AZIENDA OSPEDALIERO-UNIVERSITARIA SENESE

Dipartimento di Scienze Mediche e UOC di Reumatologia
Dir. B. Frediani

RAPPORTI FRA COLLAGENE E ARTRITE REUMATOIDE

BRUNO FREDIANI

Classificazione delle malattie reumatologiche della Società Italiana di Reumatologia

1 - MALATTIE INFIAMMATORIE ARTICOLARI E PERIARTICOLARI

1.1 ARTRITI PRIMARIE

1.1.1 Artrite reumatoide e forme correlate
1.1.1.1 Artrite reumatoide
1.1.1.2 Reumatismo palindromico
1.1.1.3 Artrite indifferenziata

1.1.2 Spondiloentesoartriti
1.1.2.1 Forme prevalentemente assiali
- Radiografica (Spondilite anchilosante)
- Non radiografica (Spondiloentesoartrite assiale non radiografica)

1.1.2.2 Forme prevalentemente periferiche
- Artrite psoriasica
- Spondiloentesoartriti enteropatiche
- Spondiloentesoartriti reattive

1.1.2.3 Spondiloentesoartriti indifferenziate

1.2 POLIMIALGIA REUMATICA

1.2.1 Isolata
1.2.2 Associata ad arterite gigantocellulare

1.3 SINDROME RS3PE
(Remitting Seronegative Symmetrical Synovitis with Pitting Edema)

2 - CONNETTIVITI E VASCULITI SISTEMICHE

2.1 CONNETTIVITI

2.1.1 Lupus Eritematoso Sistemico e forme correlate
2.1.1.1 Lupus eritematoso sistemico
2.1.1.2 Lupus indotto da farmaci
2.1.1.3 Lupus neonatale

2.1.2 Sclerosi Sistemica

2.1.3 Sindromi simil-sclerodermiche
2.1.3.1 Fascite diffusa con o senza eosinofilia
2.1.3.2 Sclerodermia da agenti fisici, chimici e farmaci
2.1.3.3 Graft versus host disease (GVHD)
2.1.3.4 Scleromixedema

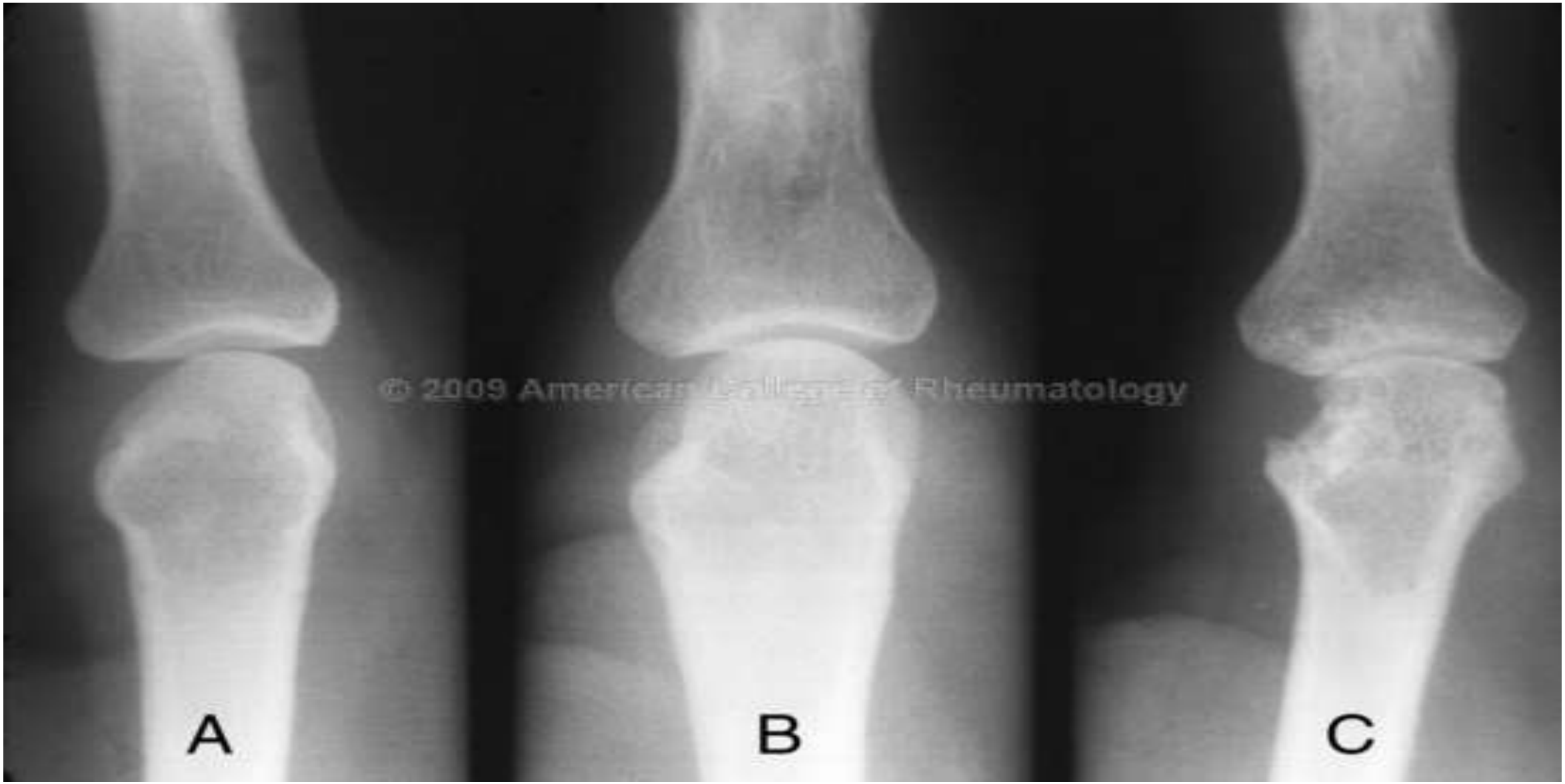
2.1.4 Miopatie
2.1.4.1 Miopatie infiammatorie
- Dermatomiosite (inclusa la variante amiopatica e quella sine dermatite)
- Polimiosite
- Miosite necrotizzante autoimmune

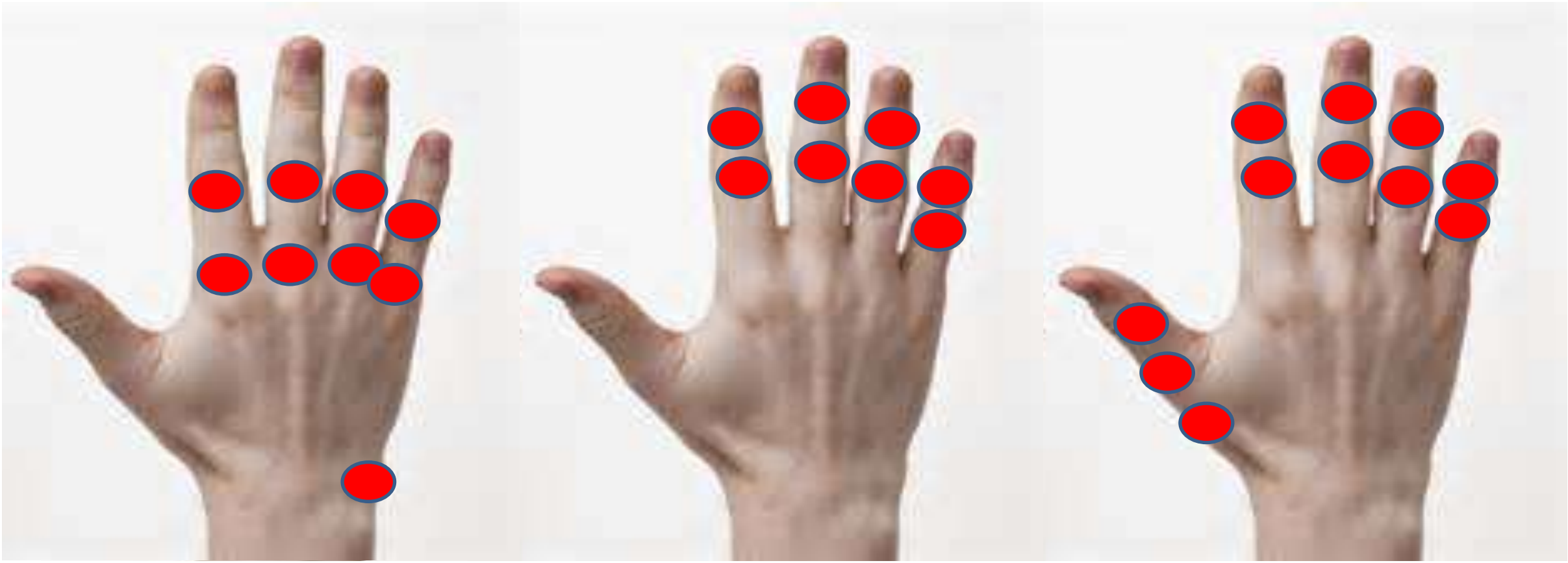
2.1.4.2 Altre miopatie
- Miopatia da corpi inclusi
- Altre

2.1.5 Sindrome di Sjögren
2.1.5.1 Sindrome di Sjögren primaria
2.1.5.2 Sindrome di Sjögren associata ad altre malattie

2.1.6 Sindromi da Sovrapposizione (Overlap)
2.1.6.1 Sindromi da Sovrapposizione con anticorpi specifici
- Connettivite Mista (anti-U1RNP)
- Sindrome da anti-sintetasi (anti-amminoacil-tRNA sintetasi)
- Sindrome sclero-miosite (anti-PM-Scl)

2.1.6.2 Sindromi da Sovrapposizione senza anticorpi specifici
- Artrite reumatoide – Lupus eritematoso sistemico (Rhupus)
- Sclerosi sistemica – Lupus eritematoso sistemico (Sclero-lupus)


© 2009 American College of Rheumatology
A
B
C

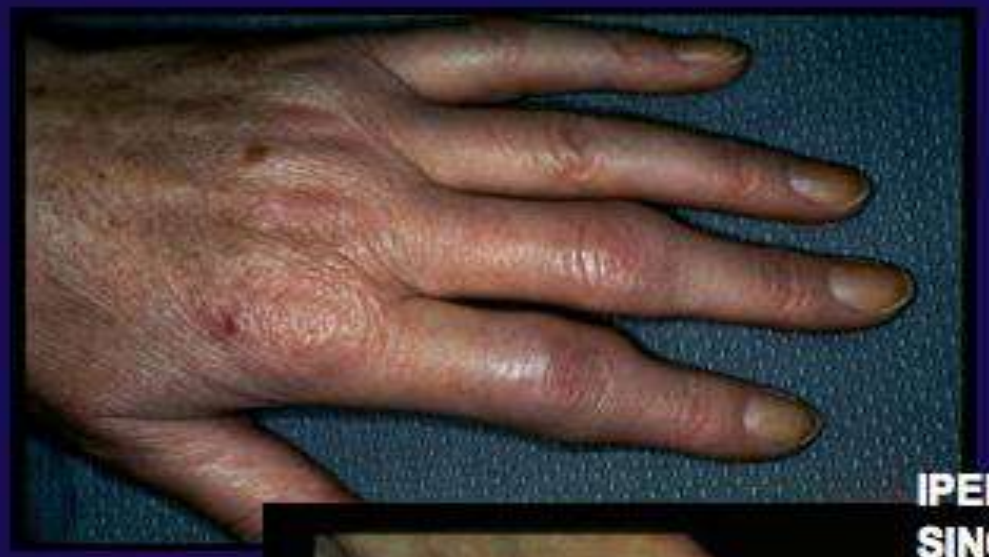


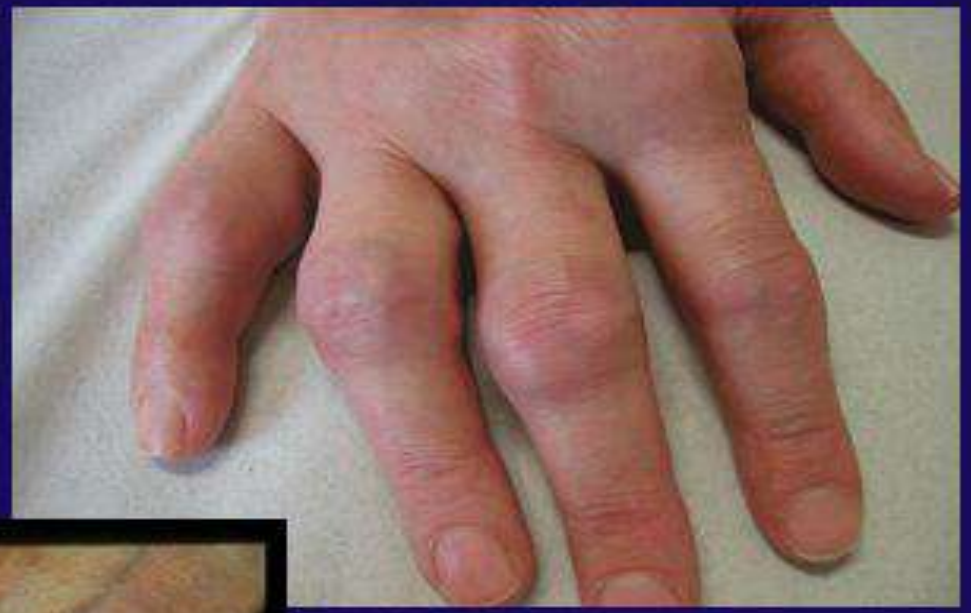
AR

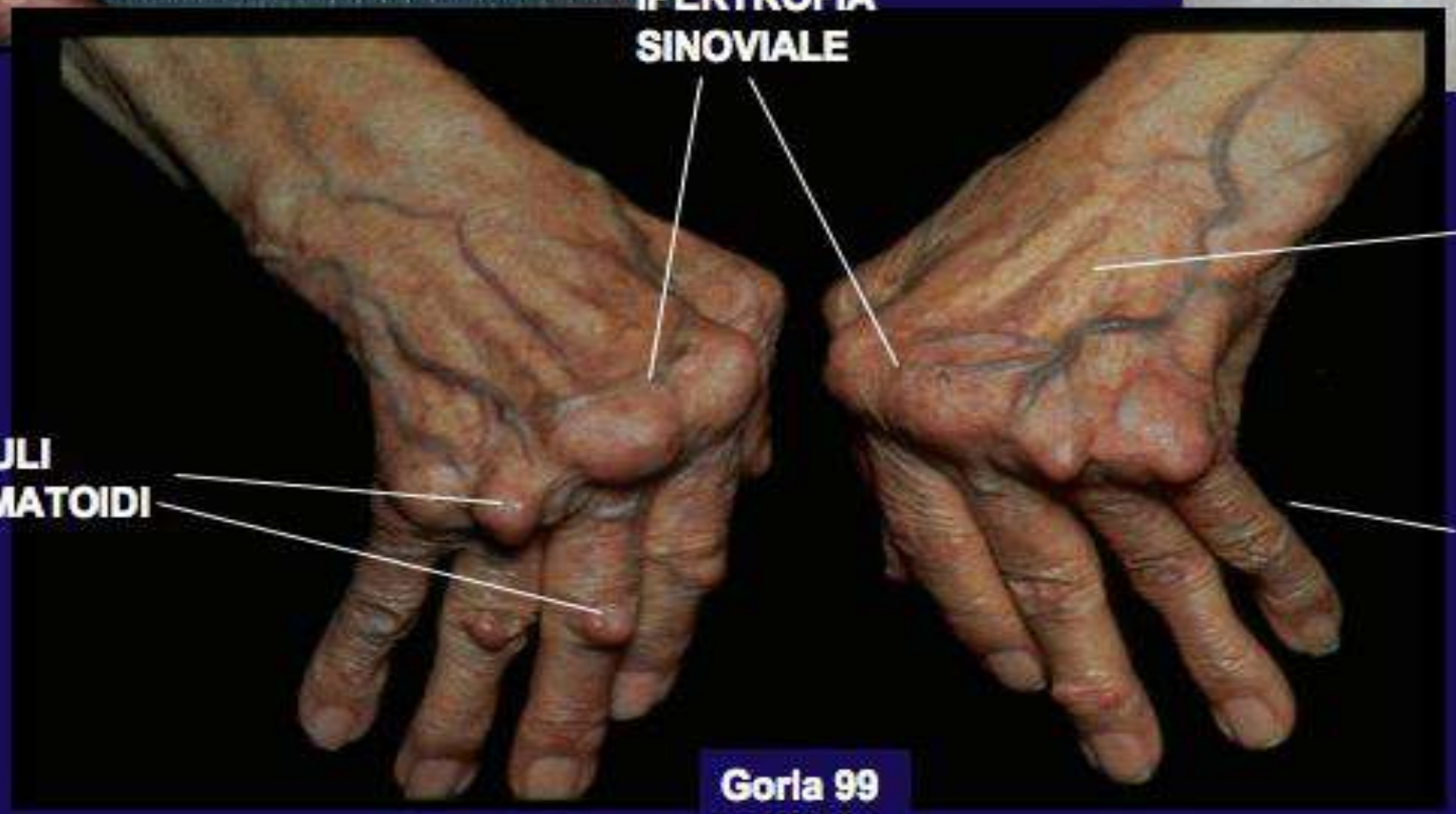
ARPS

OA

AR

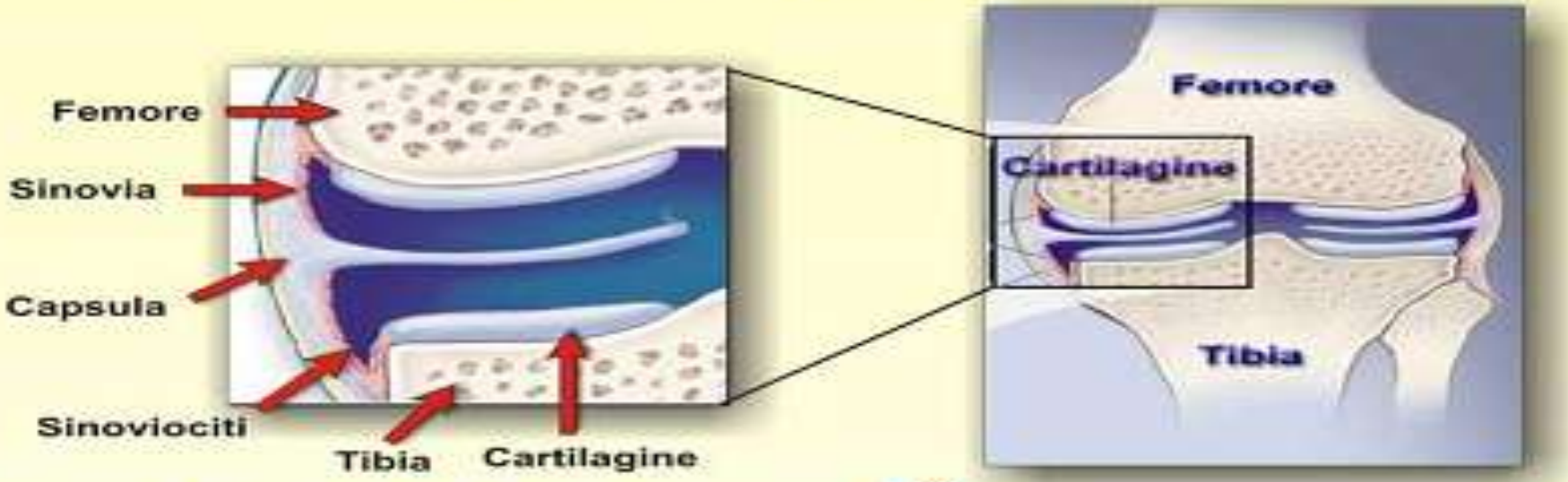




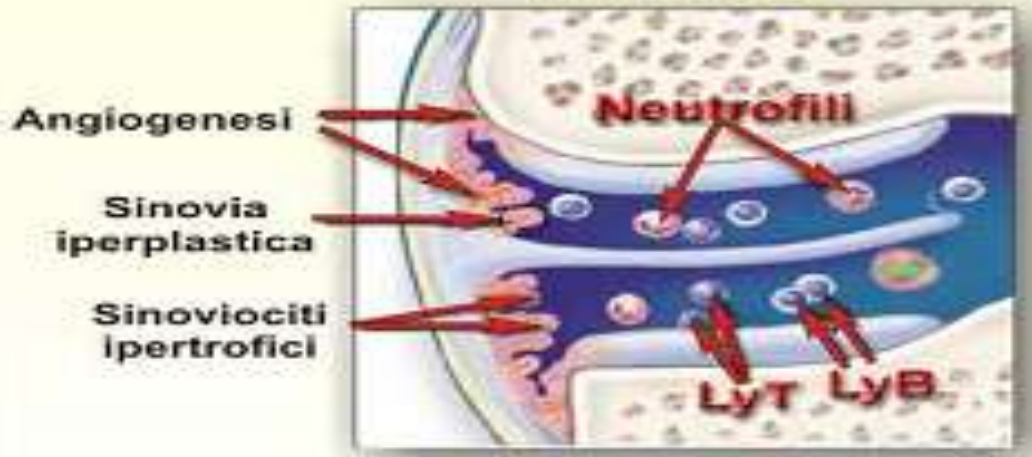

IPERTROFIA
SINOVIALE
IPOTROFIA
INTEROSSEI
NODULI
REUMATOIDI
DEVIAZIONE
ULNARE MCF

Gorla 99

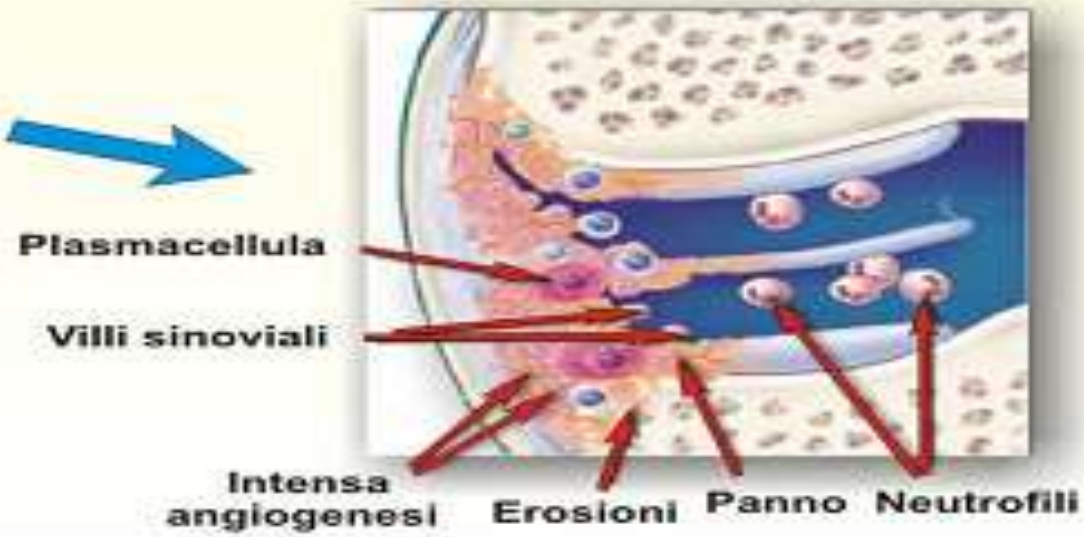
Articolazione normale



Artrite reumatoide iniziale

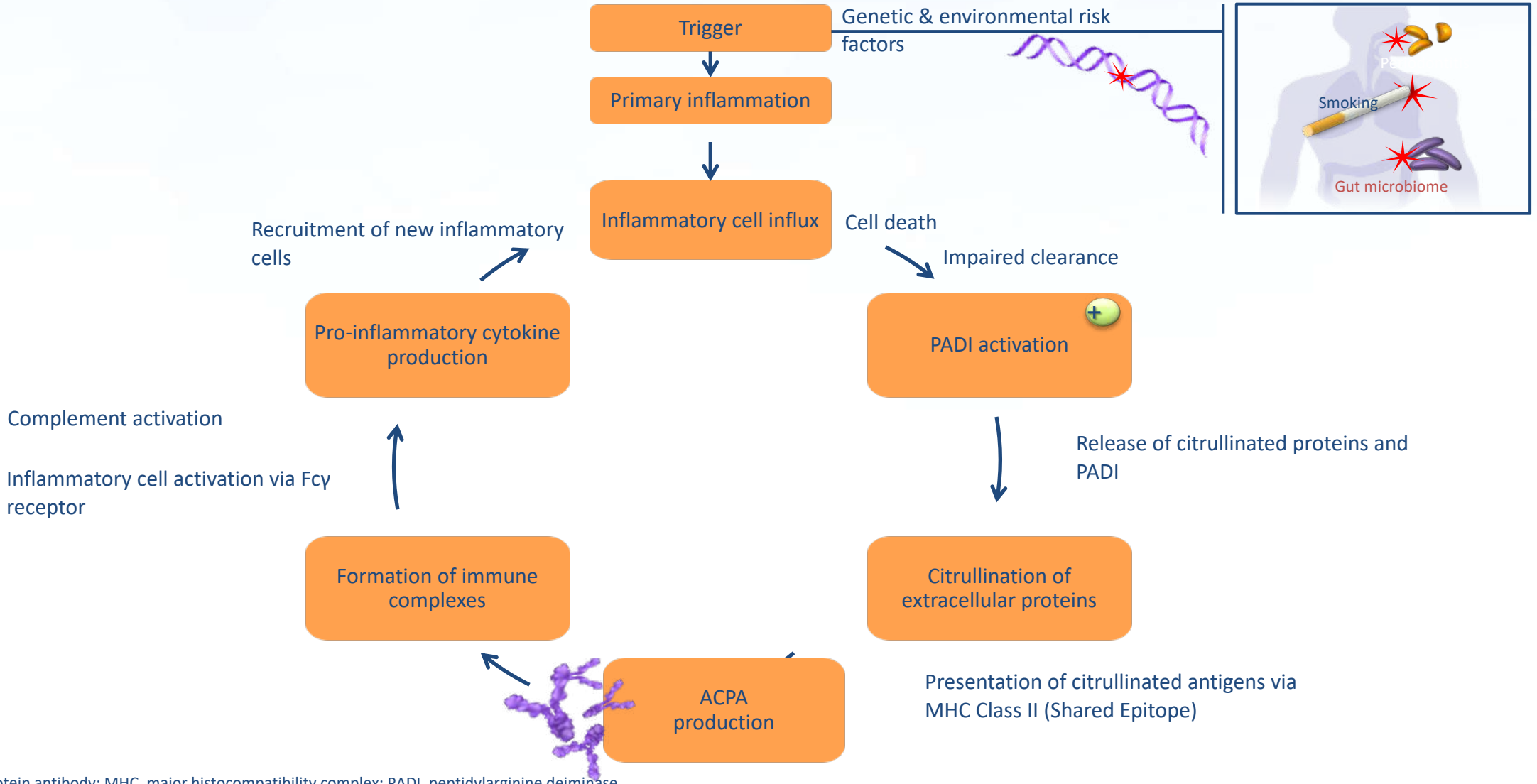


Artrite reumatoide tardiva



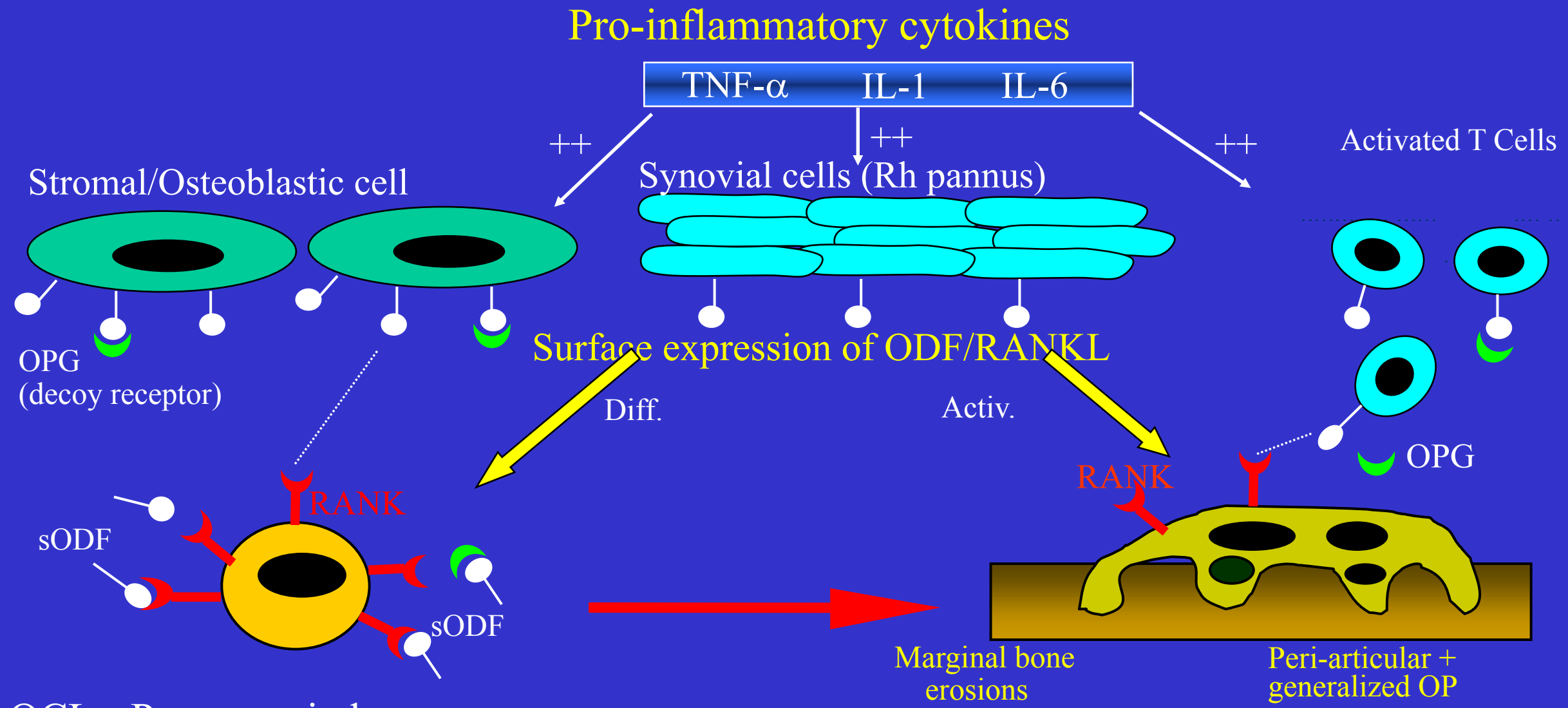
by A. Ferrante

Hypothesized Rheumatoid Arthritis Cycle



ACPA, anti-citrullinated protein antibody; MHC, major histocompatibility complex; PADI, peptidylarginine deiminase.
Adapted from 1. van Venrooij WJ, et al. *Nat Rev Rheumatol* 2011;**7**:391–8.

Molecular basis of bone disease in RA

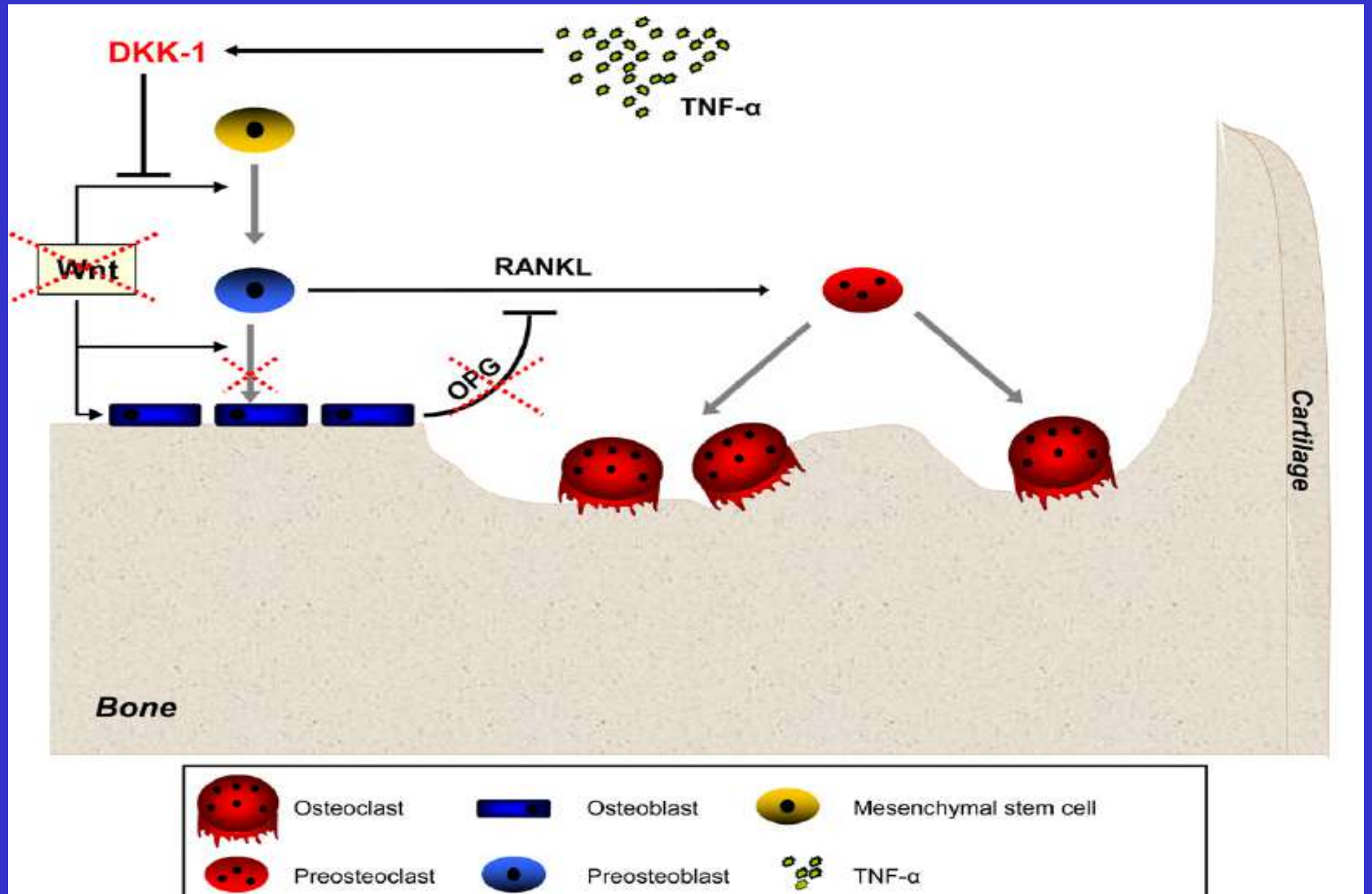


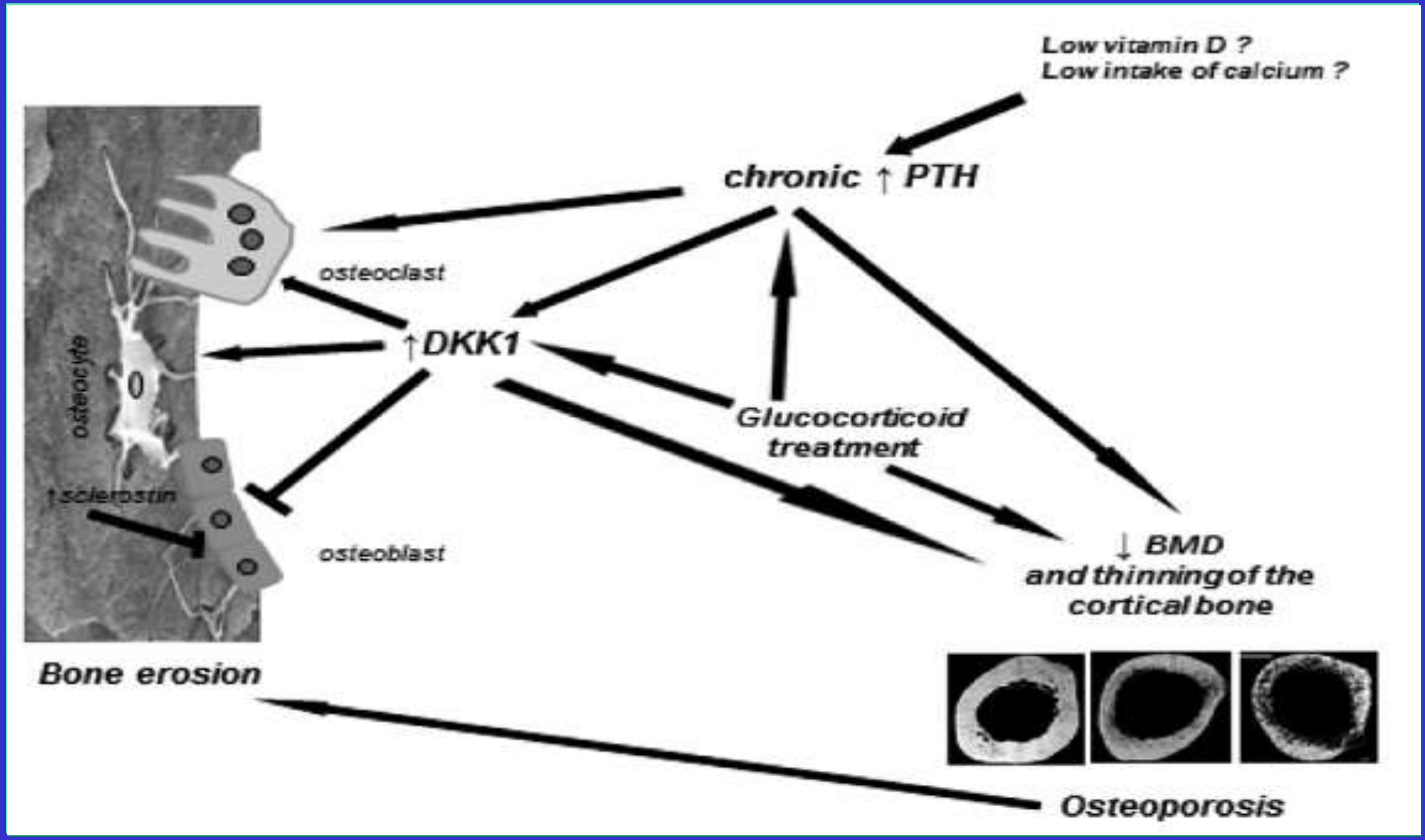
Gravallese EM et al, Arthritis Rheum,2000

Kong YY et al, Nature, 1999

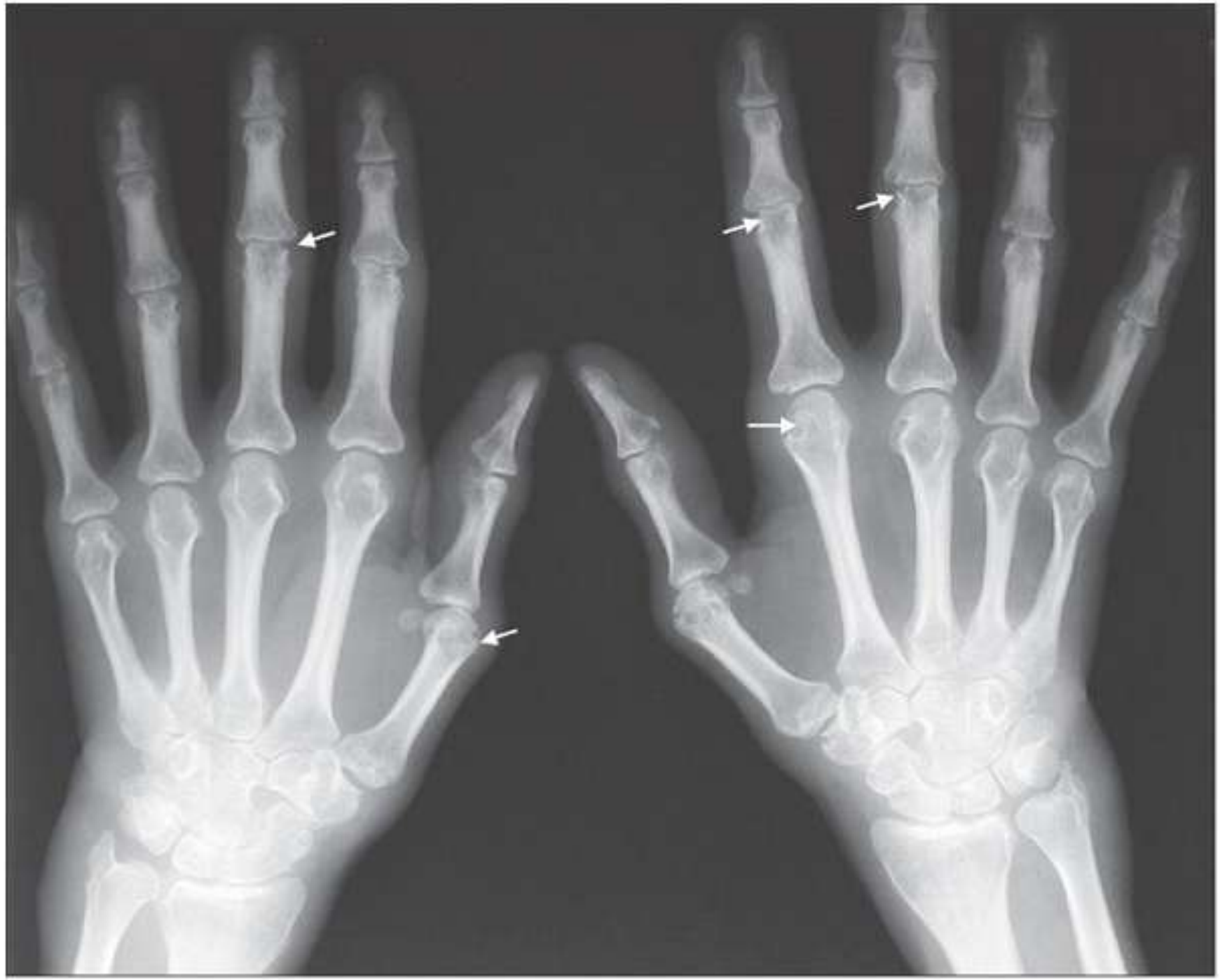
Inflammation and destruction of the joints:
TNF-alpha is strong inducer of DKK-1, an inhibitor of the Wnt pathway

Polzer K *et al*, Joint Bone Spine 2008





Rossini M., Clin Exp Rheumatol. 2015



McQueen *Arthritis Research & Therapy* 2012, **14**:224
http://arthritis-research.com/content/14/5/224

arthritis research&therapy

REVIEW

Bone marrow edema and osteitis in rheumatoid arthritis: the imaging perspective

Fiona M McQueen*

Fig. Legend

B cell

Plasma cell

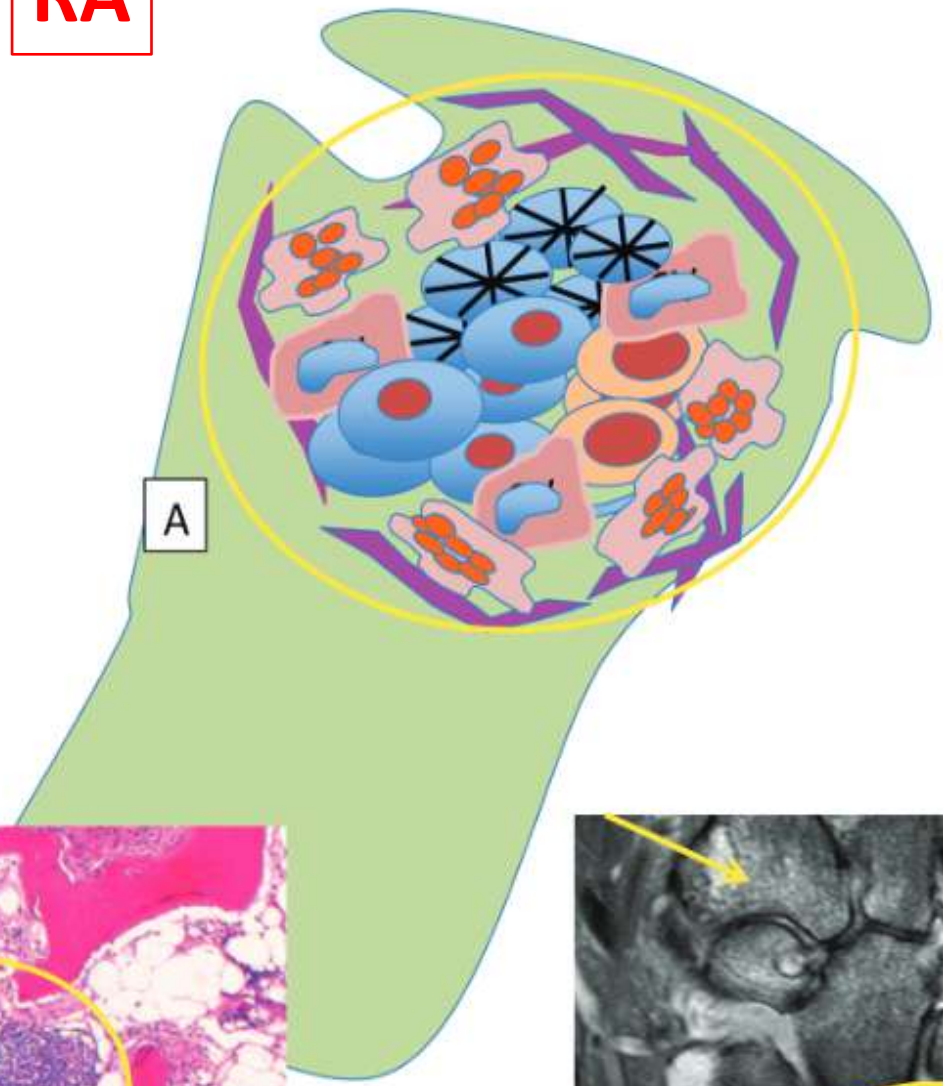
T cell

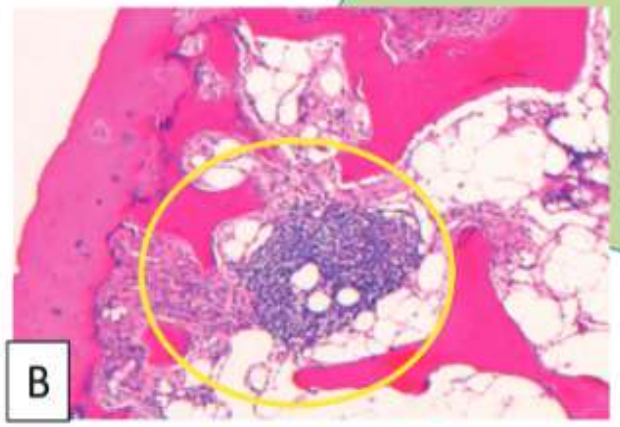
Macrophage

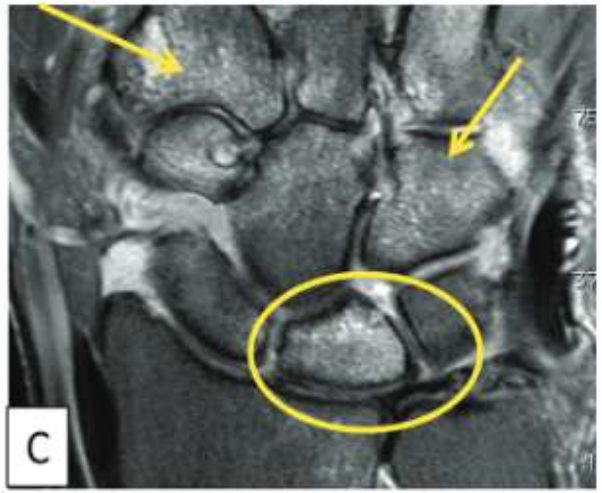
Osteoclast

Bony trabeculae

RA

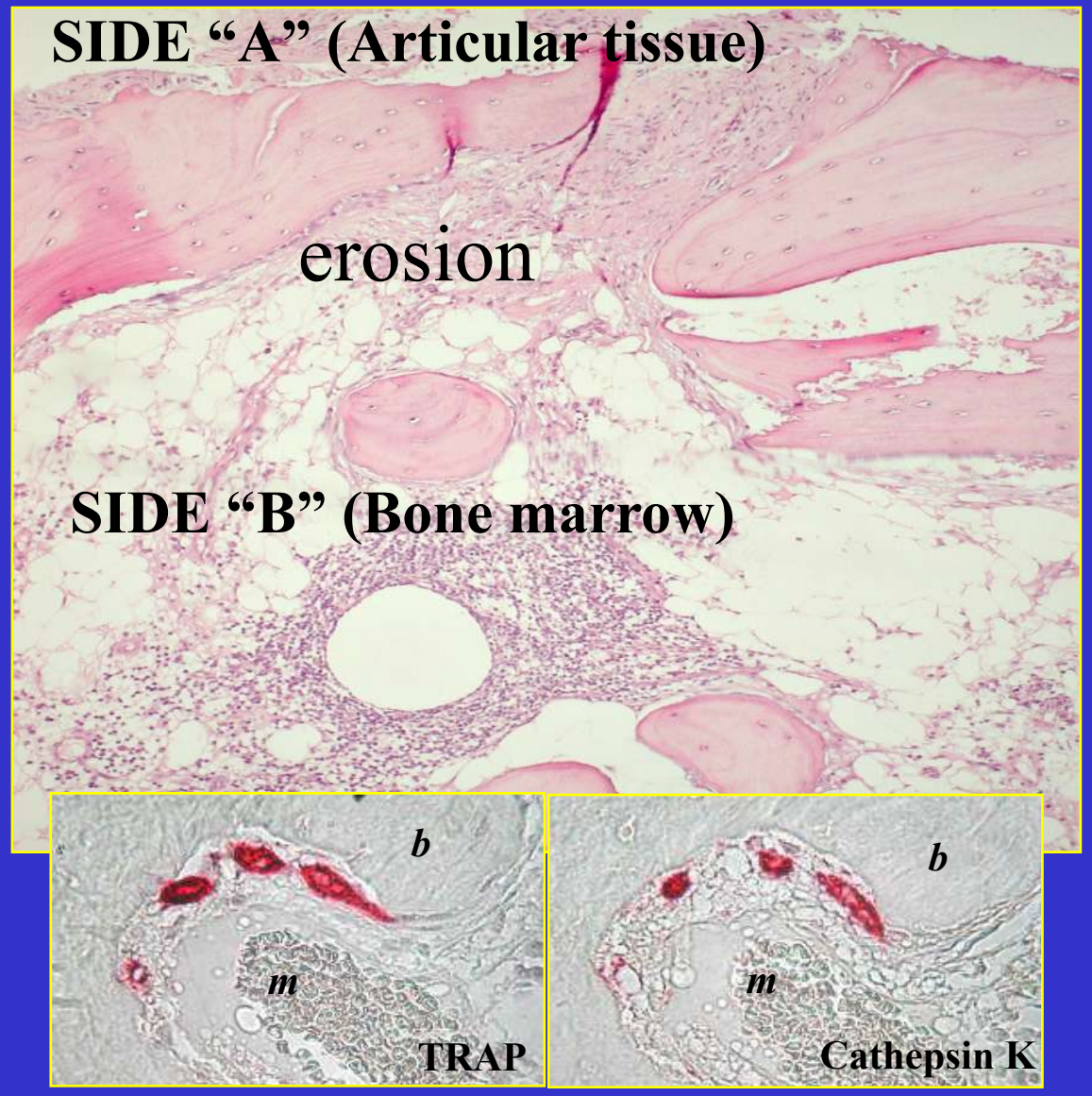


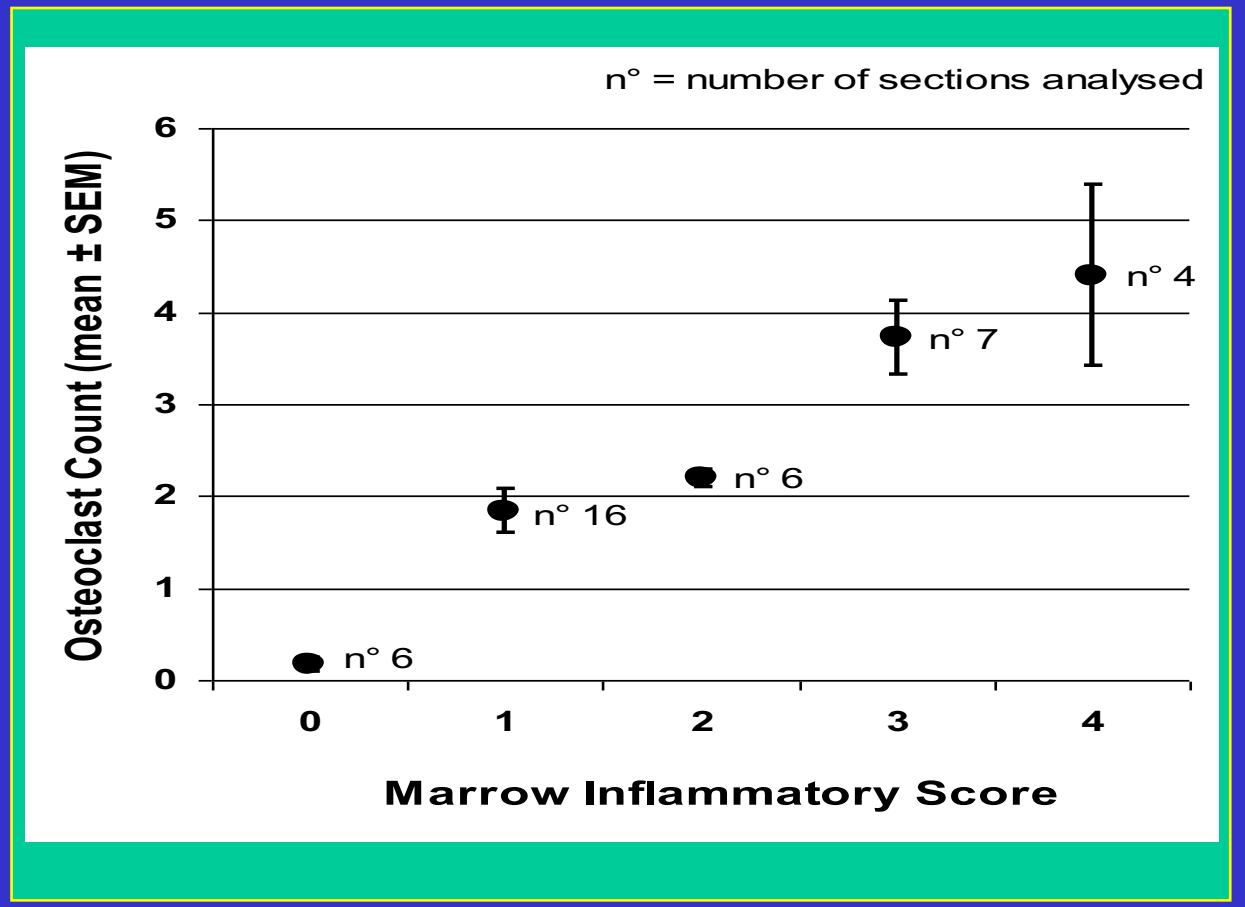




RA

Inflammation/organization and bone damage



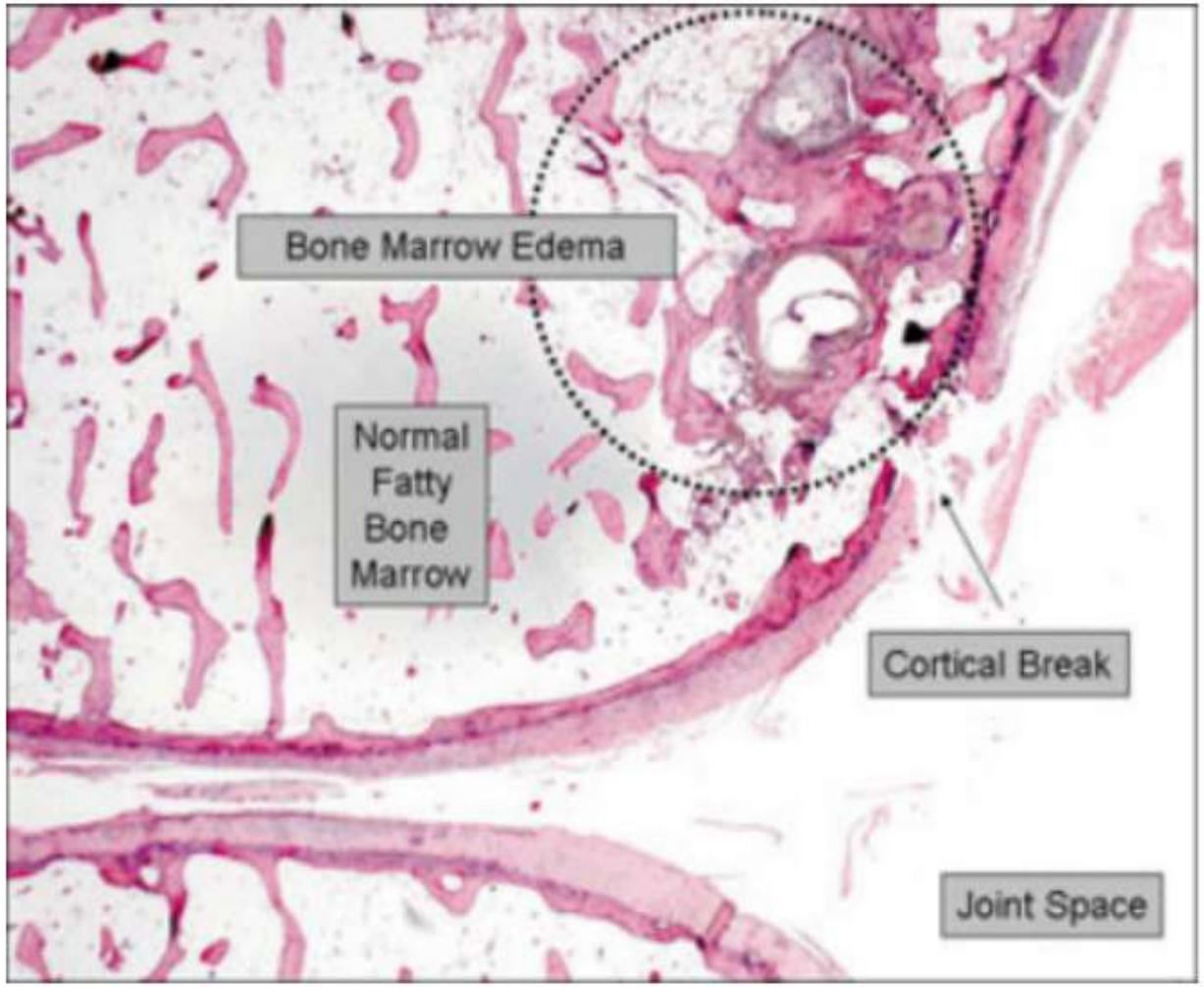


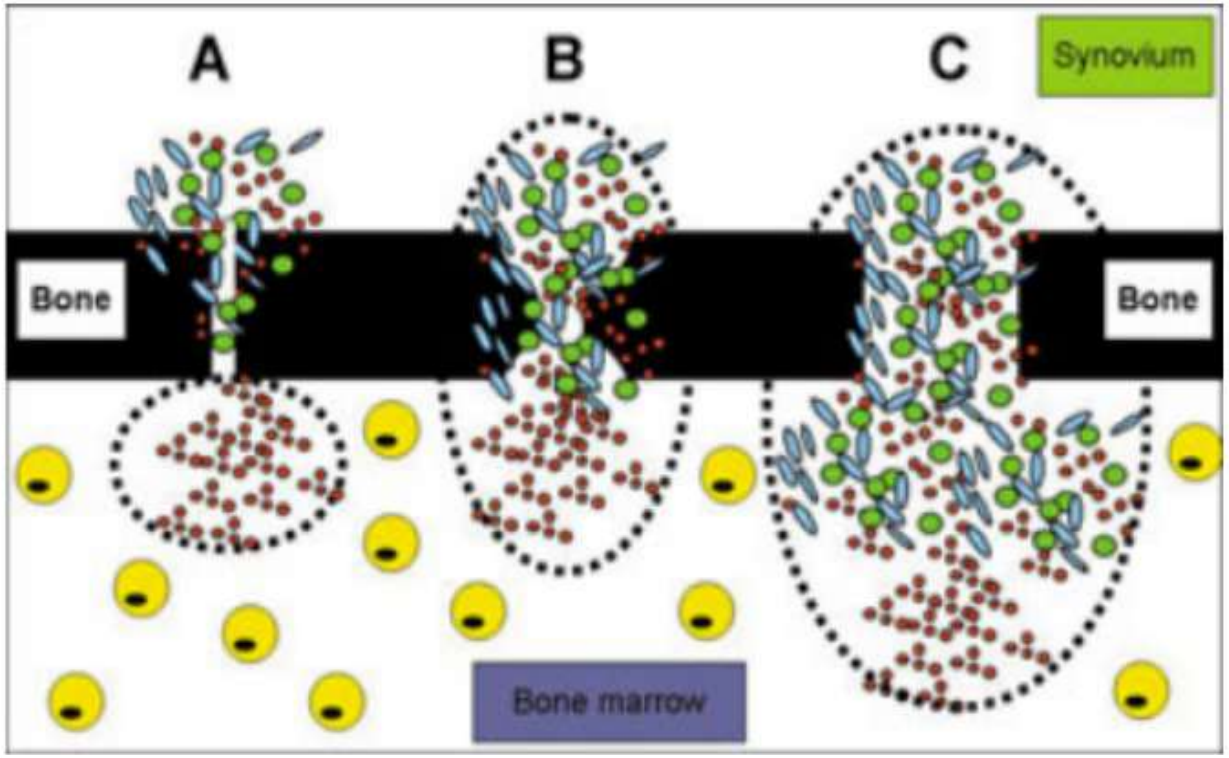
Erosion begins both inside and outside the bone

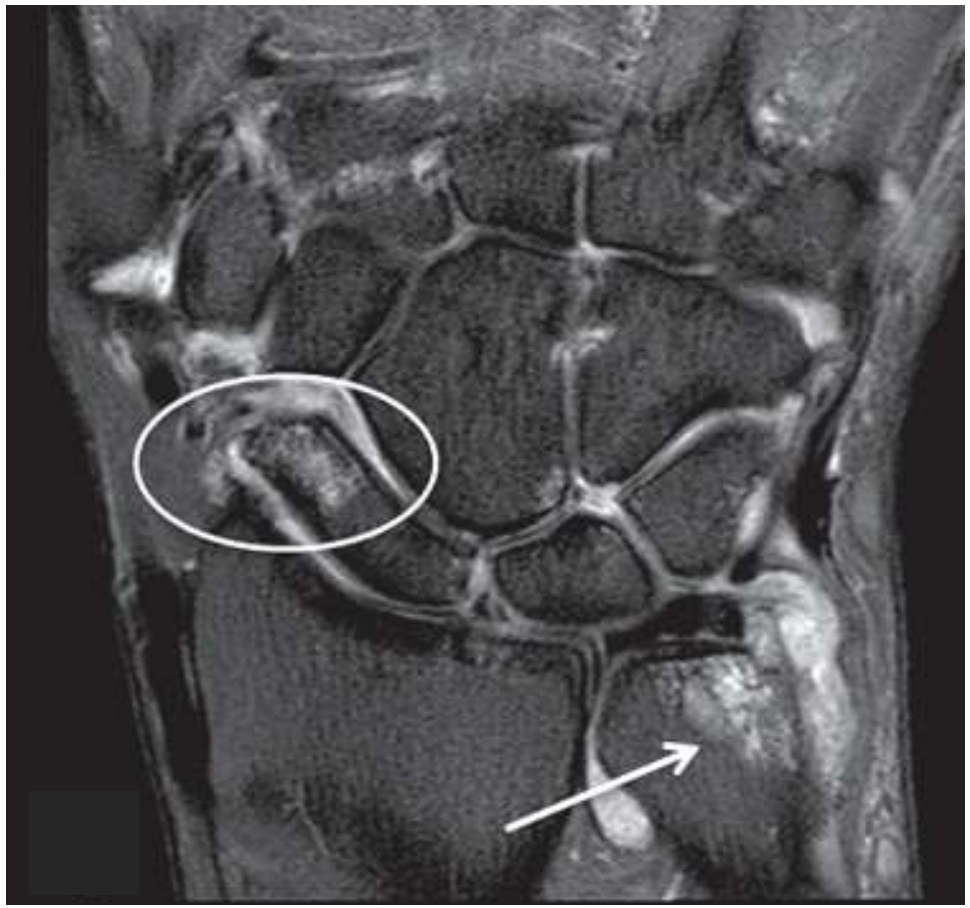
Bugatti S et al. Arthritis Rheum 2005

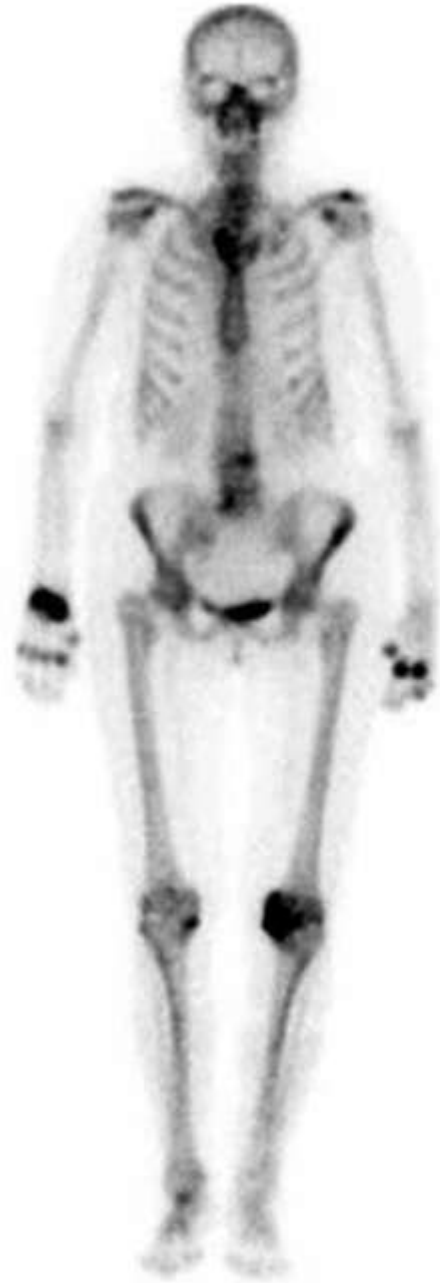
RA

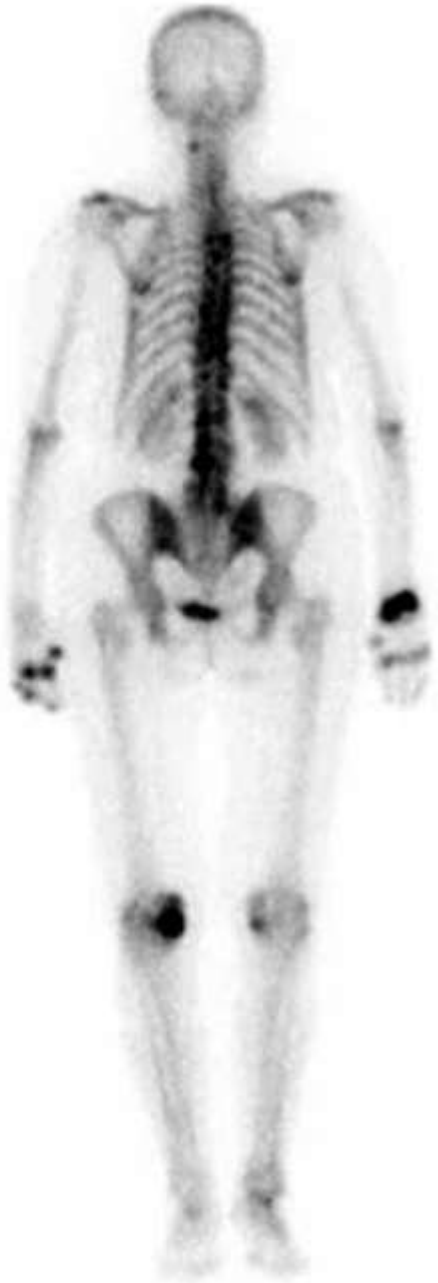
Schett: Bone Marrow Edema











Autoantibodies Associated With RA

Rheumatoid Factor (RF): Associated with RA, but also other autoimmune diseases, such as systemic lupus erythematosus, Sjögren's syndrome and cryoglobulinemia, and chronic infectious (hepatitis C virus)

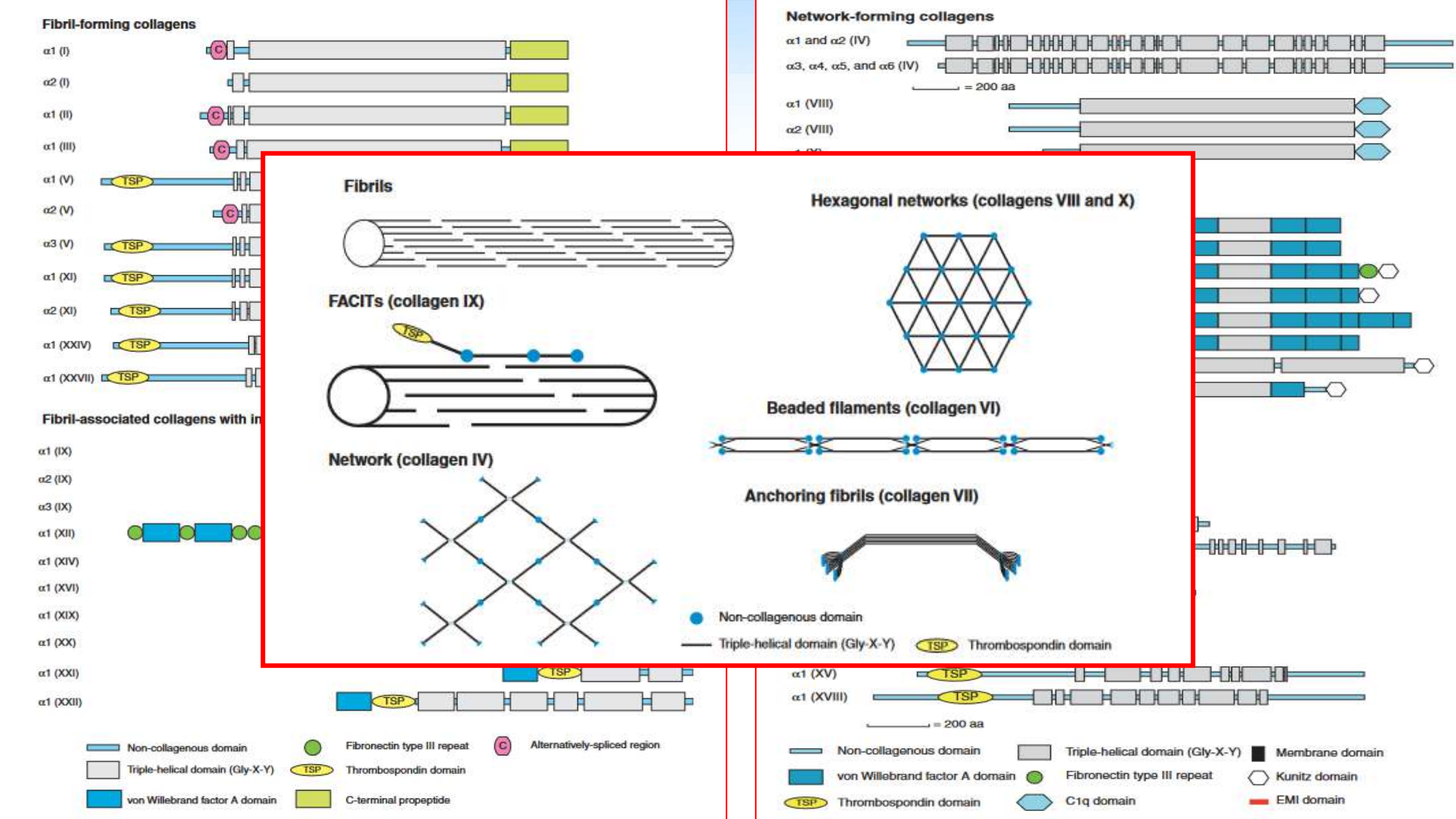
Anti-Citrullinated Protein Antibodies (ACPA): Many proteins can be citrullinated (Fibrinogen,Vimentin, Type II collagen α-enolase)

Additional Autoantibodies Associated With RA

Autoantibody	Recognizes	Details
Anti-MCV[1,2]	Mutated citrullinated vimentin	Reactive against citrullinated vimentin with mutations; may be associated with worse disease outcomes
Anti-CarP[3]	Carbamylated proteins: lysine converted to homocitrulline	May be predictive of a more severe clinical course in patients with RA
Anti-CII[4]	Type II collagen	Patients with anti–CII-positive patients may have increased joint destruction and HAQ scores at baseline compared with anti–CII-negative patients

Anti-MCV, anti–mutated citrullinated vimentin; anti-CarP, anti-carbamylated protein; anti-CII, anti–type II collagen; HAQ; Health Assessment Questionnaire; RA, rheumatoid arthritis.

1. Bang H, et al. *Arthritis Rheum* 2007;**56**:2503–11. 2. Mathsson L, et al. *Arthritis Rheum* 2008;**58**:36–45. 3. Shi J, et al. *Proc Natl Acad Sci USA.* 2011;**108**:17372–77. 4. Mullazehi M, et al. *Arthritis Res Ther* 2012;**14**:R100.


Fibril-forming collagens
α1 (I)
α2 (I)
α1 (II)
α1 (III)
α1 (V)
α2 (V)
α3 (V)
α1 (XI)
α2 (XI)
α1 (XXIV)
α1 (XXVII)
Fibril-associated collagens with in
α1 (IX)
α2 (IX)
α3 (IX)
α1 (XII)
α1 (XIV)
α1 (XVI)
α1 (XIX)
α1 (XX)
α1 (XXI)
α1 (XXII)
Network-forming collagens
α1 and α2 (IV)
α3, α4, α5, and α6 (IV)
= 200 aa
α1 (VIII)
α2 (VIII)
α1 (XV)
α1 (XVIII)
= 200 aa
Fibrils
FACITs (collagen IX)
Network (collagen IV)
Hexagonal networks (collagens VIII and X)
Beaded filaments (collagen VI)
Anchoring fibrils (collagen VII)
Non-collagenous domain
Triple-helical domain (Gly-X-Y)
Thrombospondin domain
Fibronectin type III repeat
Alternatively-spliced region
von Willebrand factor A domain
C-terminal propeptide
Triple-helical domain (Gly-X-Y)
Membrane domain
von Willebrand factor A domain
Fibronectin type III repeat
Kunitz domain
Thrombospondin domain
C1q domain
EMI domain

Tropocollageno peptidasi

N propeptide terminale staccato

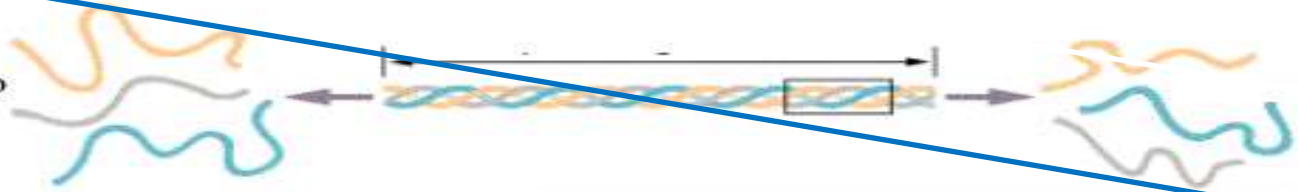
C propeptide terminale stacca

PINP

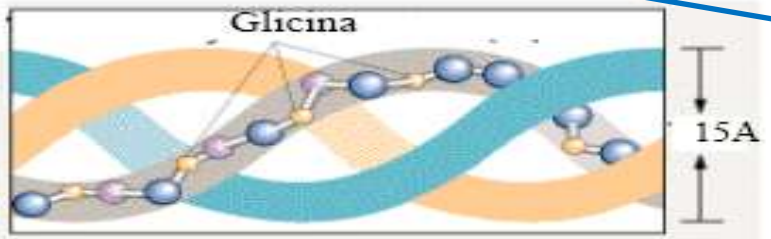
PIINP

PICP

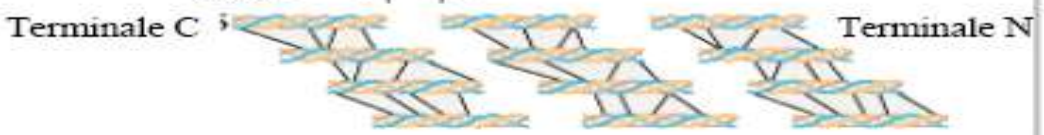
PIINP

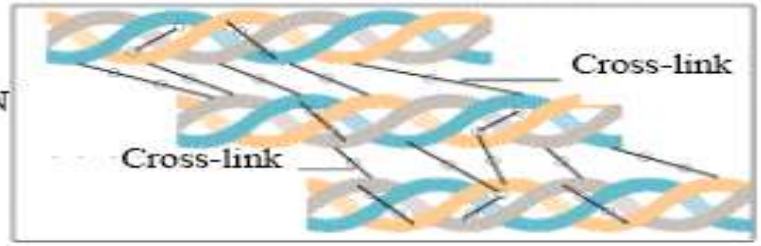


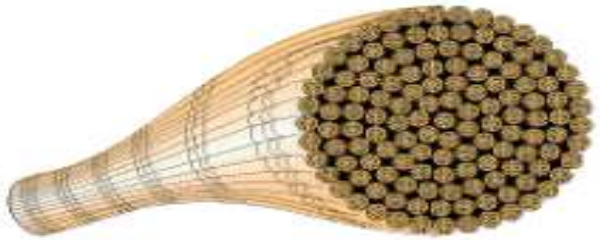
Assemblamento del tropocollageno in fibre di collageno



Formazione di cross-link covalenti







fibrilla di collageno

IL COLLAGENE: STRUTTURA

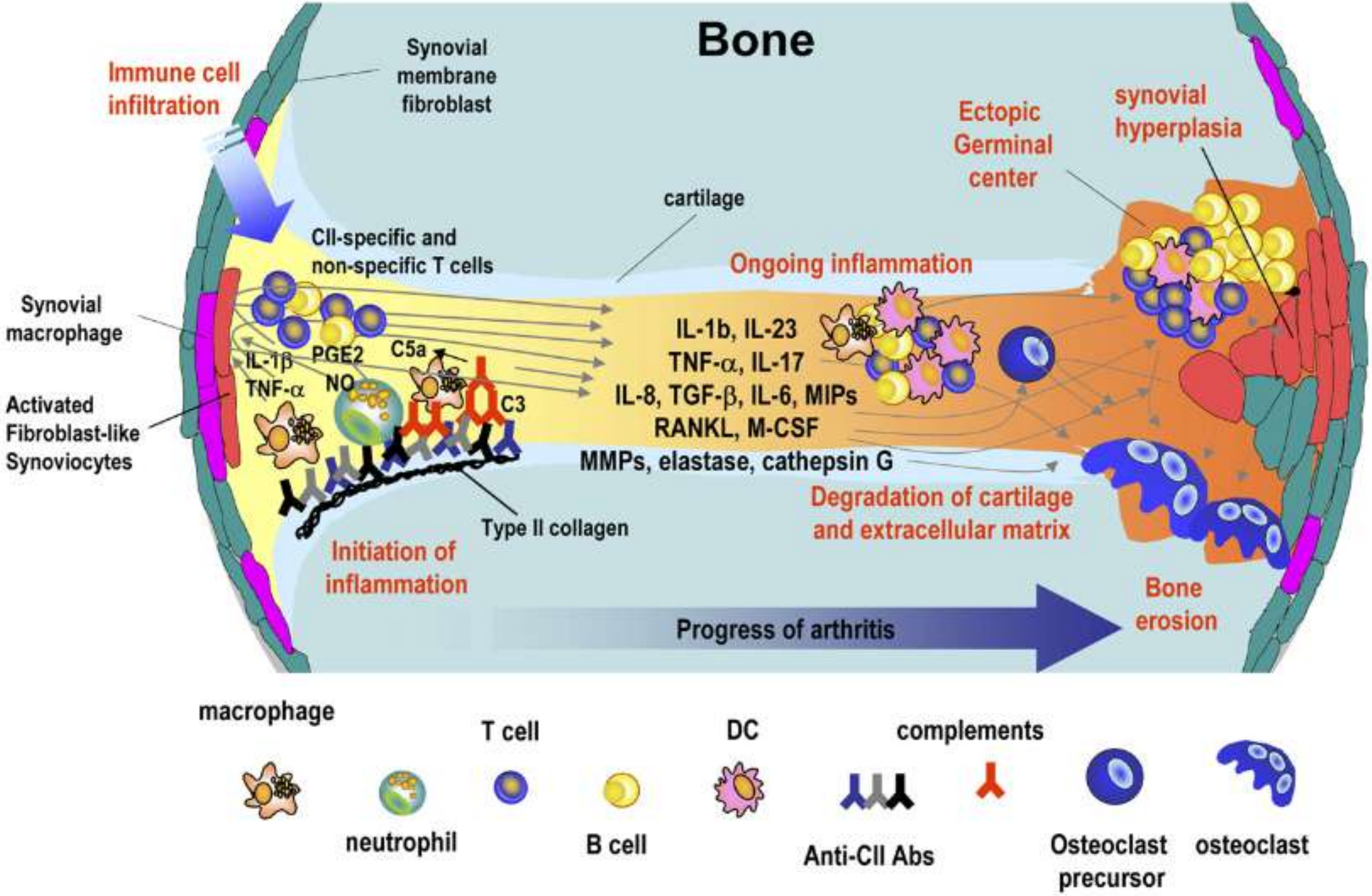
Available online at www.sciencedirect.com
ScienceDirect
Autoimmunity Reviews 7 (2007) 65–70
AUTOIMMUNITY REVIEWS
www.elsevier.com/locate/autrev

Type II collagen autoimmunity in a mouse model of human rheumatoid arthritis

Young-Gyu Cho, Mi-La Cho, So-Youn Min, Ho-Youn Kim *

Department of Medicine, Division of Rheumatology, Center for Rheumatoid Diseases and Rheumatism Research Center (RhRC), Catholic Research Institutes of Medical Sciences, Catholic University of Korea, Seoul, Republic of Korea

Received 13 July 2007; accepted 4 August 2007
Available online 30 August 2007


Bone
Immune cell infiltration
Synovial membrane fibroblast
Ectopic Germinal center
synovial hyperplasia
cartilage
CII-specific and non-specific T cells
Ongoing inflammation
Synovial macrophage
IL-1β
TNF-α
PGE2
NO
C5a
C3
IL-1b, IL-23
TNF-α, IL-17
IL-8, TGF-β, IL-6, MIPs
RANKL, M-CSF
MMPs, elastase, cathepsin G
Activated Fibroblast-like Synoviocytes
Type II collagen
Degradation of cartilage and extracellular matrix
Initiation of inflammation
Bone erosion
Progress of arthritis
macrophage
T cell
DC
complements
neutrophil
B cell
Anti-CII Abs
Osteoclast precursor
osteoclast

ARTHRITIS & RHEUMATISM
Vol. 46, No. 9, September 2002, pp 2339–2348
DOI 10.1002/art.10472

Epitope-Specific Recognition of Type II Collagen by Rheumatoid Arthritis Antibodies Is Shared With Recognition by Antibodies That Are Arthritogenic in Collagen-Induced Arthritis in the Mouse

Harald Burkhardt,[1] Tobias Koller,[1] Åke Engström,[2] Kutty Selva Nandakumar,[3] Javier Turnay,[4] Hans G. Kraetsch,[1] Joachim R. Kalden,[1] and Rikard Holmdahl[3]

Lindh *et al. Arthritis Research & Therapy* 2014, **16**:R143
http://arthritis-research.com/content/16/4/R143

arthritis research&therapy

RESEARCH ARTICLE Open Access

Type II collagen antibody response is enriched in the synovial fluid of rheumatoid joints and directed to the same major epitopes as in collagen induced arthritis in primates and mice

Ingrid Lindh[1], Omri Snir[2,4], Erik Lönnblom[1], Hüseyin Uysal[1,5], Ida Andersson[1], Kutty Selva Nandakumar[1], Michel Vierboom[3], Bert 't Hart[3], Vivianne Malmström[2] and Rikard Holmdahl[1*]

Berntson et al. Pediatric Rheumatology 2014, 12:22
http://www.ped-rheum.com/content/12/1/22

PEDIATRIC
RHEUMATOLOGY

RESEARCH Open Access

Anti-type II collagen antibodies, anti-CCP, IgA RF and IgM RF are associated with joint damage, assessed eight years after onset of juvenile idiopathic arthritis (JIA)

Lillemor Berntson[1*], Ellen Nordal[2,3], Anders Fasth[4], Kristiina Aalto[5], Troels Herlin[6], Susan Nielsen[7], Marite Rygg[8,9], Marek Zak[7], Johan Rönnelid[10] for the Nordic Study Group of Pediatric Rheumatology (NoSPeR)

Conclusions

Occurrence of anti-CII, anti-CCP, IgM RF or IgA RF analysed at an early stage of disease may predict later joint damage. Patients with more than one of these autoantibodies present merit special attention. Anti-CII in JIA seems to characterize a different subset of JIA patients than the other antibodies, associated with increased CRP levels early after disease onset, and with clinical joint damage after eight years.

Autoantibodies against collagen type II (anti-CII) have been studied in adult RA

CII is the predominant hyaline cartilage collagen.

Patients with anti-CII make up a distinct RA phenotype, found in a minority of adult RA patients, associated with acute inflammation at disease onset and early radiographic destruction.

Anti-CII has been shown to induce the proinflammatory cytokines TNFα, IL-1β and IL-8, when incorporated in immune complexes in vitro.

These findings are in concordance with earlier reports showing that high anti-CII levels are associated with higher levels of ESR, CRP, TNFα and IL-6 compared with what is found in anti-CII negative RA patients .

Anti-CII positive RA patients also experience less diagnostic delay , probably because of the high inflammatory activity.

In contrast to ACPA and RF, anti-CII does not precede the development of RA by a long time period.

Earlier studies have shown that levels of anti-CII decrease shortly after RA diagnosis

The anti-CII phenotype in adult RA thus seems to be a temporary finding around the time of symptom onset and diagnosis

Mullazehi et al. Arthritis Research & Therapy 2012, 14:R100
http://arthritis-research.com/content/14/3/R100

arthritis research&therapy

RESEARCH ARTICLE Open Access

Anti-type II collagen antibodies are associated with early radiographic destruction in rheumatoid arthritis

Mohammed Mullazehi[1], Marius C Wick[3], Lars Klareskog[2], Ronald van Vollenhoven[2] and Johan Rönnelid[1,2*]

Conclusion: In contrary to anti-CCP, anti-CII-positive patients with RA have increased joint destruction and HAQ score at baseline. Anti-CII thus characterizes an early inflammatory/destructive phenotype, in contrast to the late appearance of an inflammatory/destructive phenotype in anti-CCP positive RA patients. The anti-CII phenotype might account for part of the elderly acute onset RA phenotype with rather good prognosis.

Manivel et al. Arthritis Research & Therapy (2015) 17:8
DOI 10.1186/s13075-015-0523-7

arthritis research&therapy

RESEARCH ARTICLE Open Access

Anti-type II collagen immune complex-induced granulocyte reactivity is associated with joint erosions in RA patients with anti-collagen antibodies

Vivek Anand Manivel[1], Azita Sohrabian[1], Marius C Wick[2], Mohammed Mullazehi[1], Lena Douhan Håkansson[3] and Johan Rönnelid[1,4*]

PMN expression of CD11b, CD66b and MPO, and PBMC production of TNF-α were upregulated by anti-CII IC

Conclusion: PMN responses against anti-CII IC are more closely associated with early joint erosions than are PBMC cytokine responses. PMN reactivity against anti-CII IC may contribute to joint destruction in newly diagnosed RA patients with high levels of anti-CII.

OPEN ACCESS

EXTENDED REPORT

2017

Anticollagen type II antibodies are associated with an acute onset rheumatoid arthritis phenotype and prognosticate lower degree of inflammation during 5 years follow-up

Vivek Anand Manivel,[1] Mohammed Mullazehi,[1] Leonid Padyukov,[2] Helga Westerlind,[3] Lars Klareskog,[2] Lars Alfredsson,[3] Saedis Saevarsdottir,[2] Johan Rönnelid[1]

Conclusions Anti-CII seropositive RA represents a distinct phenotype, in many respects representing the converse to the clinical, genetic and smoking associations described for anticitrullinated protein peptide autoantibodies. Although not diagnostically useful, early anti-CII determinations predict favourable inflammatory outcome in RA.

Review paper

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Cartilage and bone damage in rheumatoid arthritis

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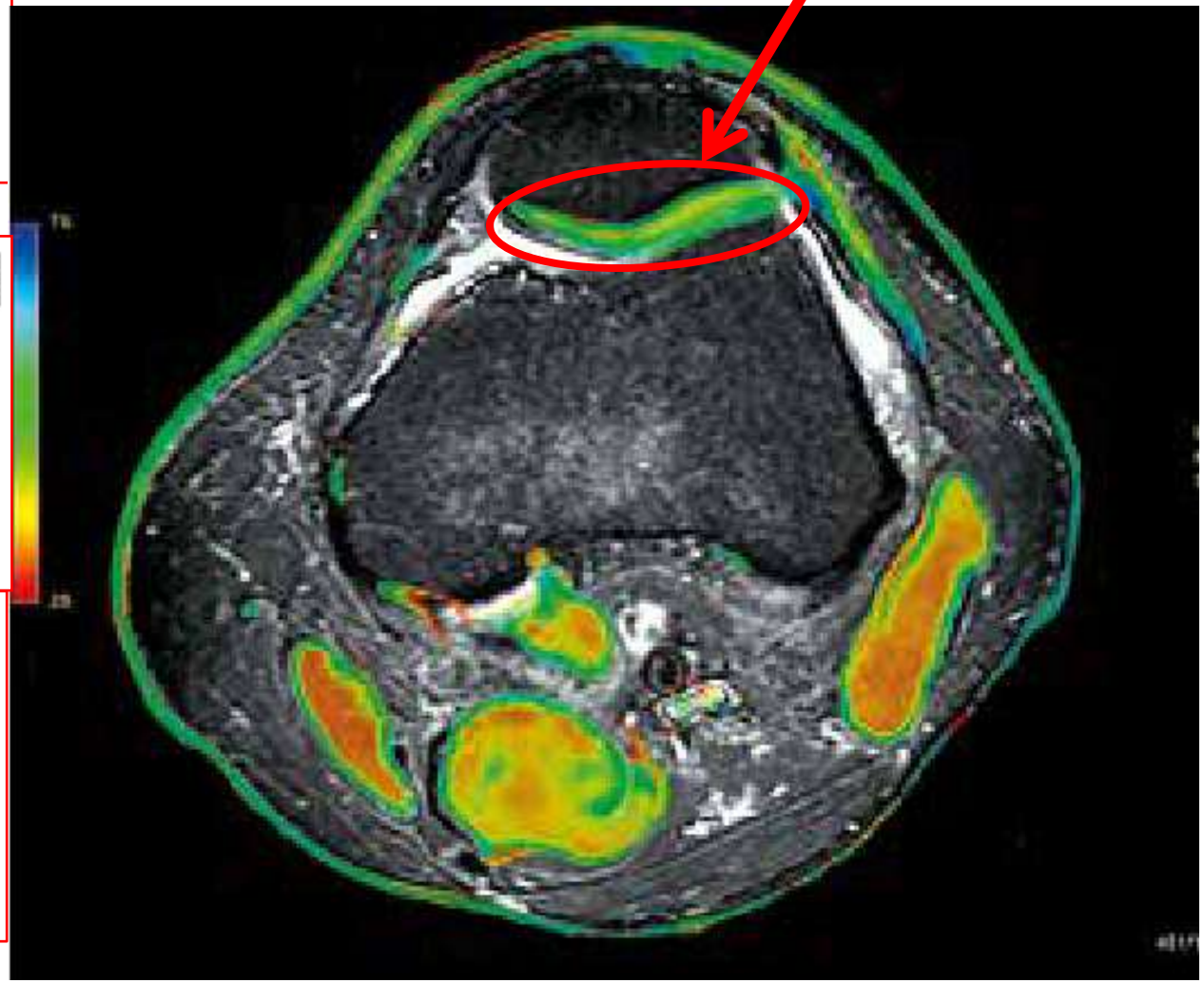
RA

MRI-T2 mapping
giallo=sofferenza cartilagine



Viewpoint

Does damage cause inflammation? Revisiting the link between joint damage and inflammation

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joint damage might be a cause of the active disease process, thus leading to a vicious cycle of events.
The autoimmune response in RA, the potential of cartilage and bone breakdown products to elicit inflammation and notions that in joints that have undergone surgery with cartilage removal RA does not flare.

PATOGENESI

Classica
Nuova (Inside)
Nuova (Cartilage)

Classica
Nuova (Tidemark/osso)