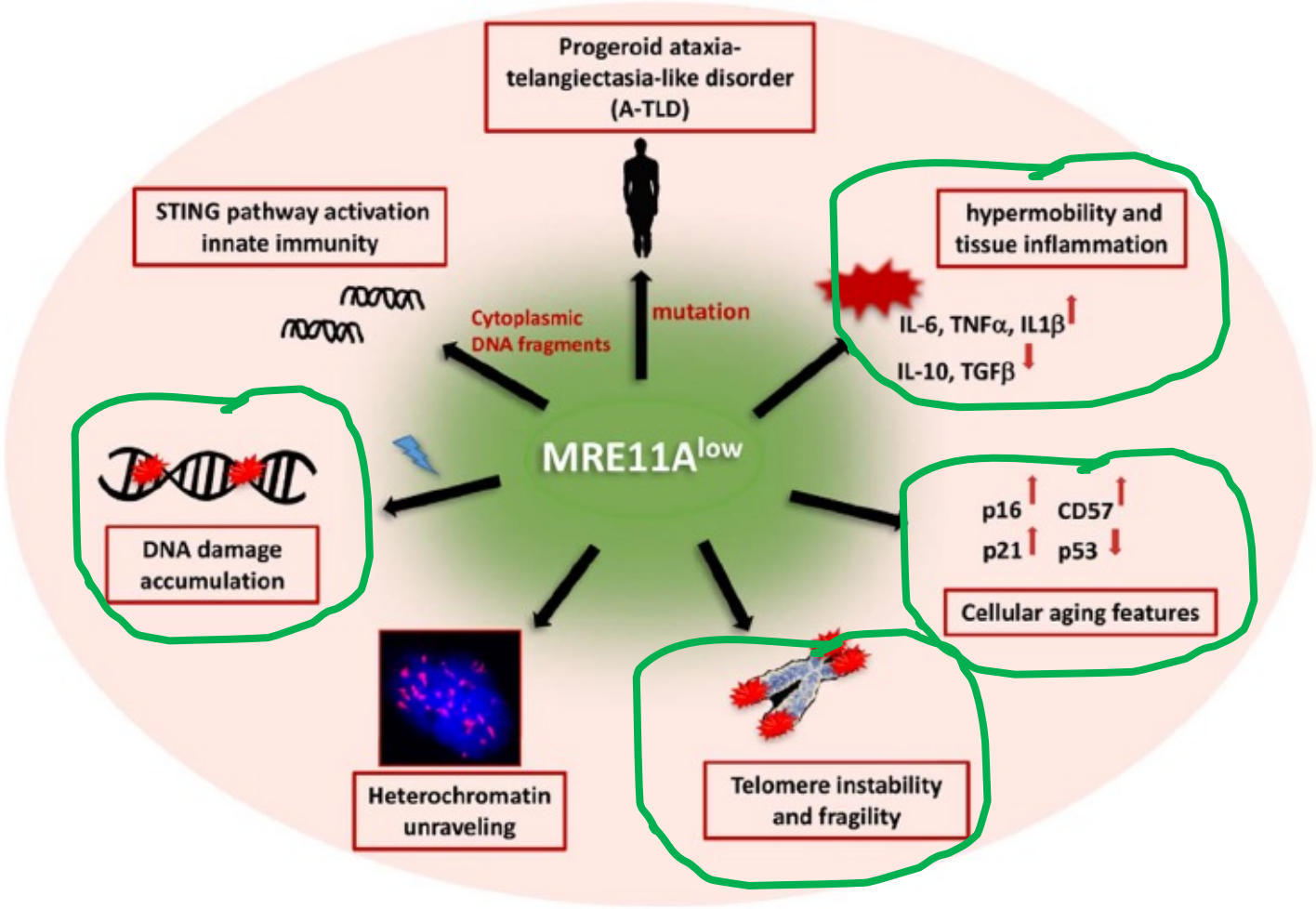
ATM^{low} T cells in RA patients promote tissue inflammation

- (ATM) : superfamily of phosphatidylinositol 3-kinase-related kinases.
- activator of the DNA damage response and DNA repair.
- ATM function is redox sensitive, connecting metabolic activity with the DNA repair machinery.



Experimental Gerontology (2017)

MRE11A Protects Synovial Tissue from Inflammation
Early RA patients have low MRE11A expression



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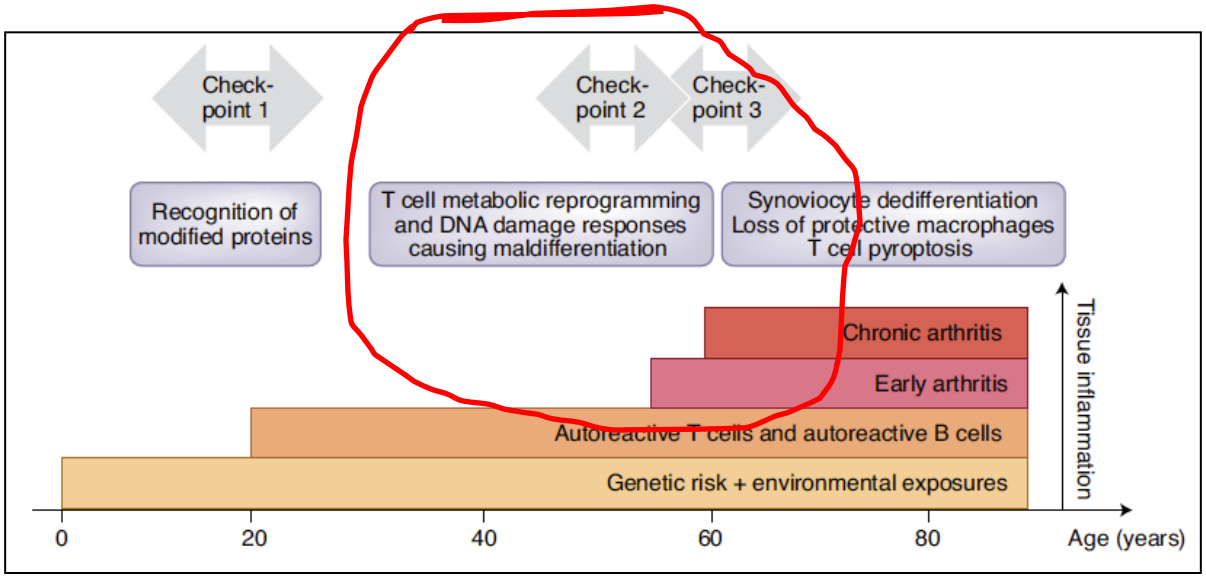
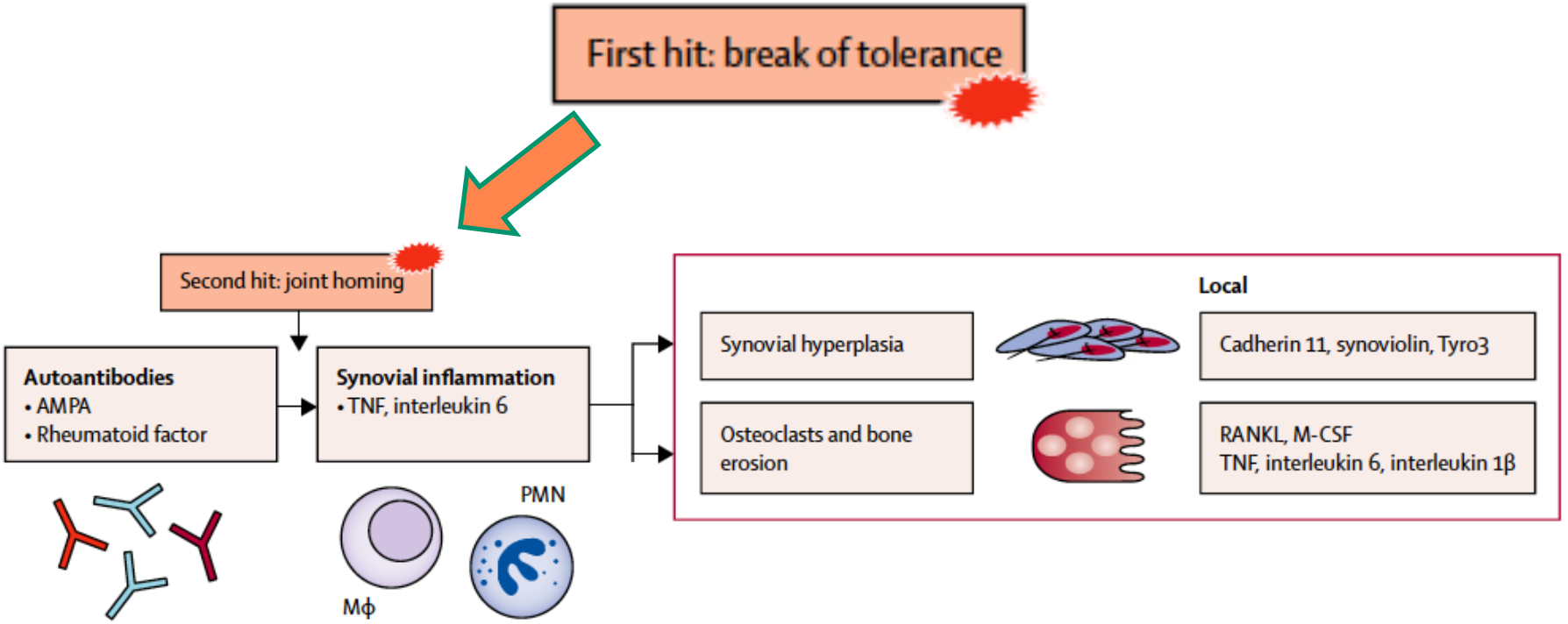


Nat Immunol. 2021 Jan;22(1):10-18

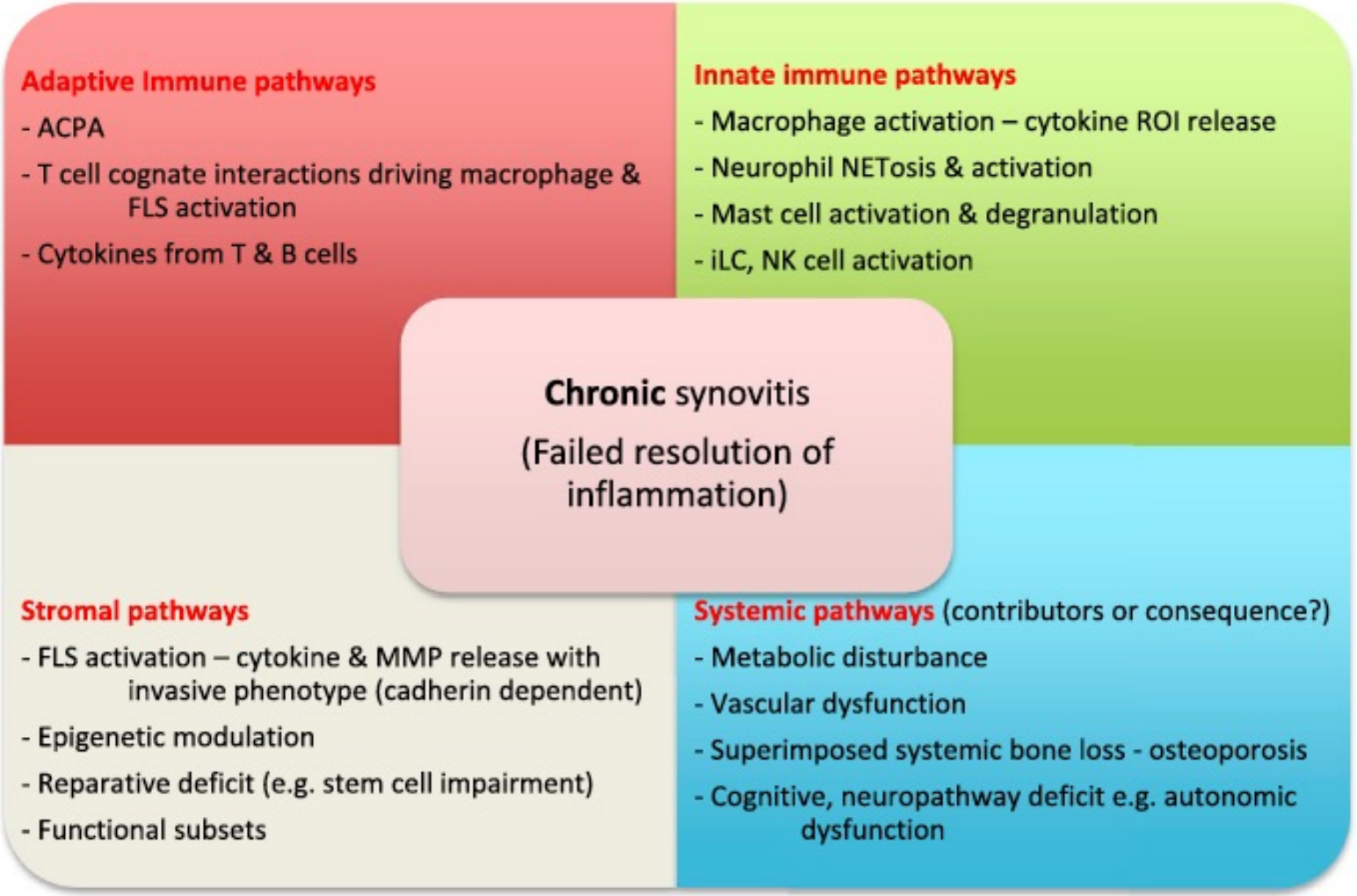
Chronic, destructive synovitis: Hyperplasia (pannus) and osteoclastogenesis



Lancet 2017; 389: 2328–37

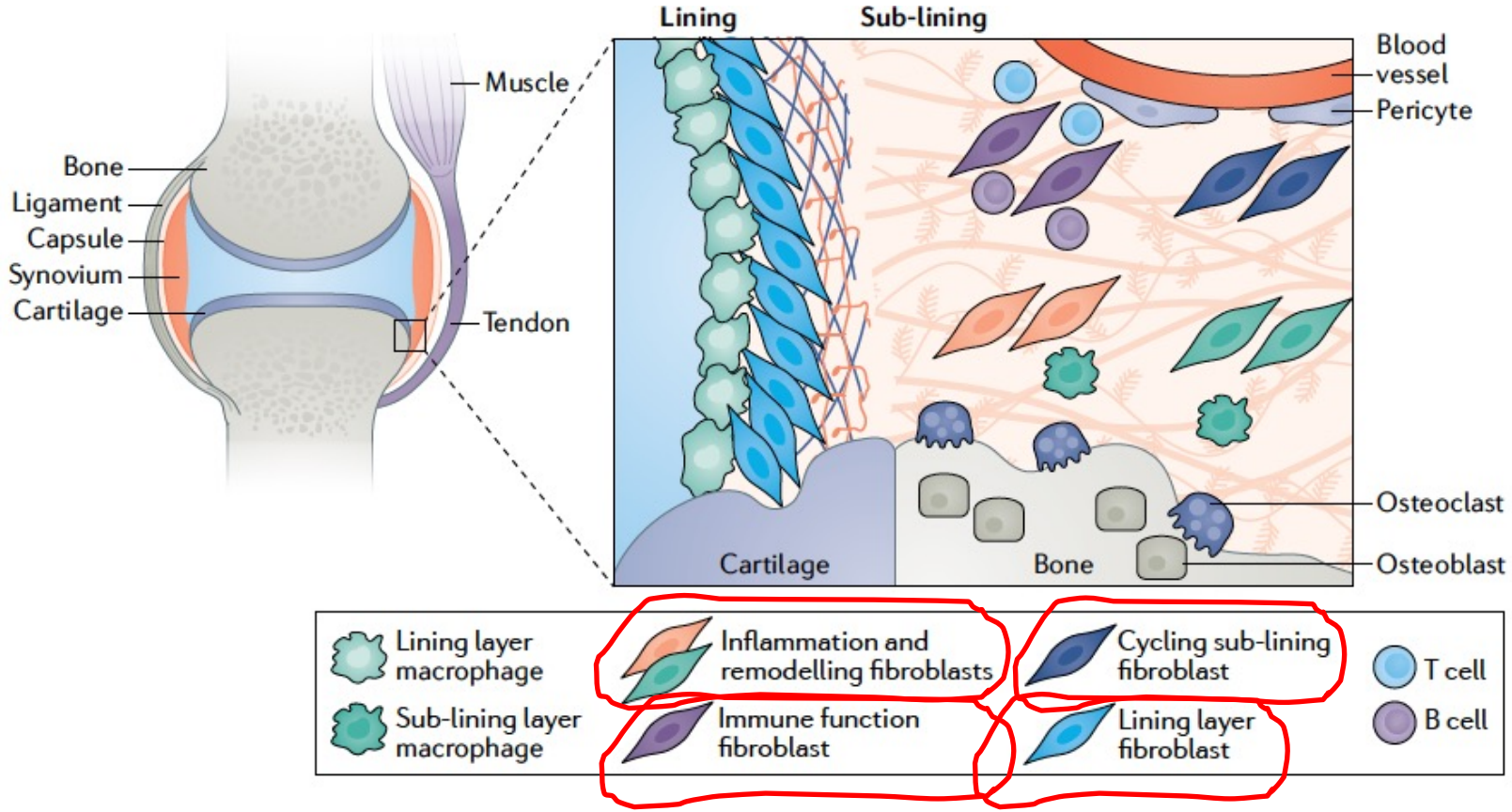
Mechanisms that Drive the Chronicity of RA:

Distinct pathways combine to mediate failed resolution of disease



Immunity 46, February 21, 2017

The multiple faces of fibroblasts in RA



Nat Rev Rheumatol. 2021 Apr;17(4):195-212

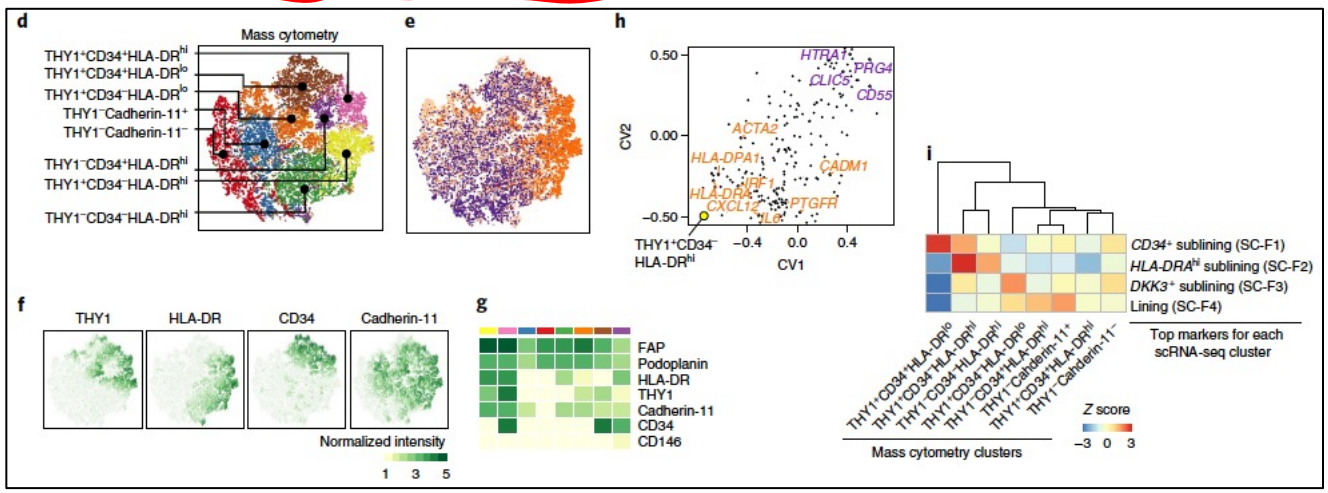
nature immunology

Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry

Nat Immunol. 2019 Jul;20(7):928-942

Table 1 | **Conserved cell populations in rheumatoid arthritis joints**

Cell subsets	Marker genes (human)	Marker genes (mouse)	Activation marker or effector genes
Fibroblasts			
Lining layer	Negative (*CD90*); positive (*CD55* and *PGR4*)	Negative (*Cd90*); positive (*Pgr4*)	*RANKL:OPG* ratio, *CCL9*, *CLIC5*, *MMP1*, *MMP2*, *MMP3*, *MMP9*, *MMP13*, *HAS1*, *HTRA4* and *DNASE1L3*
Sub-lining layer (immunomodulatory	Positive (*CD90* and *CD34*)	Positive (*Cd90* and *Cd34*)	*IL6*, *IL33*, *IL34*, *IFI30*, *LIF*, *CXCL9*, *CXCL12*, *CXCL13*, *CCL2*, *CCL19* and *CCL21*
	Negative (*CD34*); positive (*CD90* and *DKK*)		
Sub-lining layer (perivascular)	Negative (*CD34*); positive (*CD90* and *HLA-DRA*)	Negative (*Cd34*); positive (*Cd90*)	



nature immunology

Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry

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4-5 Functionally distinct fibroblast subgroups

Sublining fibroblasts as a potential therapeutic target in RA:

- Are a major source of pro-inflammatory cytokines such as IL6
- All SF subsets express TNF receptor 1, **but none is a TNF producer**
- Express MHC II (SC-F2, $THY1^{+}CD34–HLA\text{-}DR^{hi}$)

Further studies are needed to define molecular mechanisms that regulate sublining fibroblast expansion in RA.

nature immunology

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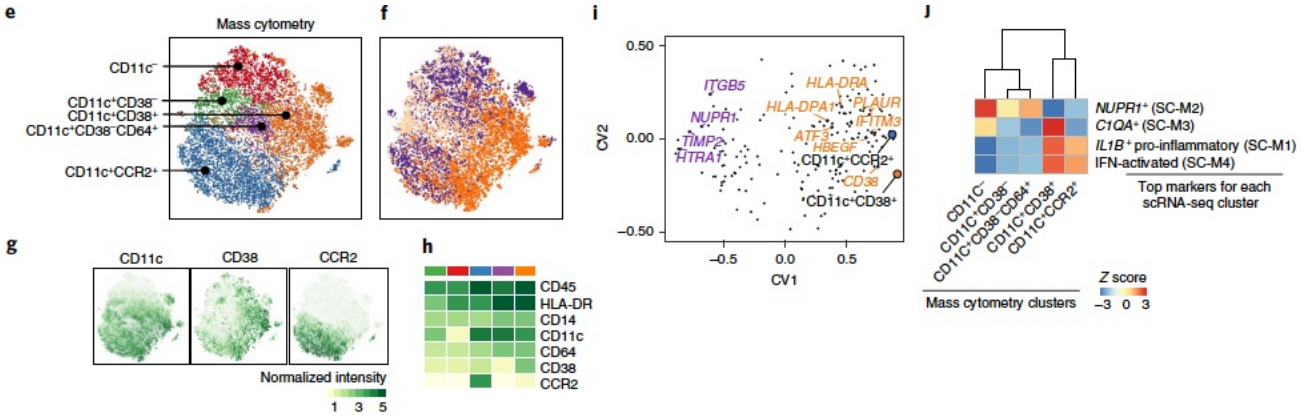
Cell subsets	Marker genes (human)	Marker genes (mouse)	Activation marker or effector genes
Macrophages			
Lining layer	Not reported	Negative (*Cfsr1*); positive (*Cx3cr1*)	*TREM2, VSIG4, AXL, MFGE8, JAM1, ZO1, CLDN5, FAT4* and *VANGL2*
Interstitial	Negative (*CD11C* and *CD38*); positive (*NURP1*)	Negative (*Cx3cr1*); positive (*Cfsr1*, MHC class II genes and *Aqp1*)	*MERTK, CTSK, HTRA1, GPNMB* and *ITGB5*
	Positive (*C1QA, CD11C* and *CD38*)	Negative (*Cx3cr1*); positive (*Cfsr1* and *Relma*)	*MRC1, CD163* and *MARCO*
Monocyte-derived (infiltrating)	Positive (*SPP1, CD11C, CCR2* and *CD38*) when activated by interferon	Negative (*Ly6c2*); positive (*Ccr2* and *Arg1*)	*ARG1, IFI6, IFI44L, LY6E* and *SPP1*
	Positive (*IL1B, CD11C, CCR2* and *CD38*)	Negative (*Ly6c2*); positive (*Ccr2* and *Il1b*)	*NR4A2, HBEGF, PLAUR, RGS2, IL1B, HTF3, CXCL2* and *EREG*



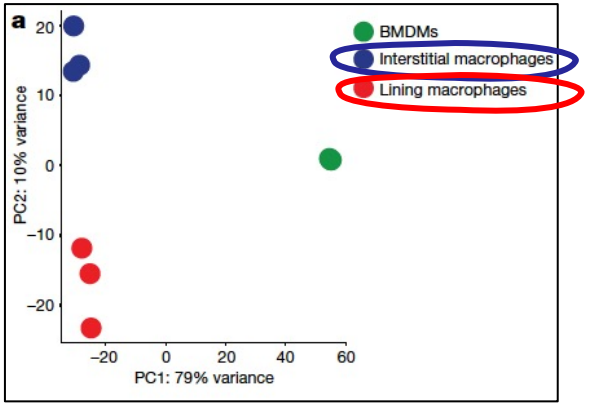
Nat Rev Rheumatol. 2021 Apr;17(4):195-212

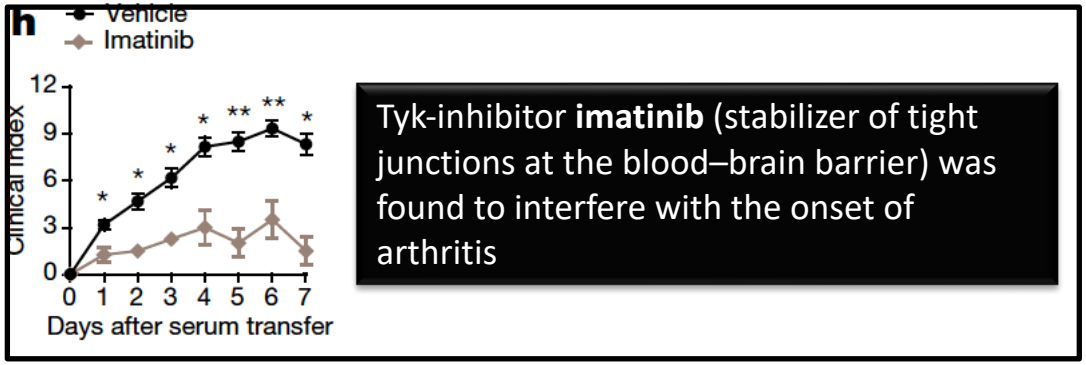
Locally renewing resident synovial macrophages provide a protective barrier for the joint

Stephan Culemann[1,2,11], Anika Grüneboom[1,2,11], José Ángel Nicolás-Ávila[3], Daniela Weidner[1,2], Katrin Franziska Lämmle[1,2], Tobias Rothe[1,2], Juan A. Quintana[3], Philipp Kirchner[4], Branislav Krljanac[5], Martin Eberhardt[6], Fulvia Ferrazzi[4], Elke Kretzschmar[7], Martin Schicht[7], Kim Fischer[1], Kolja Gelse[8], Maria Faas[1,2], René Pfeifle[1,2], Jochen A. Ackermann[1,2], Milena Pachowsky[8], Nina Renner[8], David Simon[1], Reiner F. Haseloff[9], Arif B. Ekici[4], Tobias Bäuerle[10], Ingolf E. Blasig[9], Julio Vera[6], David Voehringer[5], Arnd Kleyer[1], Friedrich Paulsen[7], Georg Schett[1], Andrés Hidalgo[3] & Gerhard Krönke[1,2*]

Nature 2019;572(7771):670-675

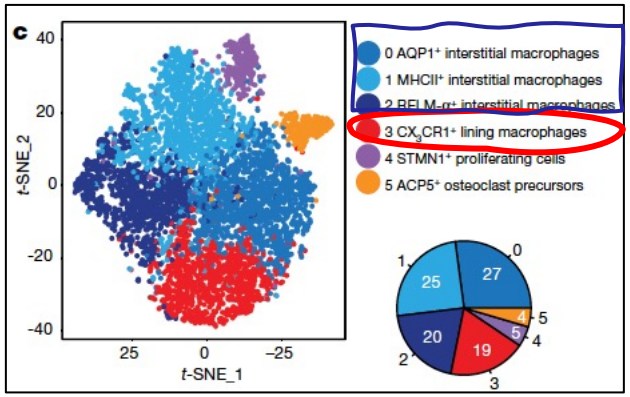
Bulk RNA sequencing of sorted steady-state CX3CR1⁺ lining Mϕ

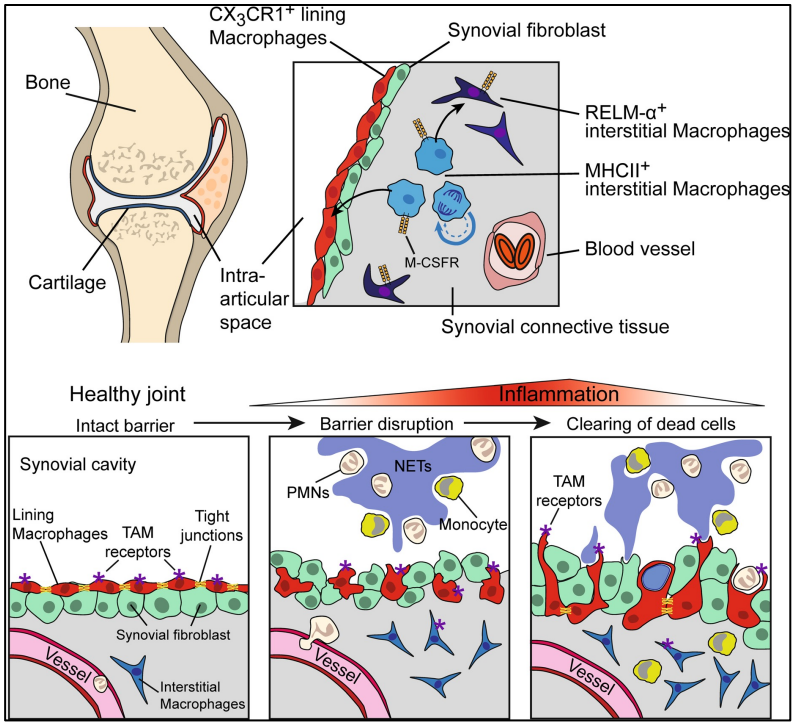




Tyk-inhibitor **imatinib** (stabilizer of tight junctions at the blood–brain barrier) was found to interfere with the onset of arthritis

Single-cell RNA sequencing of total synovial CD45+CD11b+Ly6G-mononuclear phagocytes





Key points

- **Genetic (**HLA DR) and **environmental factors** (smoking) contribute to autoimmunity to endogenous modified peptides **(citrullinated)**
- **T cell-endogenous abnormalities** present in naive T cells drive the differentiation program to favor the generation effector/inflammatory cells with tissue-invading properties
  - DNA-repair failure & a metabolic shift
- Subsets of **highly activated synovial fibroblasts** adopt proinflammatory and tissue-invasive functionalities
- **Anti-inflammatory macrophages** in the synovium fail to protect the synovium
- Potential of Novel therapies:
  - The recognition of stable stages and the molecular characterization of the relevant transition points has the potential to identify targets that could re-engineer the immune system to halt the disease process prior to irreversible tissue damage.