PHYTOTHERAPY FOR ARTHRITIS

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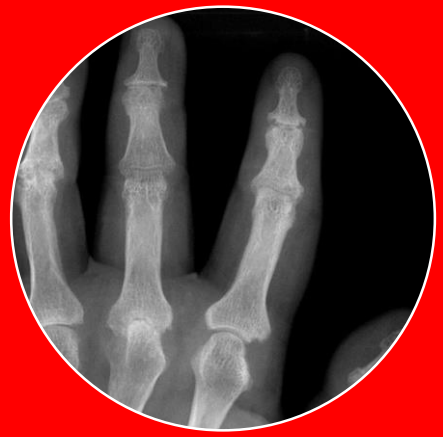


Capaian Pembelajaran (Mahasiswa mampu …)

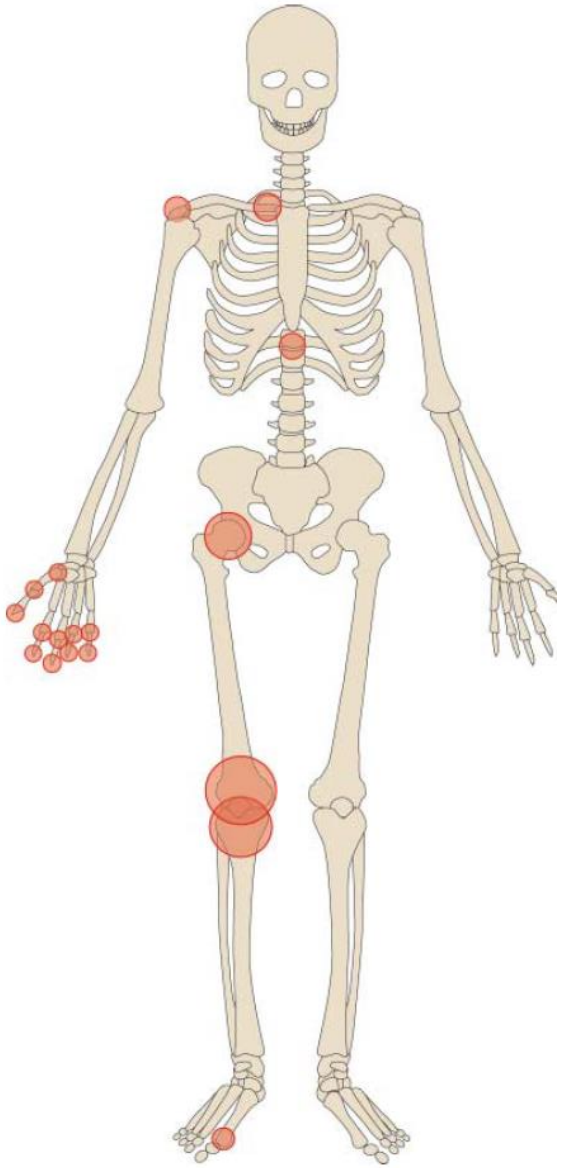
- memahami **gejala dan kondisi** osteoarthritis, RA, dan gout
- memahami **jenis tanaman obat** yang digunakan untuk arthritis
- memahami **mekanisme kerja, ESO, dan interaksi** yang berhubungan dengan penggunaan OT tsb
- **mengaplikasikan fitoterapi** pada kondisi arthritis **berdasarkan data ilmiah** masing-masing OT

Arthritis → joint (*arthro*) + inflammation (*itis*)

Osteoarthritis

Rheumatoid arthritis

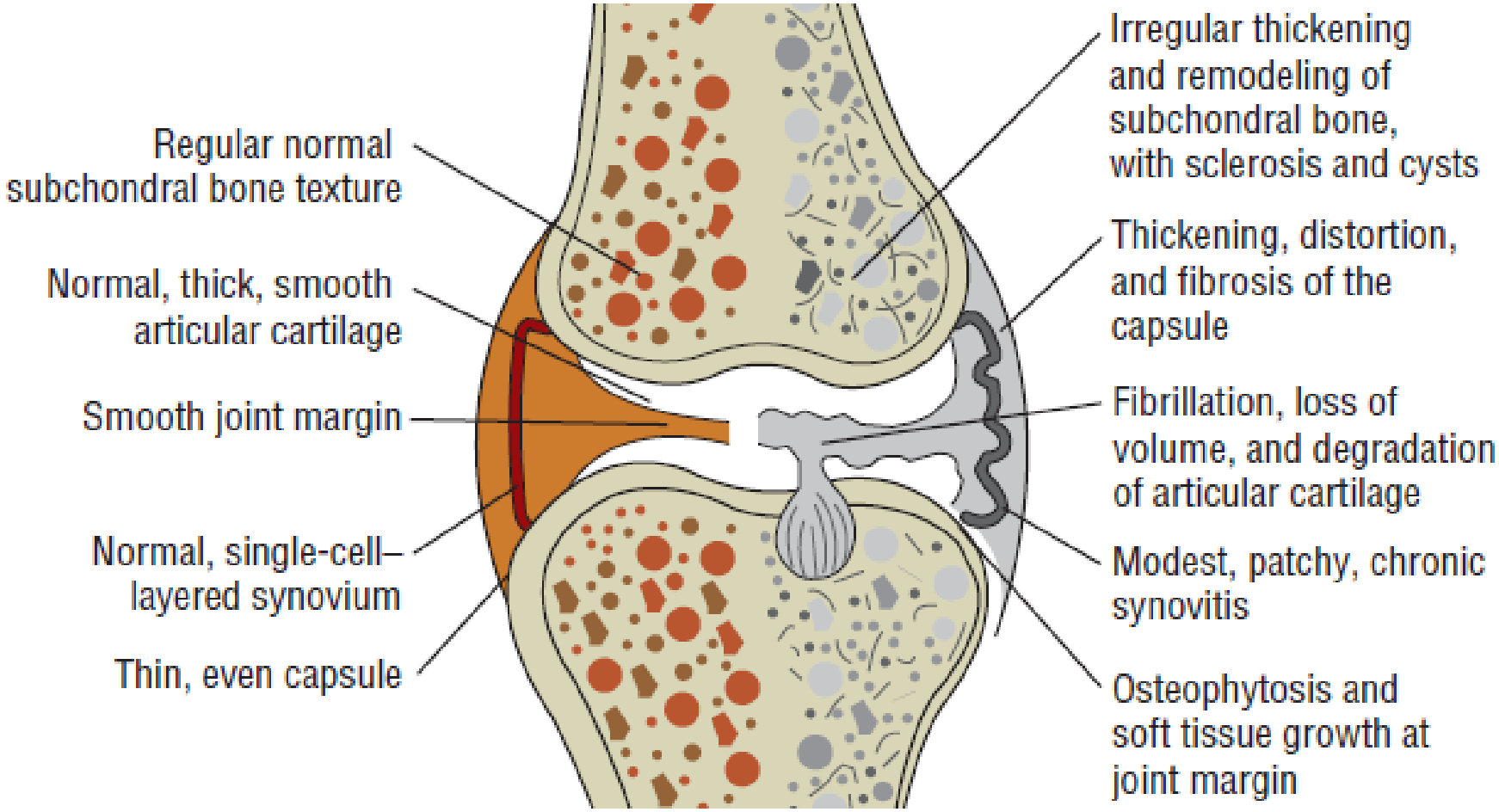
Gout



Osteoarthritis (OA)

***Degenerative joint disease* (DJD)**

Normal joint vs osteoarthritis

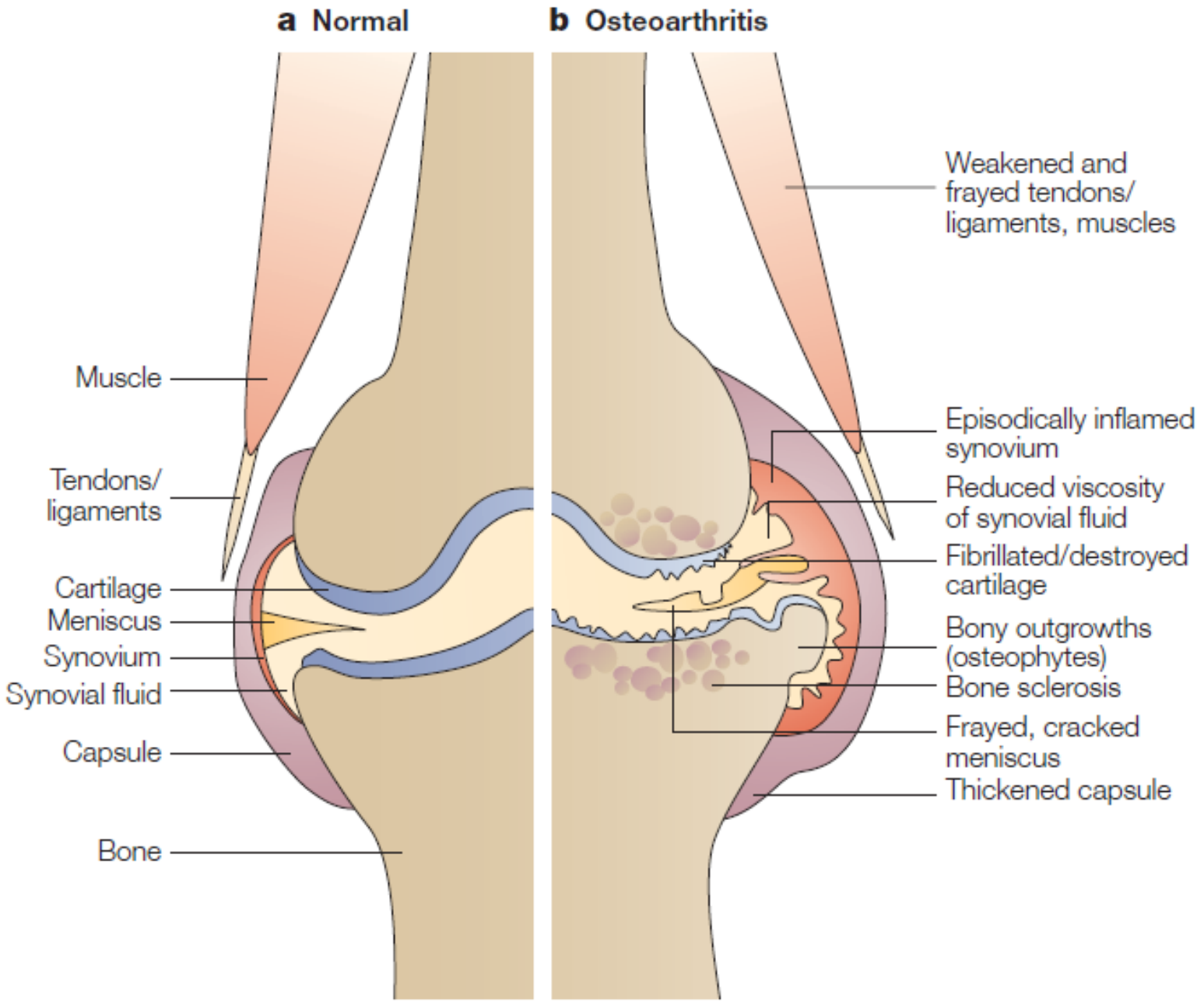


*OA represents a **failure of the chondrocytes** to maintain a proper balance between cartilage formation and destruction*

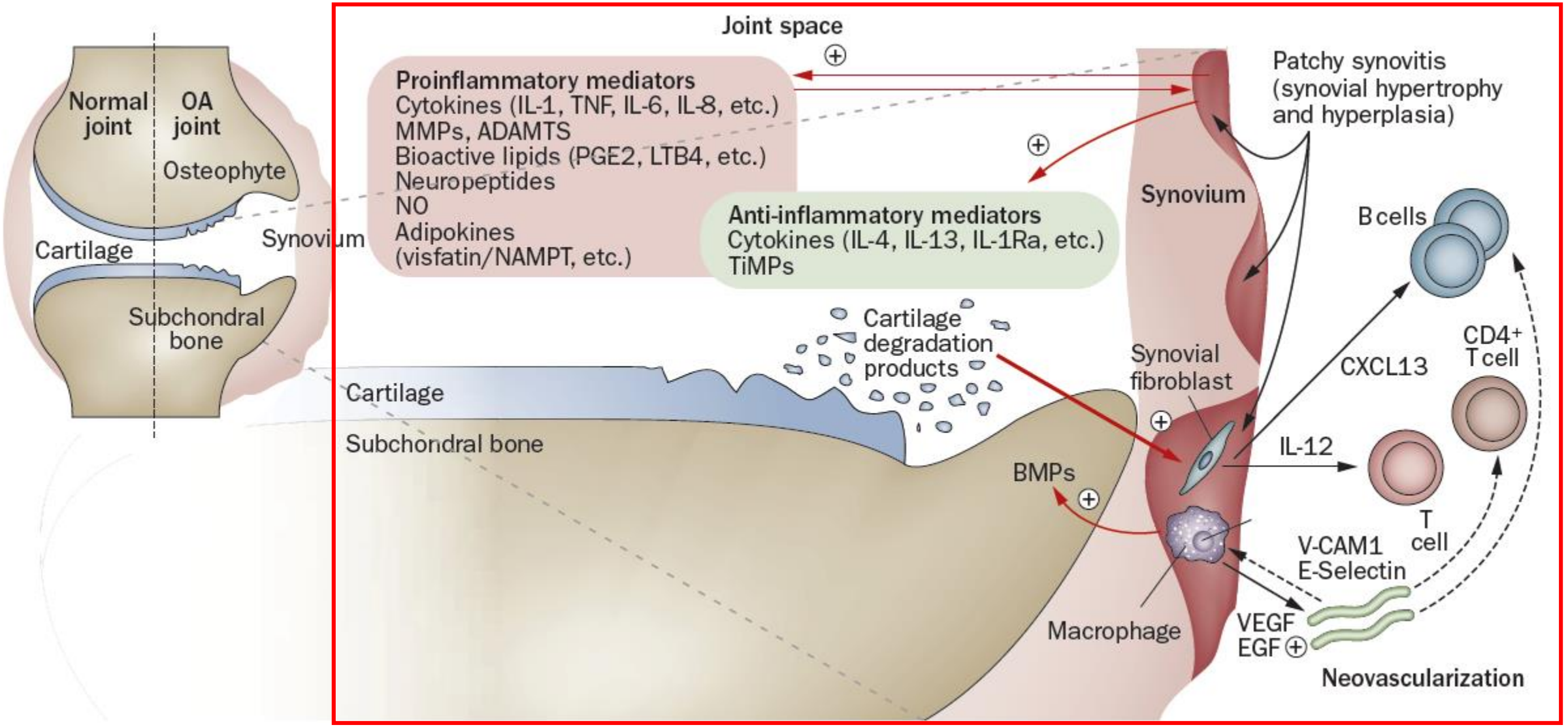
Synovial cell

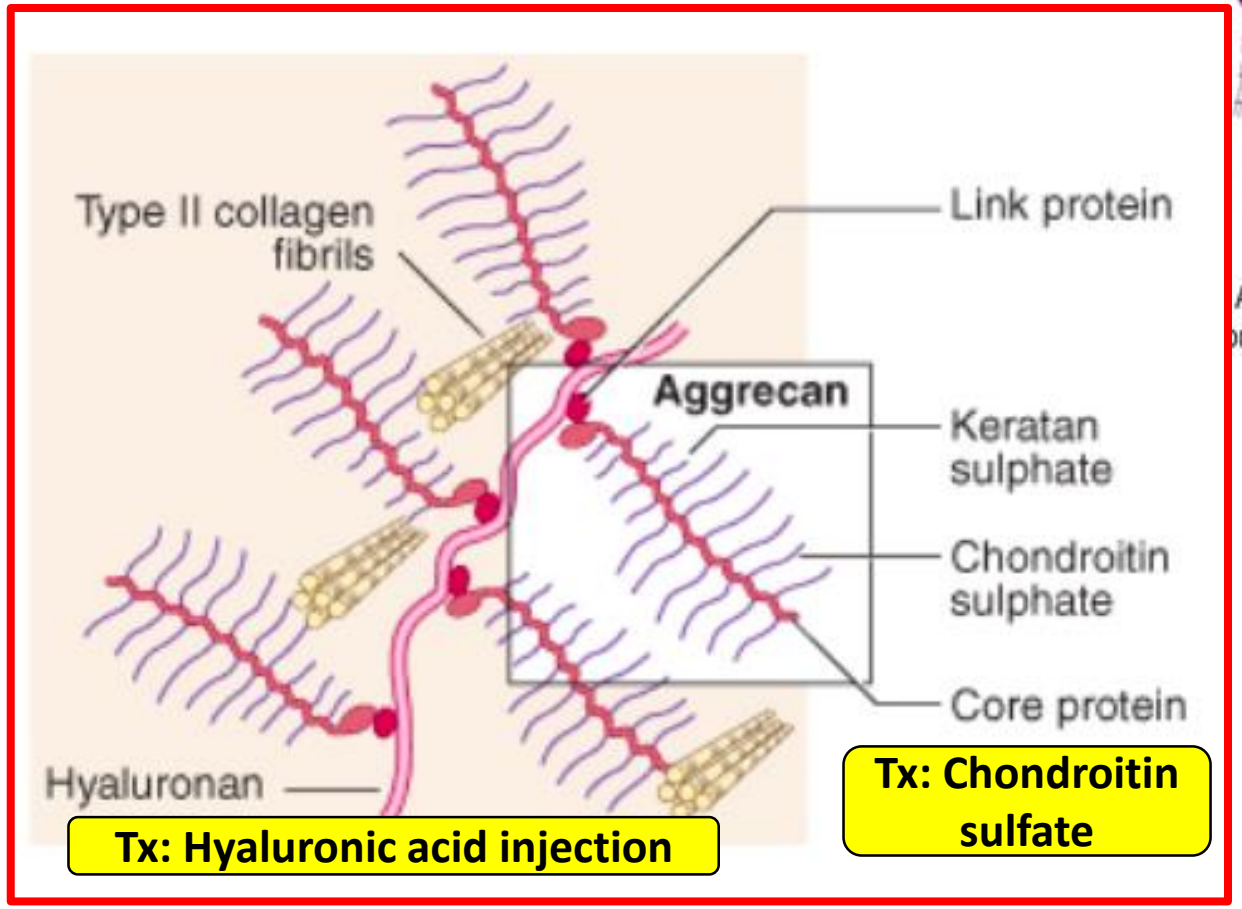
Type A: macrophage-like synovial cell → phagocytosis

Type B: fibroblast-like synovial cell → Secrete hyaluronic acid, & proteins complex (mucin) of synovial fluid



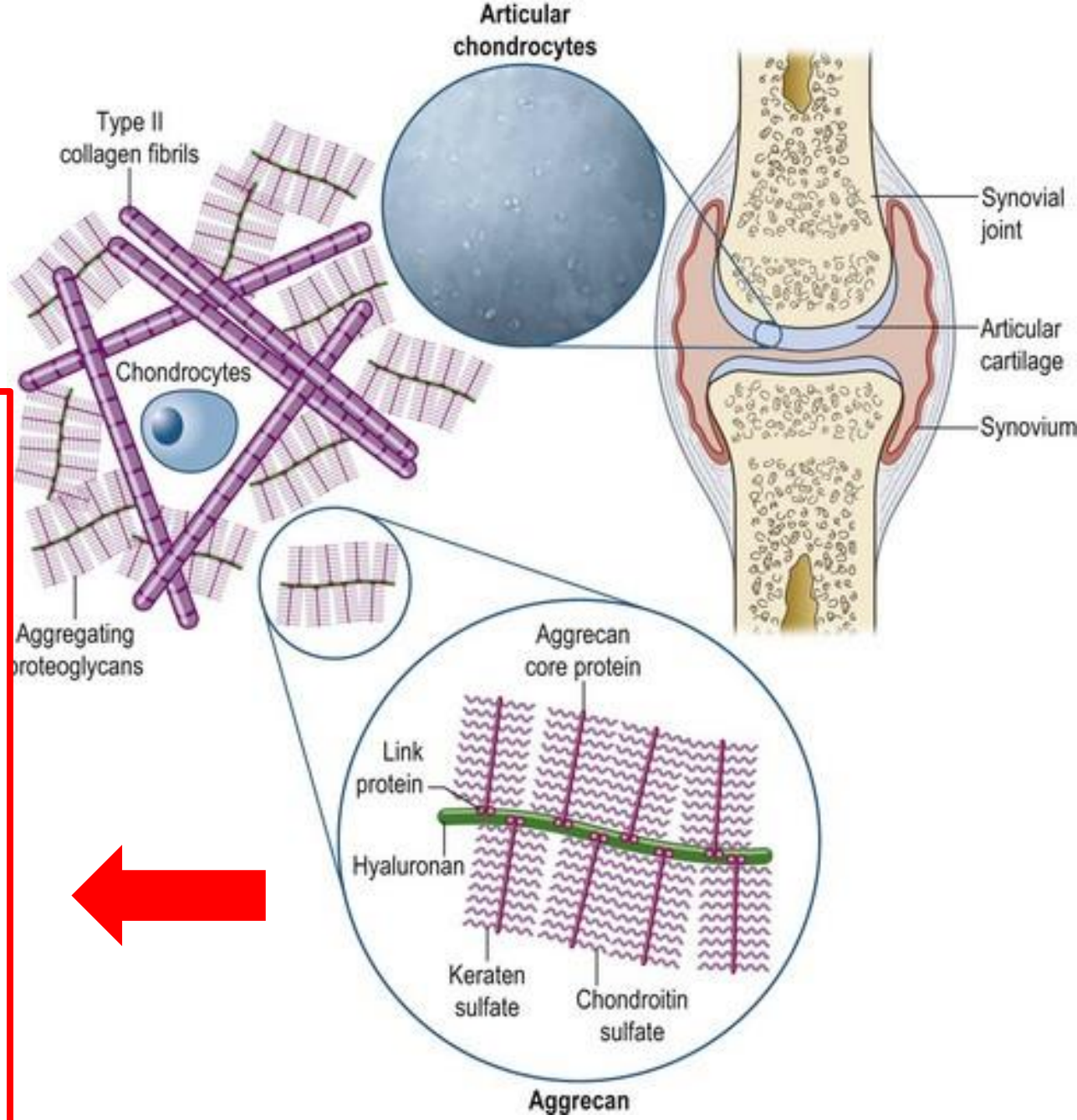
Involvement of the synovium in OA pathophysiology



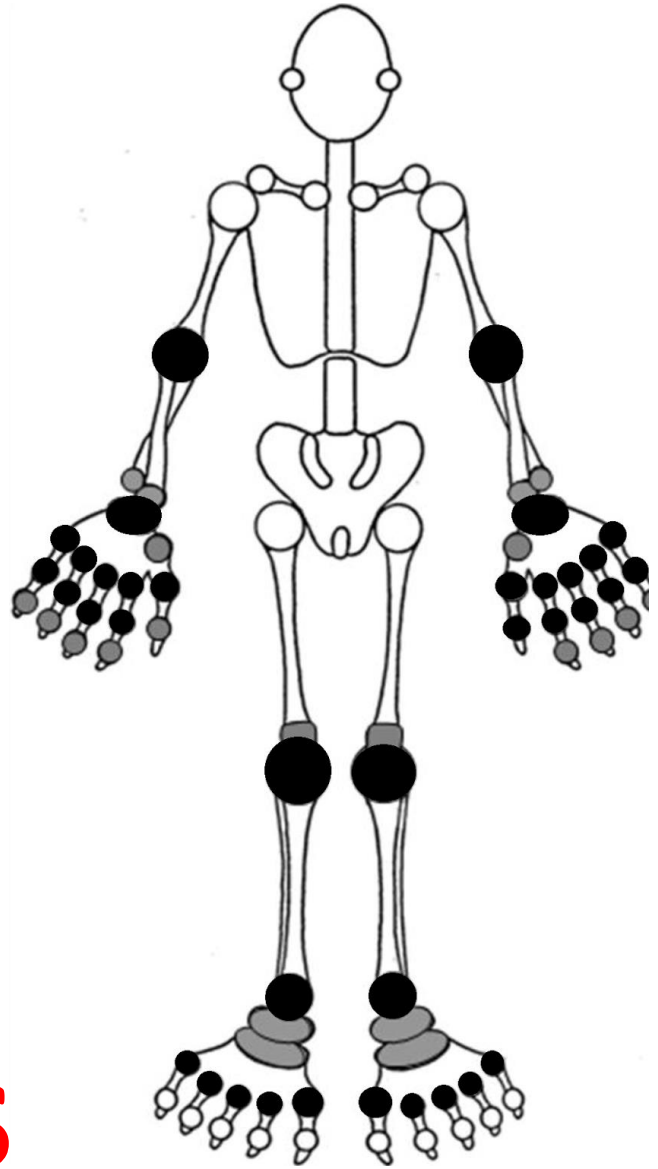


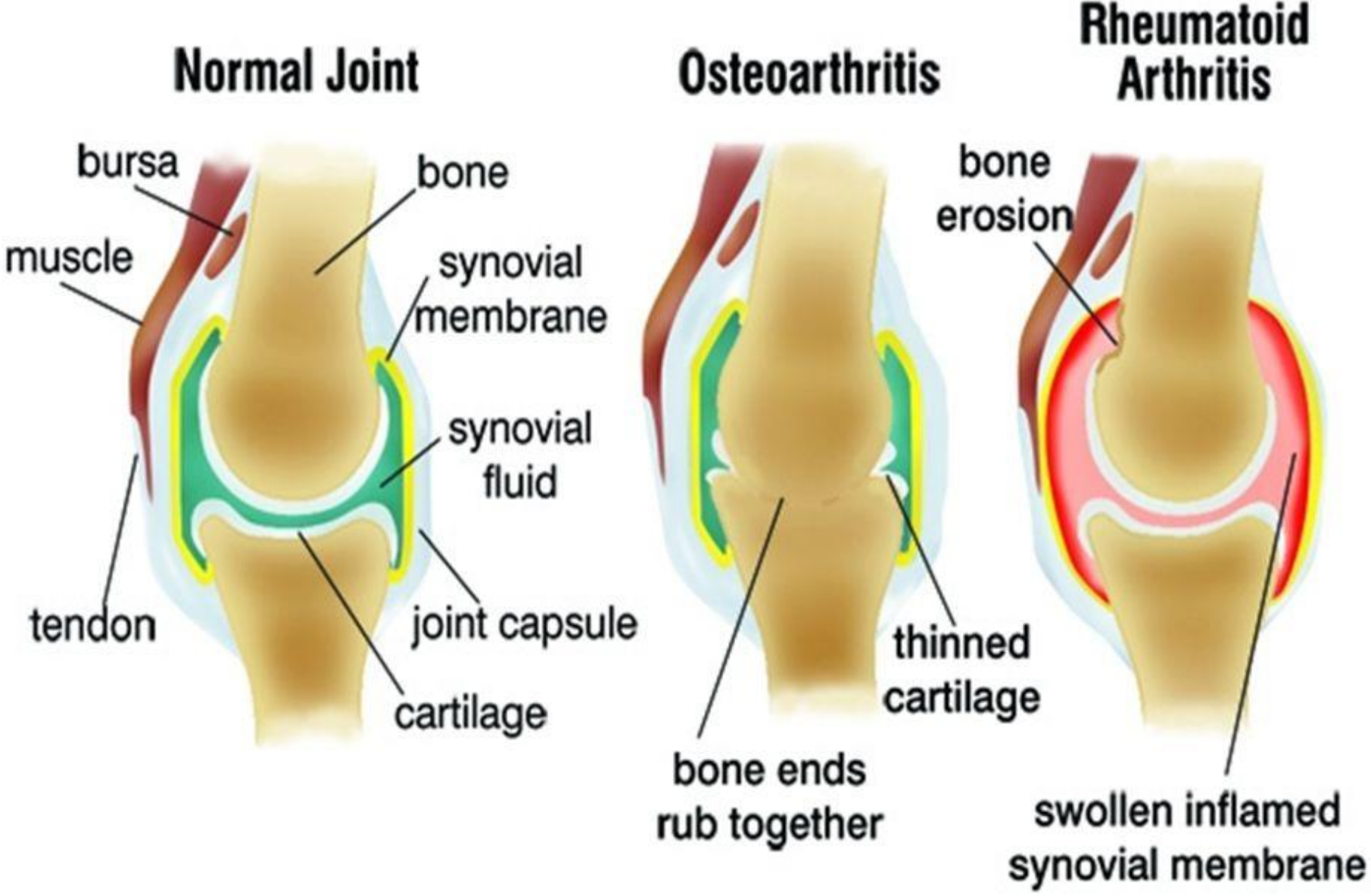
Tx: Hyaluronic acid injection

Tx: Chondroitin sulfate



Rheumatoid Arthritis





*Gout is a **systemic inflammatory disease** (**autoimmune disease**) that affects the peripheral joints in a **symmetrical pattern***

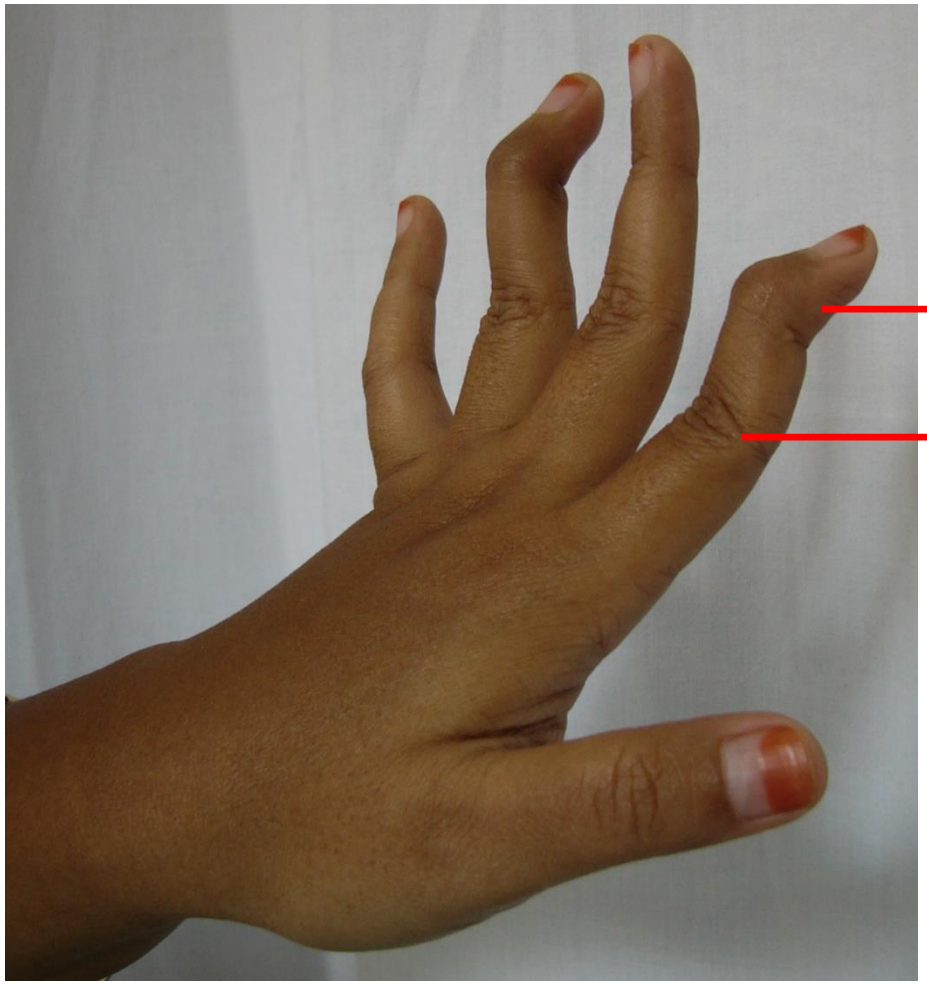
Diagnostic Criteria for RA

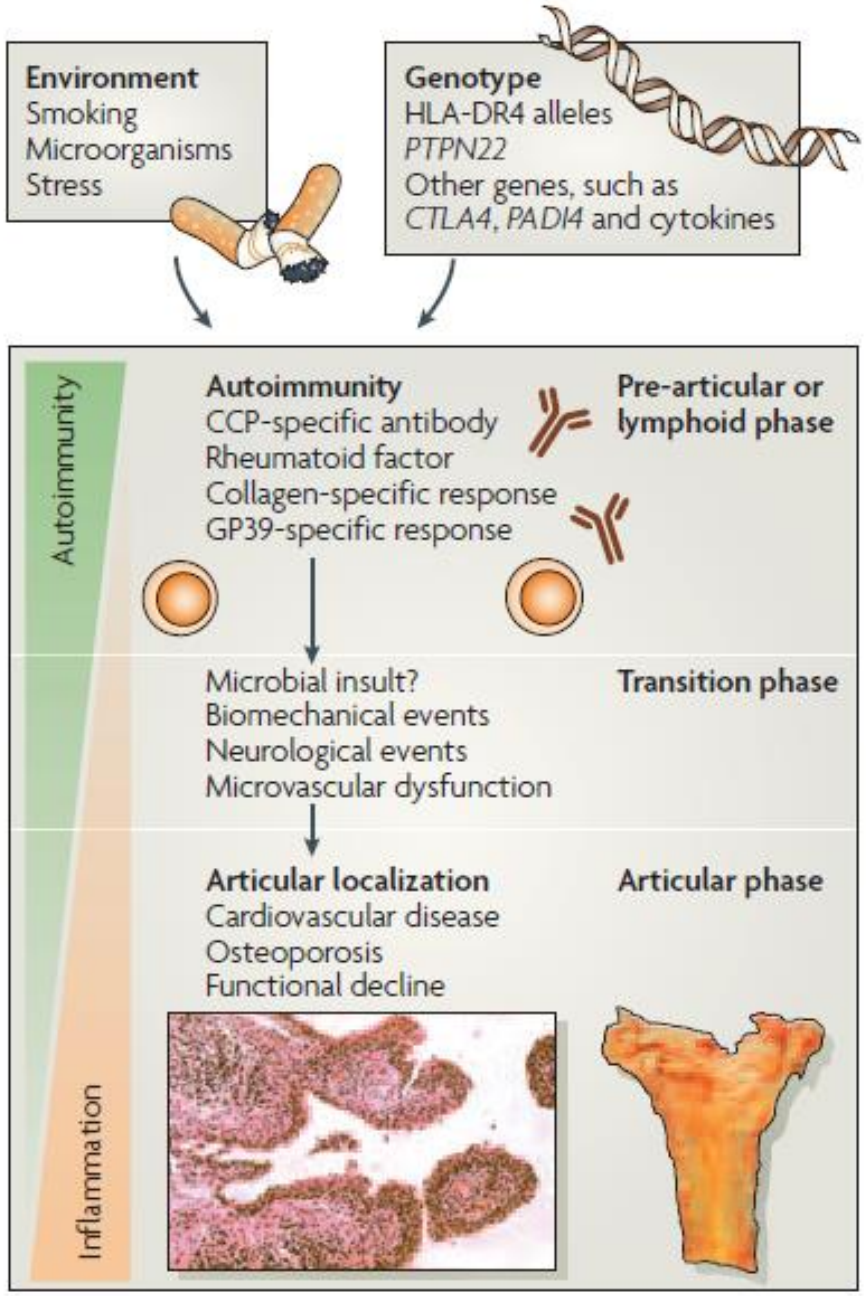
American College of Rheumatology (ACR) 1987

1. Morning stiffness
2. Arthritis of 3 or more joints
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

Rheumatoid arthritis if 4 of 7 criteria are satisfied. Criteria 1-4 must have been present for at least 6 weeks.

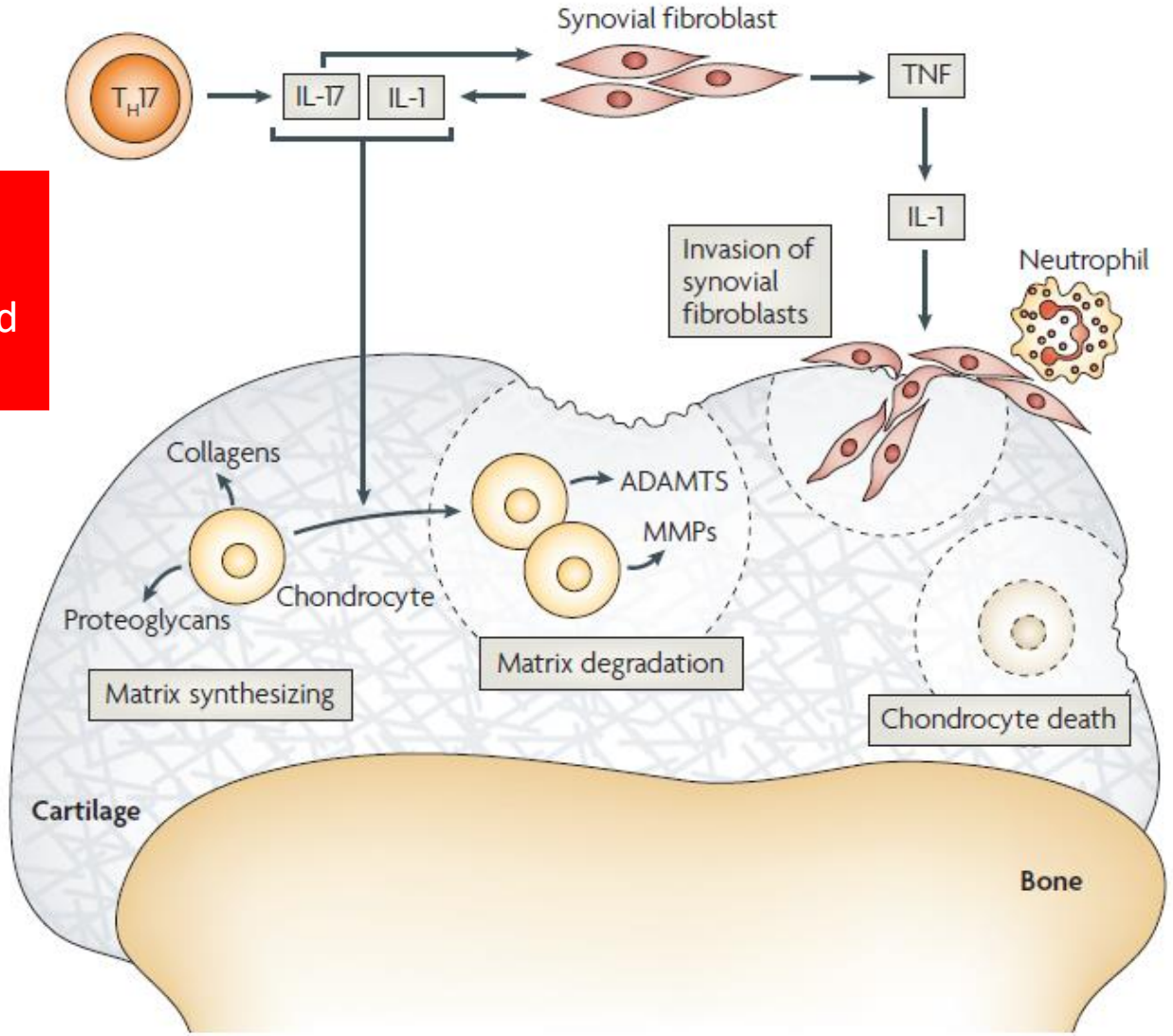
Swan neck deformities in RA





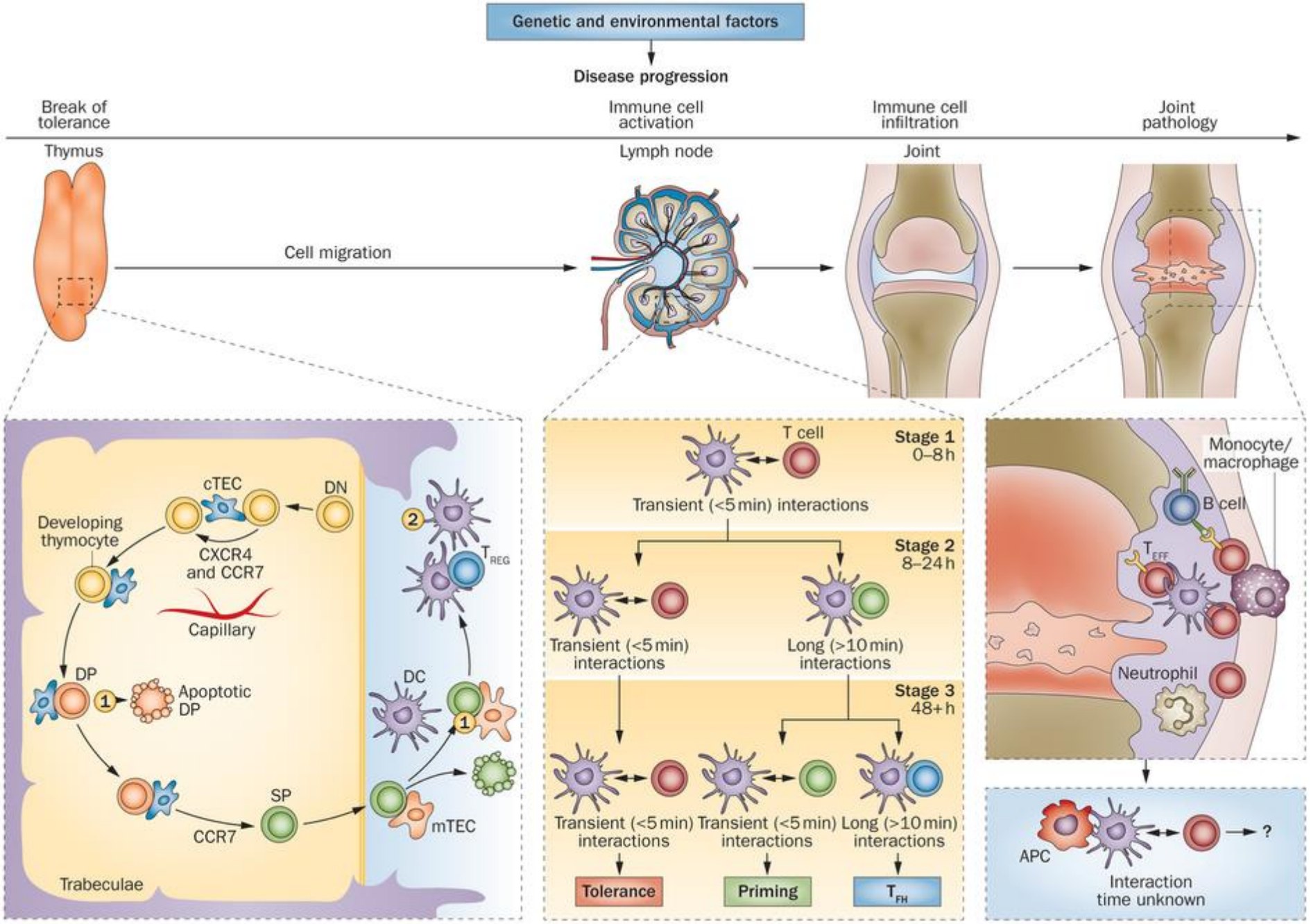
CCP: cyclic citrullinated peptide

Pathways regulating chondrocyte activation and cartilage degradation in RA



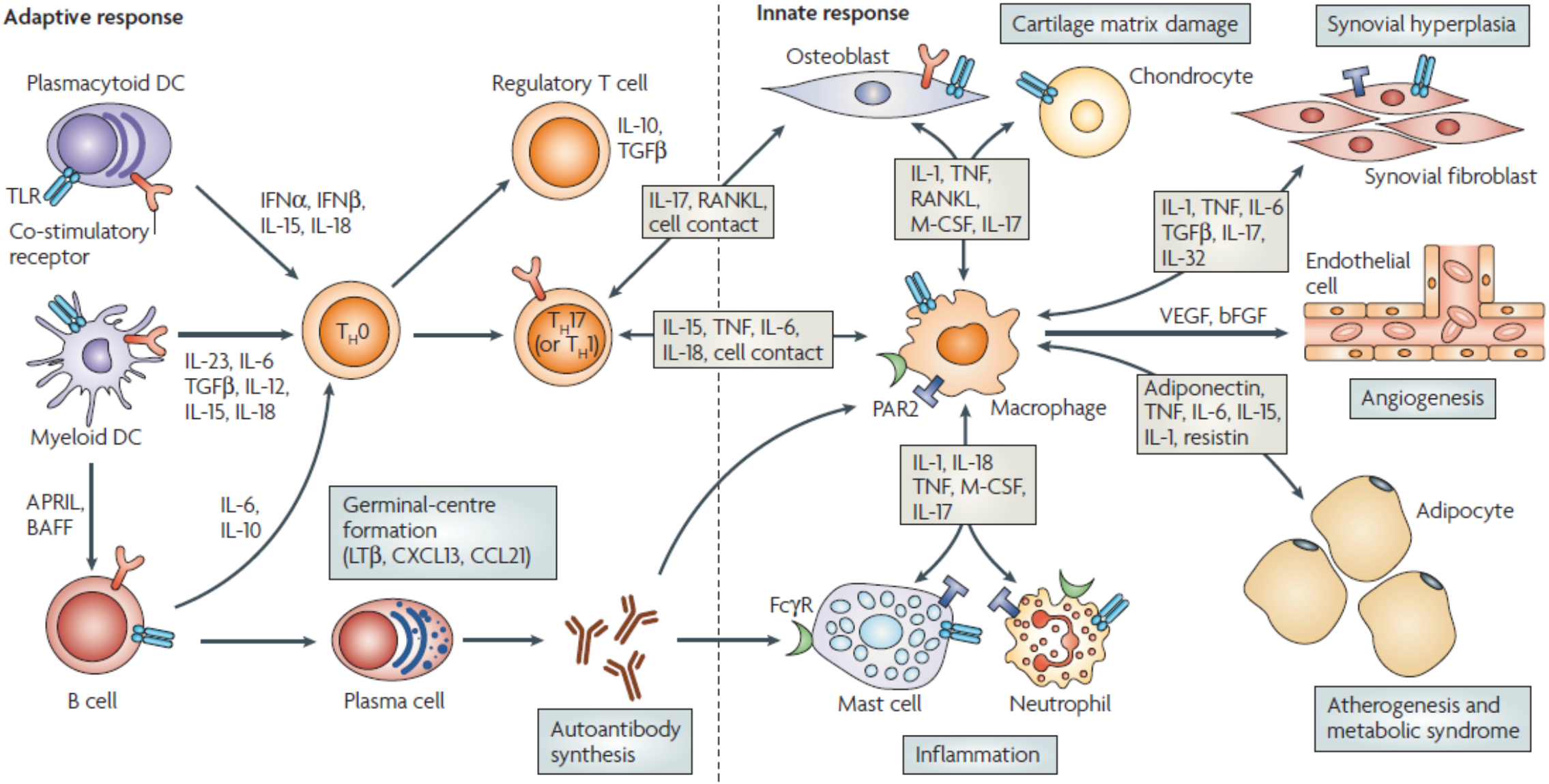
A contextual framework for the pathogenesis of RA

PATHOGENESIS OF RHEUMATOID ARTHRITIS

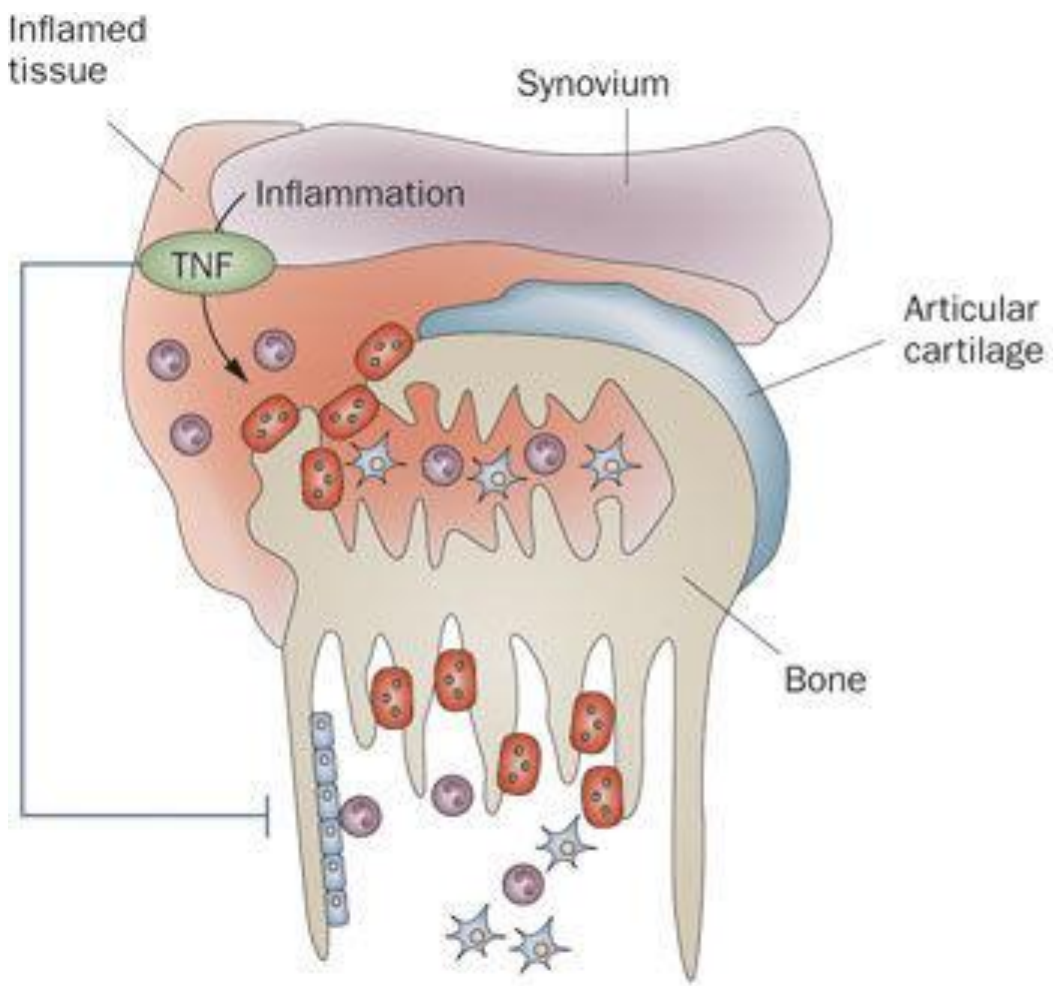


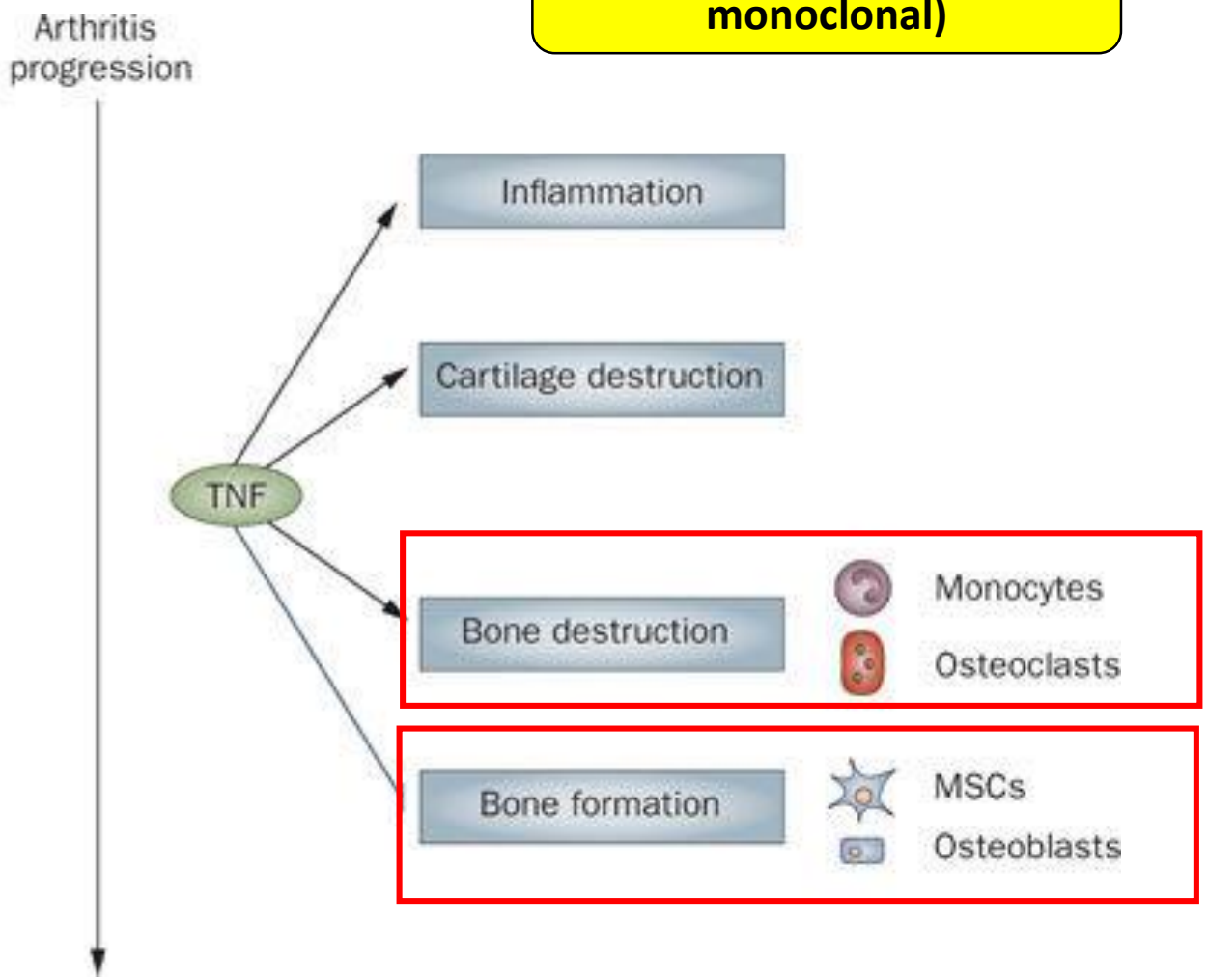
Nature Reviews | Rheumatology

An overview of the cytokine-mediated regulation of synovial interactions



Tx: Adalimumab (Anti-TNF monoclonal)





Selected key cytokine activities implicated in the pathogenesis of RA

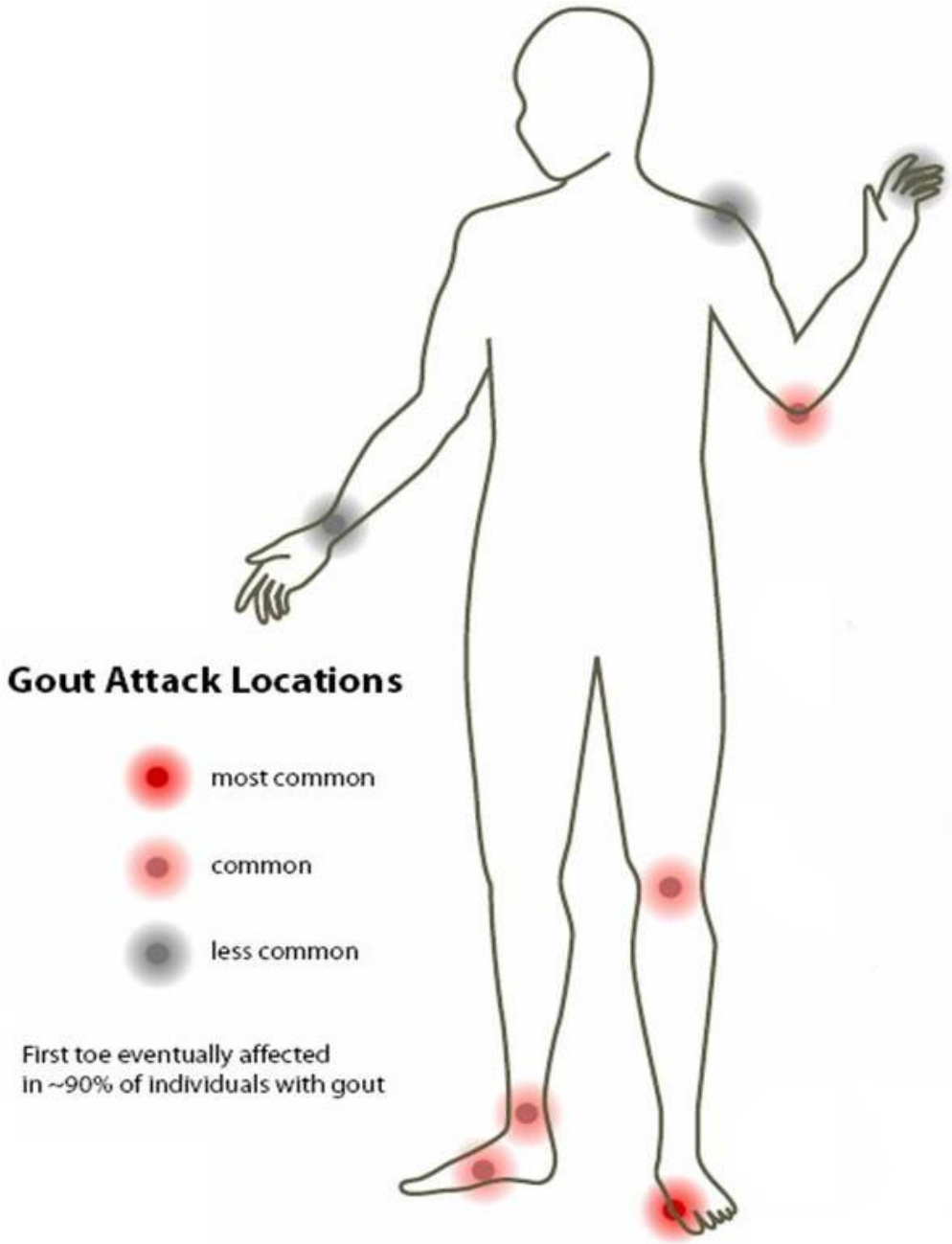
Cytokine	Articular cell expression	Potential functions in the pathogenesis of rheumatoid arthritis
IL-1α and/or IL-1β	Monocytes, B cells, synovial fibroblasts, chondrocytes	↑Synovial fibroblast cytokine, chemokine, MMP, iNOS and PG release; ↑monocyte cytokine, ROI and PG release; osteoclast activation; ↓GAG synthesis, ↑iNOS, MMP and aggrecanase; endothelial-cell adhesion molecule expression
IL-18	Monocytes, PMNs, DCs, platelets, endothelial cells	T-cell differentiation (T_H1 cells with IL-12; T_H2 cells with IL-4); NK-cell activation, cytokine release and cytotoxicity; ↓chondrocyte GAG synthesis, iNOS expression; monocyte cytokine release and adhesion molecule expression; PMN activation, cytokine release and migration; pro-angiogenic for endothelial cells
TNF	Monocytes, T cells, B cells, NK cells, PMNs, mast cells, synovial fibroblasts, osteoblasts	↑Monocyte activation, cytokine and PG release; ↑PMN priming, apoptosis and oxidative burst; T-cell apoptosis, clonal regulation and TCR dysfunction; ↑endothelial-cell adhesion molecule expression, cytokine release; ↓synovial fibroblast proliferation and collagen synthesis, ↑MMP and cytokine release; ↑adipocyte FFA release; endocrine effects
LTα and/or LTβ	T cells, monocytes, synovial fibroblasts	Peripheral lymphoid organ development; otherwise similar bioactivities to TNF
RANKL	Stromal cells, osteoblasts, T cells	Stimulates bone resorption via osteoclast maturation and activation; modulates T-cell–DC interactions
BAFF	Monocytes, T cells, DCs	B-cell proliferation, antibody secretion, isotype switching and survival; T-cell co-stimulation
APRIL	Monocytes, T cells	B-cell proliferation
IL-17A	T_H17 cells, synovial fibroblasts	↑Synovial fibroblast cytokine and MMP release; osteoclastogenesis; haematopoiesis; ↓chondrocyte GAG synthesis; ↑leukocyte cytokine production
IL-12	Macrophages, DCs	T_H1-cell proliferation and maturation; T-cell and NK-cell cytotoxicity; B-cell activation
IL-23	Macrophages, DCs	T_H17-cell proliferation
IL-7	Synovial fibroblasts, monocytes?	T-cell expansion and survival; macrophage activation; haematopoietic regulation; thymic regulation; NK-cell maturation
IL-15	Monocytes, synovial fibroblasts, mast cells, B cells, PMNs, DCs	T-cell chemokinesis, activation and memory maintenance; B-cell differentiation and isotype switching; NK-cell activation and cytotoxicity; synovial fibroblast activation; macrophage activation/suppression (dose dependent); PMN activation, adhesion molecule expression and oxidative burst

Selected key cytokine activities implicated in the pathogenesis of RA

IL-10	Monocytes, T cells, B cells DCs, epithelial cells	↑Macrophage cytokine release, iNOS and soluble receptor expression, ↓ROI; T-cell cytokine release, ↓MHC expression, anergy induction, T_{Reg}-cell maturation and effector function(?); ↓DC activation and cytokine release; ↓synovial fibroblast MMP and collagen release; ↑B-cell isotype switching
IL-6	Monocytes, synovial fibroblasts, B cells, T cells	B-cell proliferation and antibody production; haematopoiesis and thrombopoiesis; T-cell proliferation, differentiation and cytotoxicity; ↑hepatic acute-phase response; ↑neuroendocrine effects
Oncostatin M	Monocytes, activated T cells	Megakaryocyte differentiation; ↑synovial fibroblast TIMP and cytokine release, ↑acute-phase reactants, ↑protease inhibitors; ↓monocyte TNF release, ↓IL-1 effector function; ↑neuroendocrine effects and corticosteroid release; osteoblast modulation(?)
TGFβ	Synovial fibroblasts, monocytes, T cells, platelets	Wound repair, matrix maintenance and fibrosis; T_H17- and T_{Reg}-cell proliferation; ↓NK-cell proliferation and effector function; initial activation then suppression of inflammatory responses; ↑early phase leukocyte chemoattractant, gelatinase and integrin expression; early macrophage activation then suppression; ↓ iNOS expression
BMP family (BMP2–BMP15)	Epithelial cells, synovial fibroblasts, mesenchymal embryonic tissues	Regulate crucial chemotaxis, mitosis and differentiation processes during chondrogenesis and osteogenesis; tissue morphogenesis
PDGF	Platelets, macrophages, endothelial cells, synovial fibroblasts	Paracrine and/or autocrine growth factor for various lineages; wound healing
FGF family	Synovial fibroblasts, monocytes	Growth and differentiation of mesenchymal, epithelial and neuroectodermal cells
VEGF	Monocytes, endothelial cells, synovial fibroblasts	Angiogenesis
IL-32	Epithelial cells, monocytes(?), synovial fibroblasts(?)	Macrophage cytokine, PG and MMP release
MIF	Macrophages, activated T cells, synovial fibroblasts	↑Macrophage phagocytosis, cytokine and NO release; T-cell activation, DTH; fibroblast proliferation, COX expression, PLA_2 expression and intrinsic oxidoreductase activity ('cytozyme')
Type I IFNs	Widespread	Antiviral response; broad immunomodulatory effects; ↑MHC expression; macrophage activation; lymphocyte activation, differentiation, survival (antiproliferative) and cytoskeletal alterations

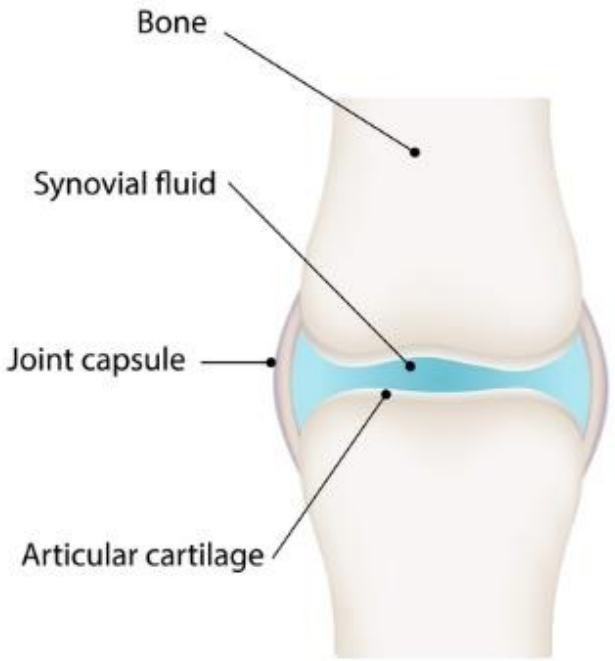
APRIL, a proliferation-inducing ligand;
BAFF, B-cell activating factor;
BMP, bone morphogenetic protein;
COX, cyclooxygenase;
DTH, delayed-type hypersensitivity;
DC, dendritic cell;
FFA, free fatty acid;
FGF, fibroblast growth factor;
GAG, glycosaminoglycans;
IFN, interferon;
IL, interleukin;
iNOS, inducible nitric-oxide synthase;
LT, lymphotoxin;
MIF, macrophage migration-inhibitory factor;
MMP, matrix metalloproteinase;
NK, natural killer;
PDGF, platelet-derived growth factor;
PG, prostaglandin;
PLA2, phospholipase A2;
PMN, polymorphonuclear leukocyte;
RANKL, receptor activator of nuclear factor-κB (RANK) ligand;
ROI, reactive oxygen intermediate;
TCR, T-cell receptor;
TGFβ, transforming growth factor-β;
TH, T helper;
TIMP, tissue inhibitor of MMPs;
TNF, tumour-necrosis factor;
TReg, regulatory T;
VEGF, vascular endothelial growth factor.

Gout

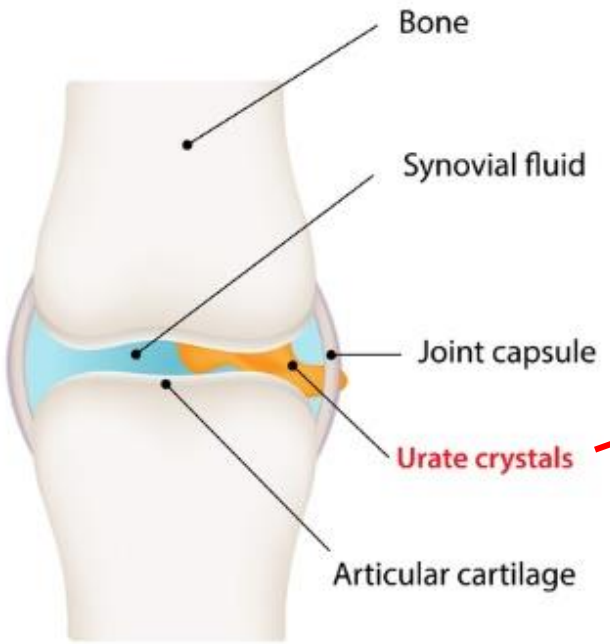

Gout Attack Locations
most common
common
less common
First toe eventually affected
in ~90% of individuals with gout

Gout

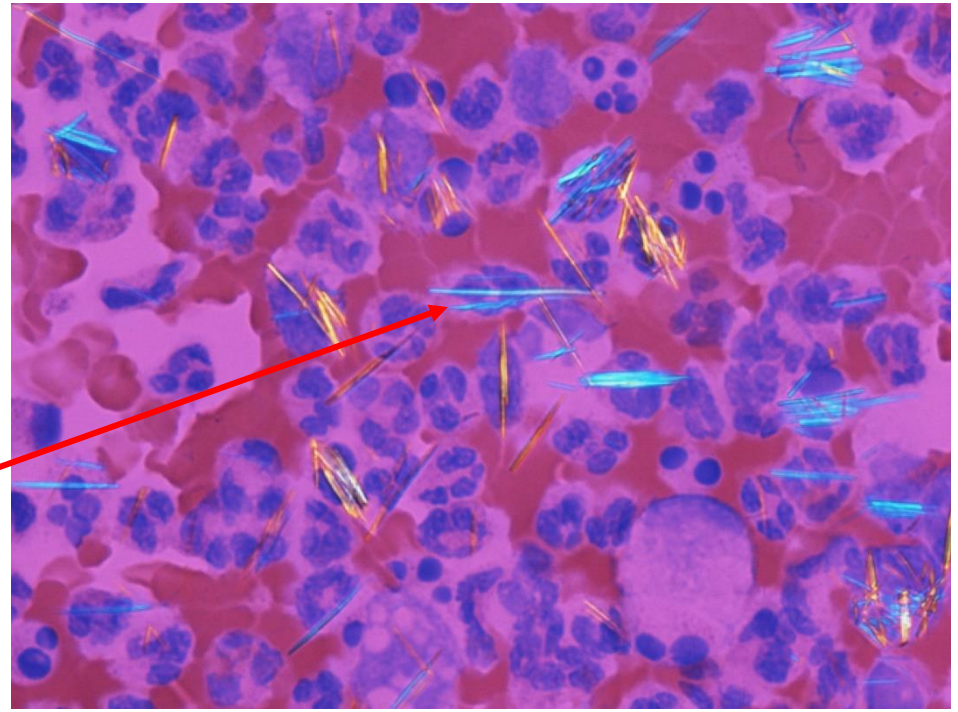
Normal Joint



Joint with Gout

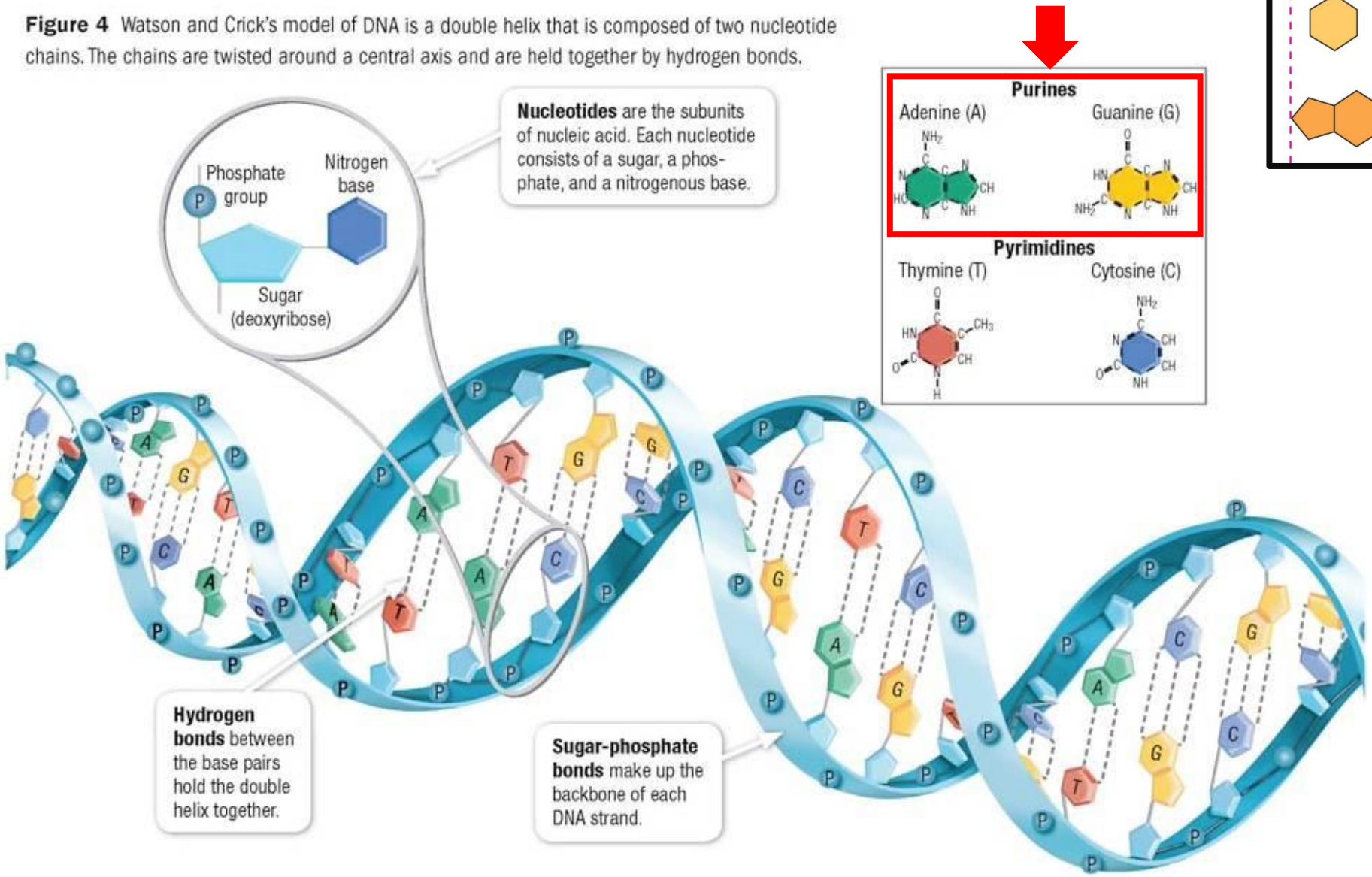


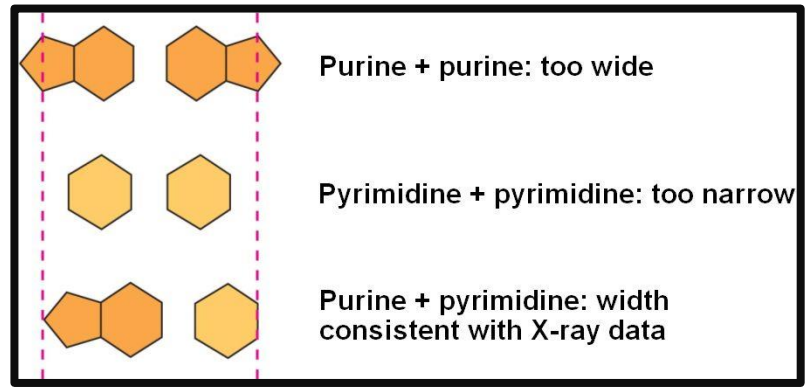
Tophi are aggregates of sodium urate monohydrate crystals

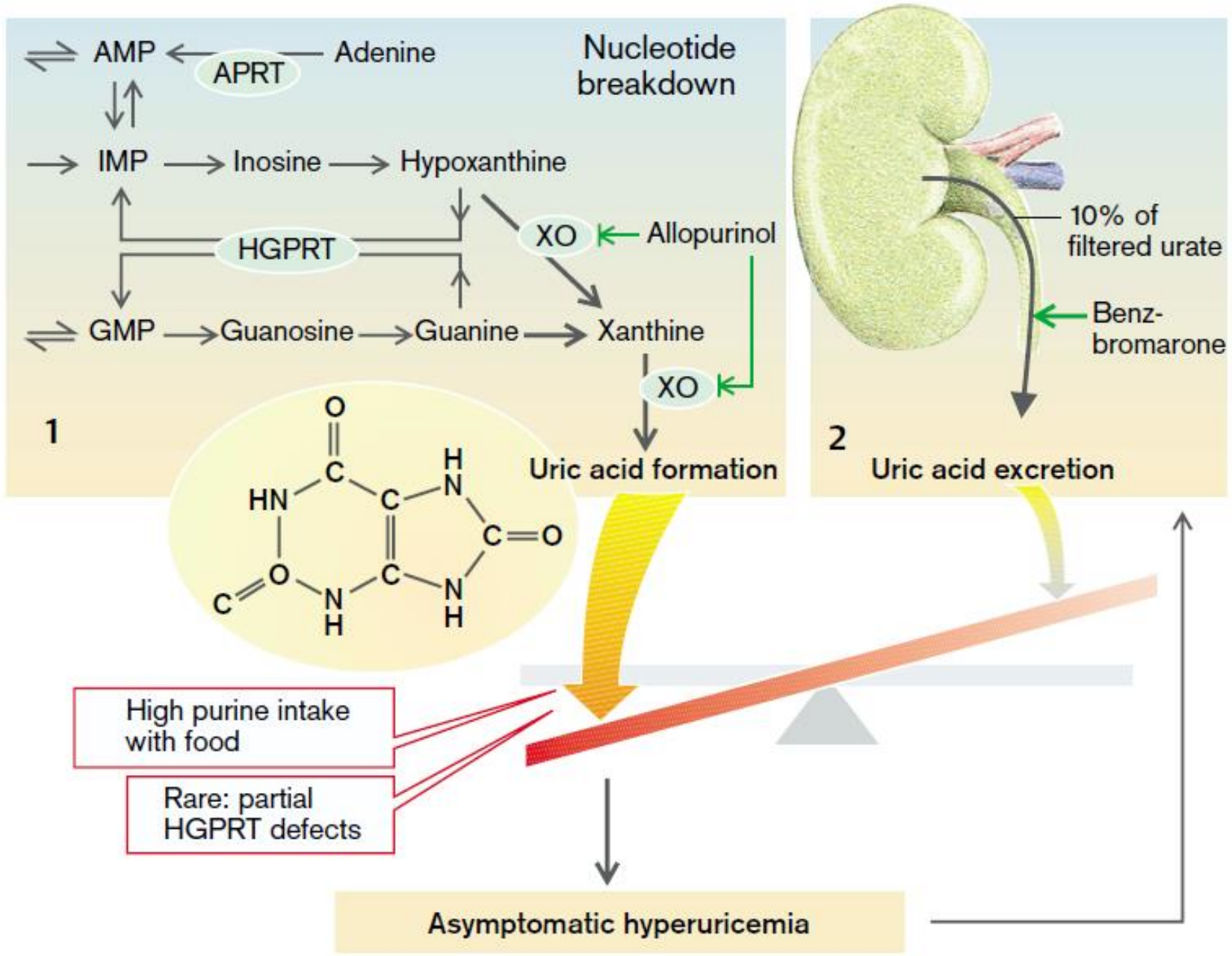


*Gout is the result of chronically **elevated uric acid/urate concentration** in plasma (**hyperuricemia: > 7 mg/dL**)*

Figure 4 Watson and Crick's model of DNA is a double helix that is composed of two nucleotide chains. The chains are twisted around a central axis and are held together by hydrogen bonds.



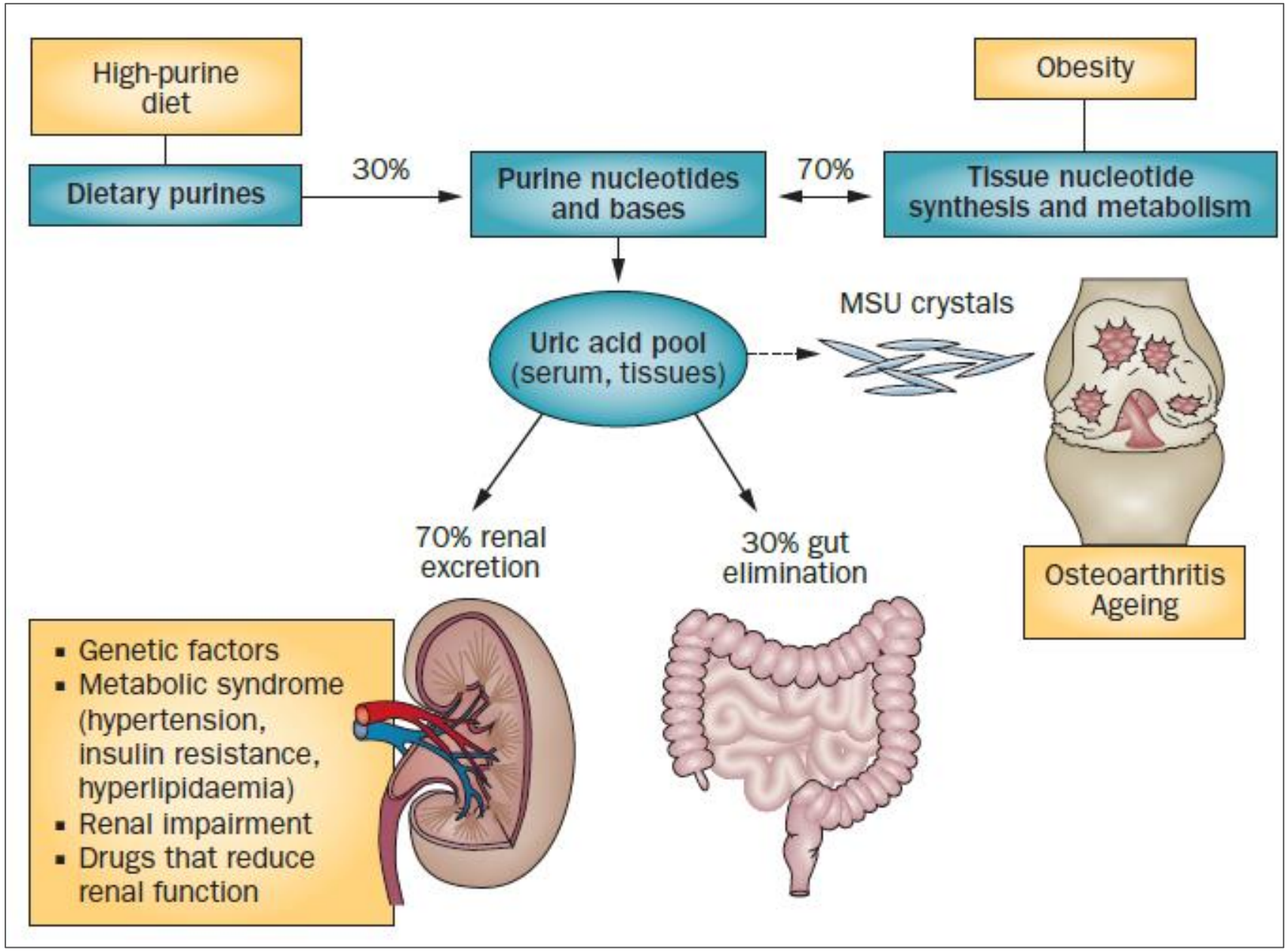




Tx: Allopurinol (xanthine oxidase inhibitor)

APRT: adenine phosphoribosyltransferase

HGPRT: hypoxanthine guanine phosphoribosyltransferase



METABOLISM OF URIC ACID AND RISK FACTORS FOR GOUT

Crystallization of **monosodium urate (MSU)** occurs **when uric acid levels exceed the saturation point**, through inefficient elimination or excessive production of uric acid

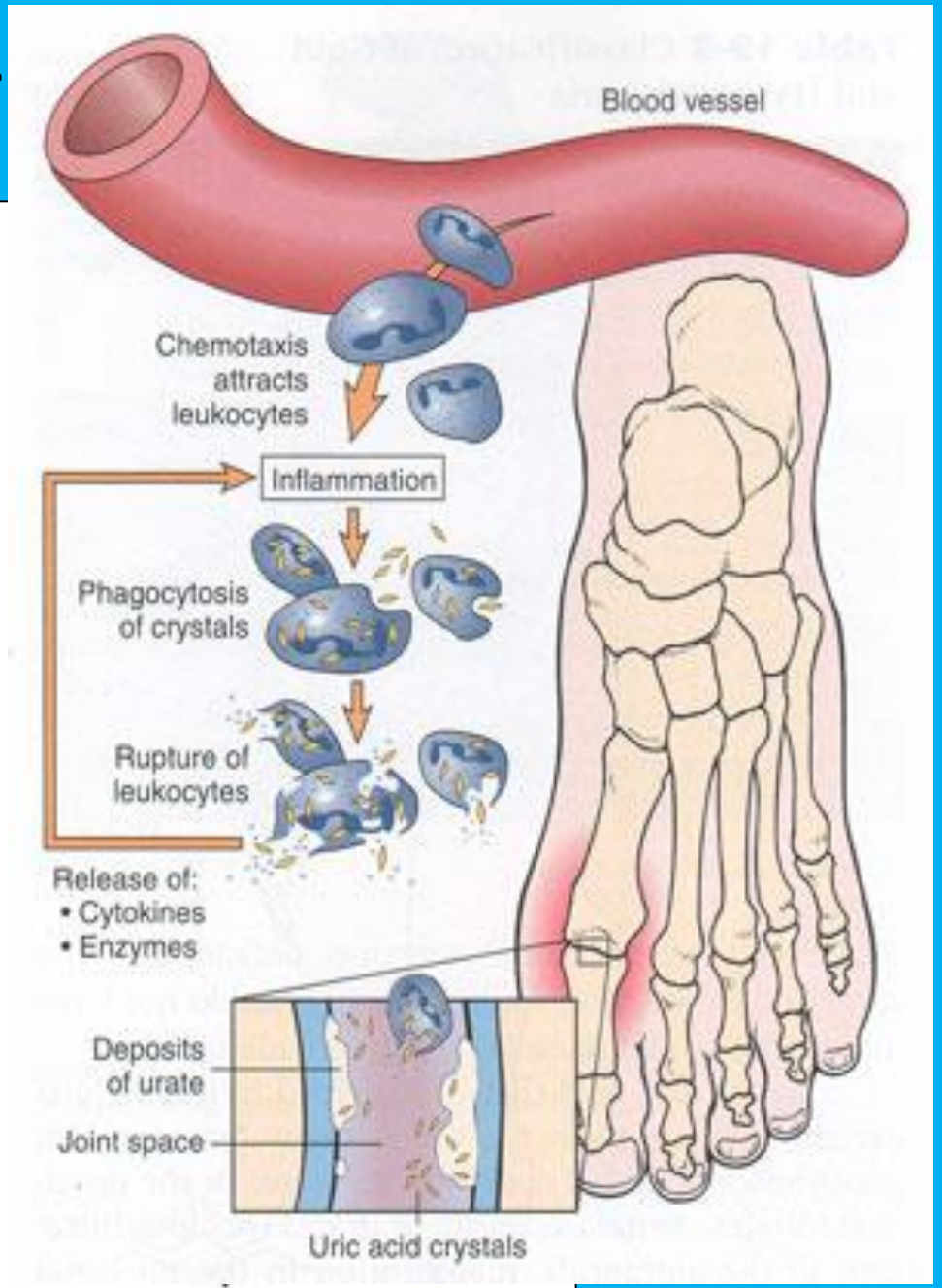
IMMUNOPATHOGENESIS OF GOUT

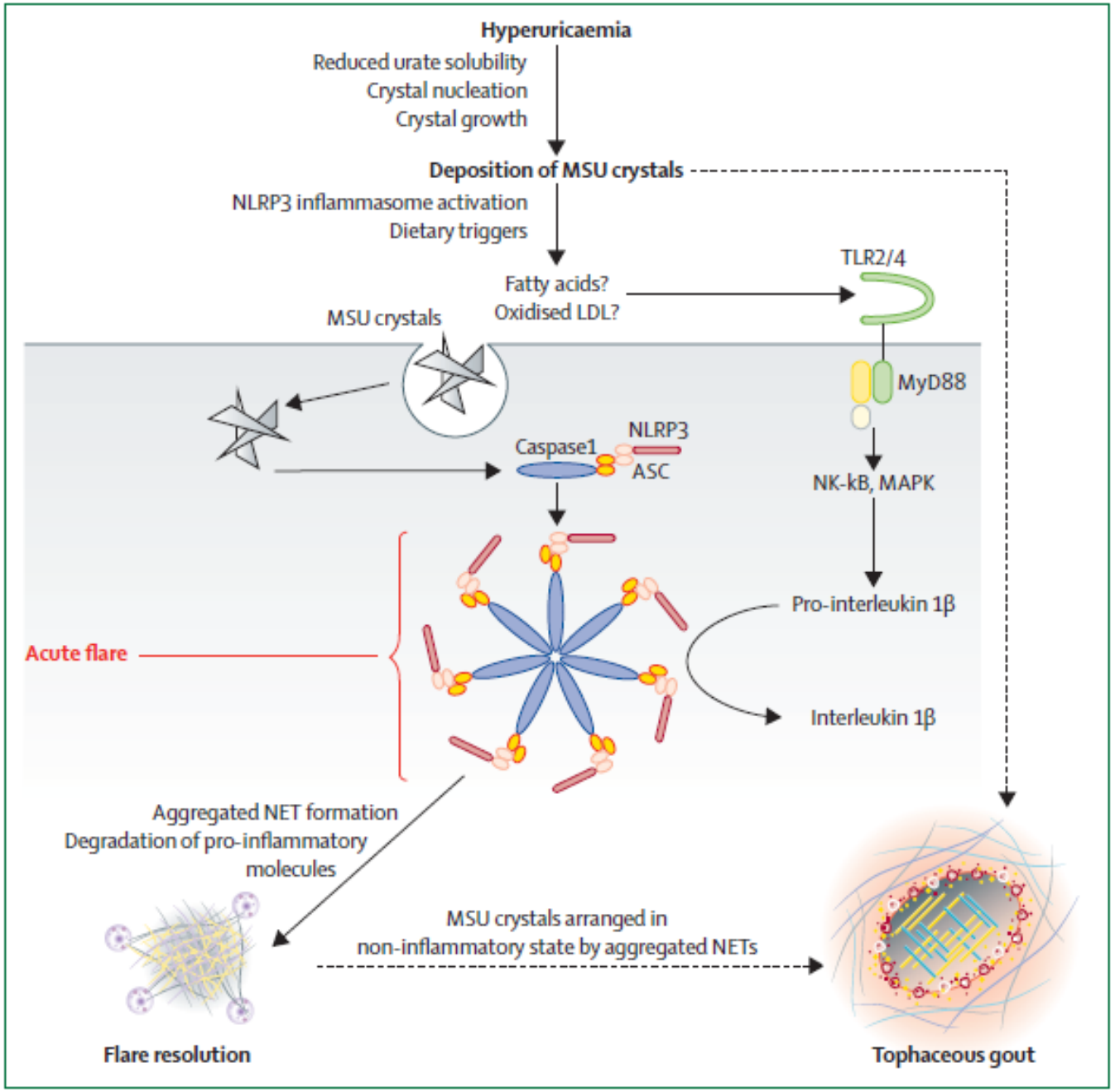
1. Formation of MSU Crystals

- Hyperuricaemia
- **Precipitation** of MSU crystals
- **Deposition** in articular and periarticuar tissue

2. Acute Gout Attack

- **Phagocytosis** of Crystals
- Cell Swelling and **Inflammasome** Activation
- **Cytokine p**roduction and vasodilatation
- Neutrophil and monocyte influx





CHECKPOINTS IN THE PROGRESSION FROM HYPERURICAEMIA TO THE CLINICAL MANIFESTATIONS OF GOUT

Uptake of MSU crystals by monocytes involves interaction with components of the innate immune system, including Toll-like receptors (TLRs) and the NALP-3 (NLRP 3) **inflammasome complex** that drives production of **interleukin(IL)-1β** → The inflammatory effects of MSU are IL-1-dependent

Explanation of the causes of gout, including the following key point:

We know its cause: **deposition of urate crystals** in and around peripheral joints

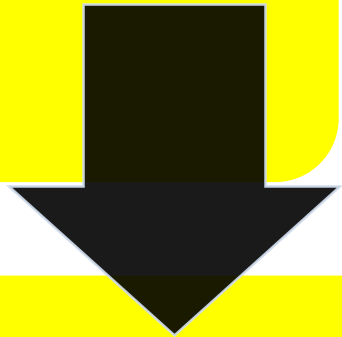
Crystals **form when serum uric acid (SUA) levels rise above the critical 'saturation point'** for crystal formation

In people with persistently raised SUA levels, crystals slowly but continuously accumulate without causing symptoms

When sufficient crystals have formed in cartilage, some occasionally 'spill out' into the joint cavity, triggering severe inflammation of the joint lining and presenting as an **acute attack** → Over many years, acute attacks can increase in frequency and spread to involve other joints

Explanation of the causes of gout, including the following key point:

In addition to acute attacks, continuing crystal deposition might eventually result in hard, slowly expanding lumps of crystals (**tophi**) that can cause pressure damage to joint cartilage and bone and can even appear as palpable lumps under the skin
→ In some people, tophi could result in irreversible joint damage and cause regular chronic pain on using the joints



Reduction and maintenance of SUA levels below the saturation point stops production of new crystals and encourages existing crystals to dissolve, so eventually there are no crystals and therefore no gout

Phytotherapy

Selected herbal therapies

Herbs	Diseases	Grades
Aenina	OA	C
Ash	Gout	C
Ashwagandha	OA	C
Avocado	OA	B
Black cohosh	OA, RA	C
Borage	RA	B
Boswellia	OA, RA	C
Bromelain	RA	C
Cat’s claw	OA, RA	C
Cherry	Arthritis, gout	B
Devil’s claw	OA	B
Feverfew	RA	C

Selected herbal therapies

Herbs	Diseases	Grades
Ginger	OA, RA	C
Mistletoe	Arthritis	C
Rose hip	OA	B
Stinging nettle	Arthritis	C
Turmeric	OA, RA	C
Willow	OA RA	A C

Herb and spice constituents may inhibit extravasation in the inflammatory response

Table 8.1 Inhibition of extravasation

Herb or spice constituemt	Properties
Ajoene	Inhibits tumour–endothelial cell adhesion, as well as the in vivo TNF-alpha response to LPS in mouse melanoma cells.[14]
Allicin	Inhibits the spontaneous and TNF-alpha-induced secretion of IL-1beta, IL-8, IP-10 and MIG in a dose-dependent manner from intestinal epithelial cells in vitro, suppresses the expression of IL-8 and IL-1beta mRNA levels.[15]
Allyl isothiocyanate	Significantly inhibits the cellular production of pro-inflammatory mediators such as TNF-alpha and NO.[16]
Anethole	Inhibits NF-kappaB activation induced by TNF, TRAF2 and NIK in vitro, suppresses TNF-induced activation of the transcription factor AP-1, JNK and MAPK in vitro.[17]
Apigenin	Inhibits TNF-alpha in LPS stimulated macrophages resulting in diminished MCP-1 and inhibition of IL-1beta in vitro.[18]
Capsaicin	Blocks the STAT3 activation pathway in multiple myeloma cells in vitro leading to downregulation of cyclin D1, Bcl-2, Bcl-xL, survivin and VEGF.[19]
Carnosol	Decreases LPS-induced iNOS mRNA and protein expression, reduces NF-kappaB subunits translocation and NF-kappaB DNA binding activity in activated macrophages due to inhibition of IKK, inhibits iNOS and NF-kappaB promoter activity.[20]
Caryophyllene	Inhibits the LPS-induced NF-kappaB activation and neutrophil migration in rat paw oedema in vivo.[21]
Cinnamaldehyde	Inhibits age-related NF-kappaB activation and targets inflammatory iNOS and COX-2, inhibits the activation of NF-kappaB via three signal transduction pathways, NIK/IKK, ERK, and p38 MAPK.[22]
Curcumin	Downregulates the constitutive activity of NF-kappaB, decreases expression of NF-kappaB target genes COX-2 and cyclin D1, and induces apoptosis in mouse melanoma cells in vitro.[23] Significantly inhibits the cellular production of proinflammatory mediators such as TNF-alpha and NO.[16]

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Herb and spice constituents may inhibit extravasation in the inflammatory response

Diallyl sulphide	Significantly reduces the production of and serum levels of IL-1beta, IL-6, TNF-alpha and GM-CSF in mice with melanoma.[24]
Eugenol	Blocks the release of IL-1beta, TNF-alpha and prostaglandin E2 and suppresses the mRNA expression of IL-1beta, TNF-alpha and COX-2 in LPS-stimulated human macrophages in vitro.[25]
[6]-Gingerol	Inhibits the production of TNF-alpha, IL-1beta and IL-12 in murine peritoneal macrophages exposed to several doses of 6-gingerol in the presence of LPS stimulation.[26]
Humulene	Inhibits the LPS-induced NF-kappaB activation and neutrophil migration in rat paw oedema, prevents the production of TNF-alpha and IL-1beta and the in vivo upregulation of kinin B(1) receptors.[21]
Limonene / myrcene	Inhibits the LPS-induced inflammation including cell migration and production of NO along with significant inhibition of gamma-interferon and IL-4 production in mouse model of pleurisy.[27]
Perillyl alcohol	Reduces NF-kappaB DNA-binding activity.[28]
Phytic acid	Modulates IL-8 and IL-6 release from colonic epithelial cells stimulated with LPS and IL-1beta, suppresses IL-8 basal release, and it dose-dependently reduces IL-8 secretion by colonocytes and downregulates IL-6.[29]
Piperine	Significantly reduces the expression of IL-1beta, IL-6, TNF-alpha, GM-CSF and IL-12p40 genes in melanoma cells.[30]
Quercetin	Attenuates PMACI-induced activation of NF-kappaB,[31] inhibits LPS-induced NO and TNF-alpha production in murine macrophages.[32]
Ursolic acid	Inhibits IKK and p65 phosphorylation leading to the suppression of NF-kappaB activation induced by various carcinogens; this correlates with the downregulation of COX-2, MMP-9 and cyclin D1 in vitro.[33]
Zingerone	Significantly inhibits the cellular production of proinflammatory mediators such as TNF-alpha and NO and inhibits the release of MCP-1 from 3T3-L1 adipocytes.[34]

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Herbs may inhibit migration through inflamed endothelial cells

Table 8.2 Inhibition of invasion	
Herb or spice constituemt	**Properties**
Allicin	Inhibited TNF-alpha induced ICAM-1 expression in human endothelial cells.[35]
Allyl isothiocyanate	Downregulated mRNA level and activity of MMP-2/MMP-9 in human hepatoma SK-Hep1 cells.[36]
Apigenin/kaempferol	Inhibited TNF-alpha induced ICAM-1 expression.[37]
Caffeic acid	Inhibited MMP-9 activity in human hepatocellular carcinoma cell line.[38]
Curcumin	Downregulated MMP-2 expression and activity and expression of integrin receptors, FAK and MT1-MMP in Hep2 cells.[39]
Diallyl disulfide	Inhibited activity of MMP-2 and MMP-9 in human endothelial cells.[24]
[6]-Gingerol	Suppressed expression and enzymatic activity of MMP-2/MMP-9 in human breast cancer cells.[40]
Myricetin	Inhibited expression and activity of MMP-2 in colorectal cancer cells.[41]
Quercetin	Decreased the expressions of MMP-2 and MMP-9 in PC-3 cells.[42]

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Phytotherapy for Osteoarthritis

POTENTIAL RENAL ACID LOADS (PRAL) OF CERTAIN FOOD GROUPS AND COMBINED FOODS

Food group	PRAL (mEq/100 g)
Fats and oils	0
Fish	7.9
Fruits and fruit juices	–3.1
Grain products	
Bread	3.5
Flour	7.0
Noodles	6.7
Meat and meat products	9.5
Milk and dairy products	
Milk and non-cheese products	1.0
Cheese with lower protein content*	8.0
Cheeses with higher protein content**	23.6
Vegetables	–2.8

*Less than 15 g protein per 100 g.

**More than 15 g protein per 100 g.

- A **positive** value means that the food is **acidic**
- A **negative** value indicates **alkalinity**

Phytotherapy for OA

Alkaline-forming herbs

- Key herb: Apium (celery seed) → ↑ the excretion of acidic metabolites in the urine (also has anti-inflammatory activity)
- Dandelion leaves

Depuratives (alteratives)

- Burdock and yellow dock → clearance of metabolic waste from the body
- Key herb: nettle leaf

Anti-inflammatory herbs

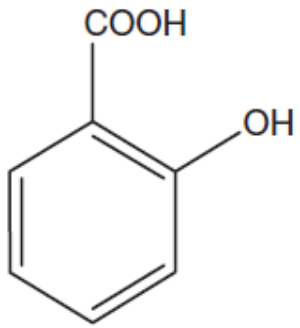
- Boswellia, ginger and turmeric
- Rehmannia, Bupleurum and Boswellia → modify cytokines and other inflammatory processes
- Feverfew → working on NF-κB activation

Analgesic herb

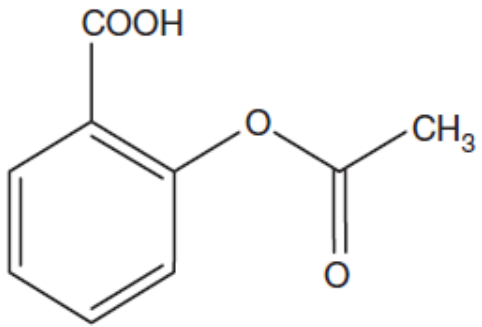
- Key heb: Willow bark

Willow (salix spp.)

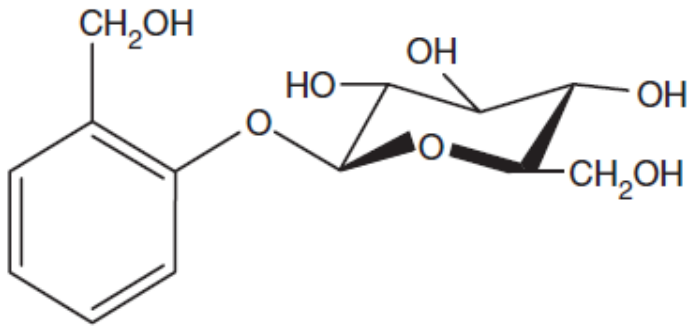
Grade A: Strong evidence for OA



Salicylic acid



Aspirin

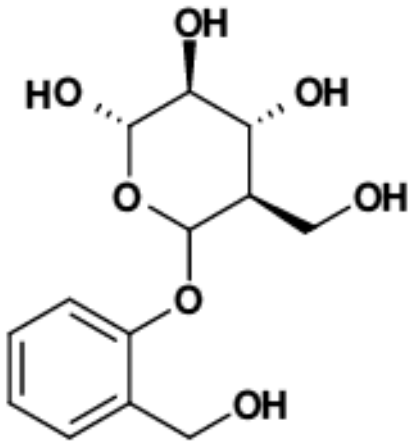


Salicin

MoA

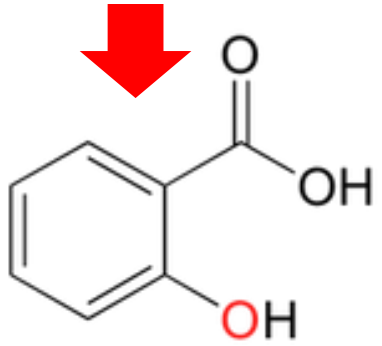
Inhibit COX-2

Inhibit proinflammatory cytokines (TNF-α, IL-1β, IL-6) → weak



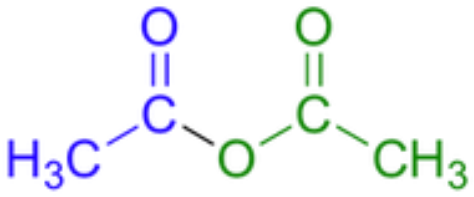
Salicin **(Willow bark)**

Anti pyretic
Anti inflammatory
Antiplatelet

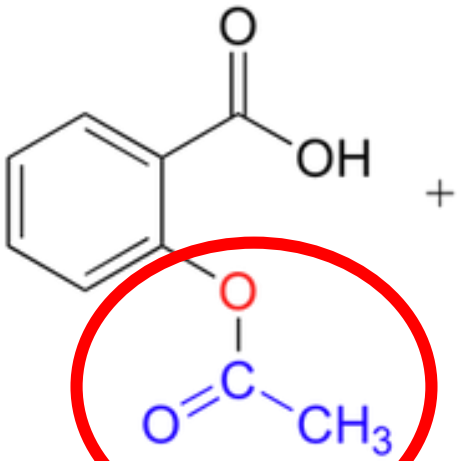


salicylic acid

+

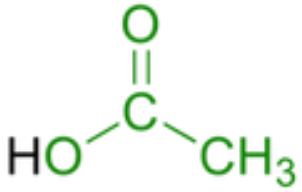


acetic anhydride



acetylsalicyic acid
(aspirin)

+



acetic acid

Anti pyretic
Anti inflammatory

Gastric irritant

To minimalize gastric irritant

Avocado (*Persenia americana*)

Grade B: Good evidence for OA of the knee & hip

Avocado oil

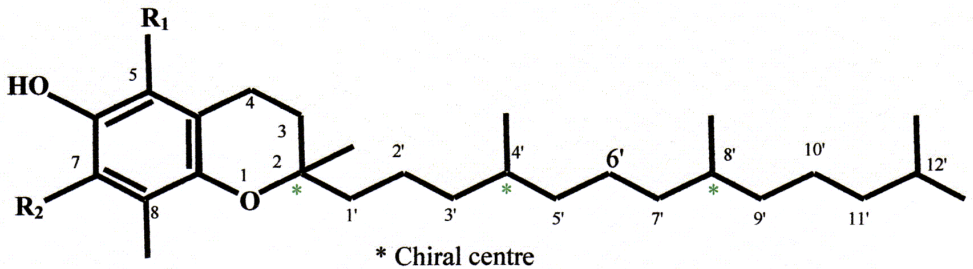
+

Soybean oil

→

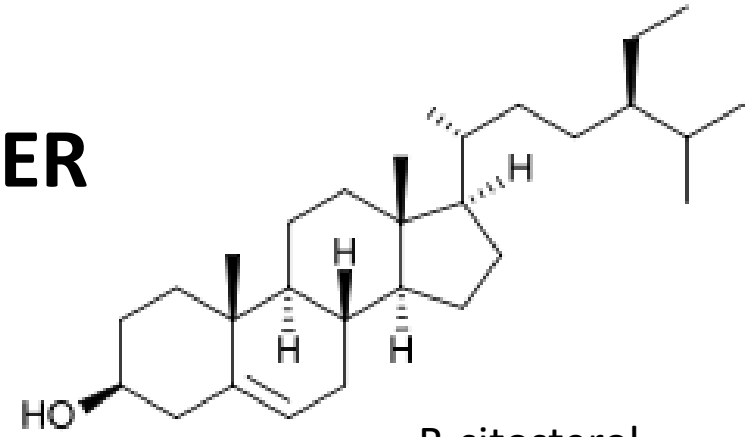
Avocado/ Soybean Unsaponifiable (ASU)

FREE-RADICAL SCAVENGER

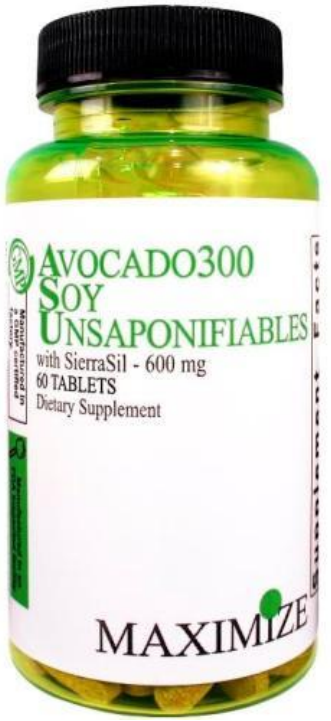


* Chiral centre

$R_1 = R_2 = CH_3$:	α-Tocopherol
$R_1 = CH_3$, $R_2 = H$:	β-Tocopherol
$R_1 = H$, $R_2 = CH_3$:	γ-Tocopherol
$R_1 = R_2 = H$:	δ-Tocopherol

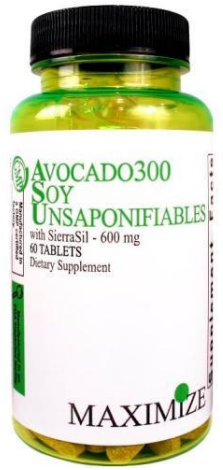


B-sitosterol



Avocado (*Persenia americana*)

Grade B: Good evidence for OA of the knee & hip



MoA

Prevent the breakdown the cartilage & promote cartilage repair

- ↑ synthesis of aggrecan, a key component of cartilage
- Inhibit inflammatory cytokine IL-1, which cause cartilage breakdown
- Prevent mononuclear cells for entering inflamed tissue surrounding cartilage → inhibit IL-1 release
- ↑ production of molecule that may protect cartilage, including TGFβ-1 & -2 and PAF-1

Dose

- When used as fruit, avocado is not standarized
- 300-600 mg for 3 month to 2 years

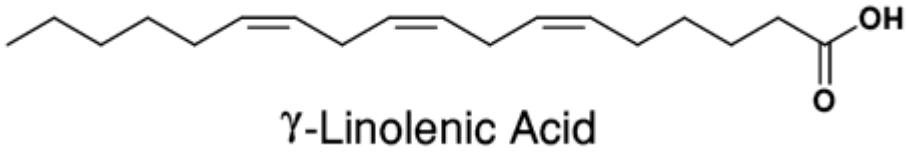
Phytotherapy for Rheumatoid arthritis

Borage (*Borage officinalis*)

Grade B: Good scientific evidence for RA

MoA

GLA increases levels of PGE and cAMP which suppress the TNF-α synthesis



γ-Linolenic Acid

Dose

In clinical studies → borage oil has been standardized to 23-25% GLA

For RA → 1-3 g of GLA in borage seed oil 1dd1 up to 24 weeks or 9 capsules of borage oil (1,1 g of GLA) 1dd1 for 12 weeks

A Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active RA

Curcumin is known to possess potent antiinflammatory and antiarthritic properties. This pilot clinical study evaluated the safety and effectiveness of curcumin alone, and in combination with diclofenac sodium in patients with active rheumatoid arthritis (RA). Forty-five patients diagnosed with RAwere randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination. The primary endpoints were reduction in Disease Activity Score (DAS) 28. The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients in all three treatment groups showed statistically significant changes in their DAS scores. Interestingly, the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 and 70) and these scores were significantly better than the patients in the diclofenac sodium group. More importantly, curcumin treatment was found to be safe and did not relate with any adverse events. Our study provides the first evidence for the safety and superiority of curcumin treatment in patients with active RA, and highlights the need for future large-scale trials to validate these findings in patients with RA and other arthritic conditions

Chandran & Goel, 2012

Phytotherapy for Gout

Phytotherapy for gout

Uricosuric agent

- key herb: celery seed → its activity can be improved by combination with dandelion leaves
- Gravel root → inhibit xanthine oxidase
- Nettle and birch leaves → assisting uric acid removal

Depurative herbs

- Key herb: sarsaparilla

Anti-inflammatory herbs

- Herbs containing significant levels of salicylates (willow bark and meadowsweet) are probably **best avoided**→ inhibit uric acid excretion
- Same with anti-inflammatory for OA

Choleretic herbs

- indicated in a patient who exhibits symptoms of poor bile production.
- Key herb: dandelion root and globe artichoke

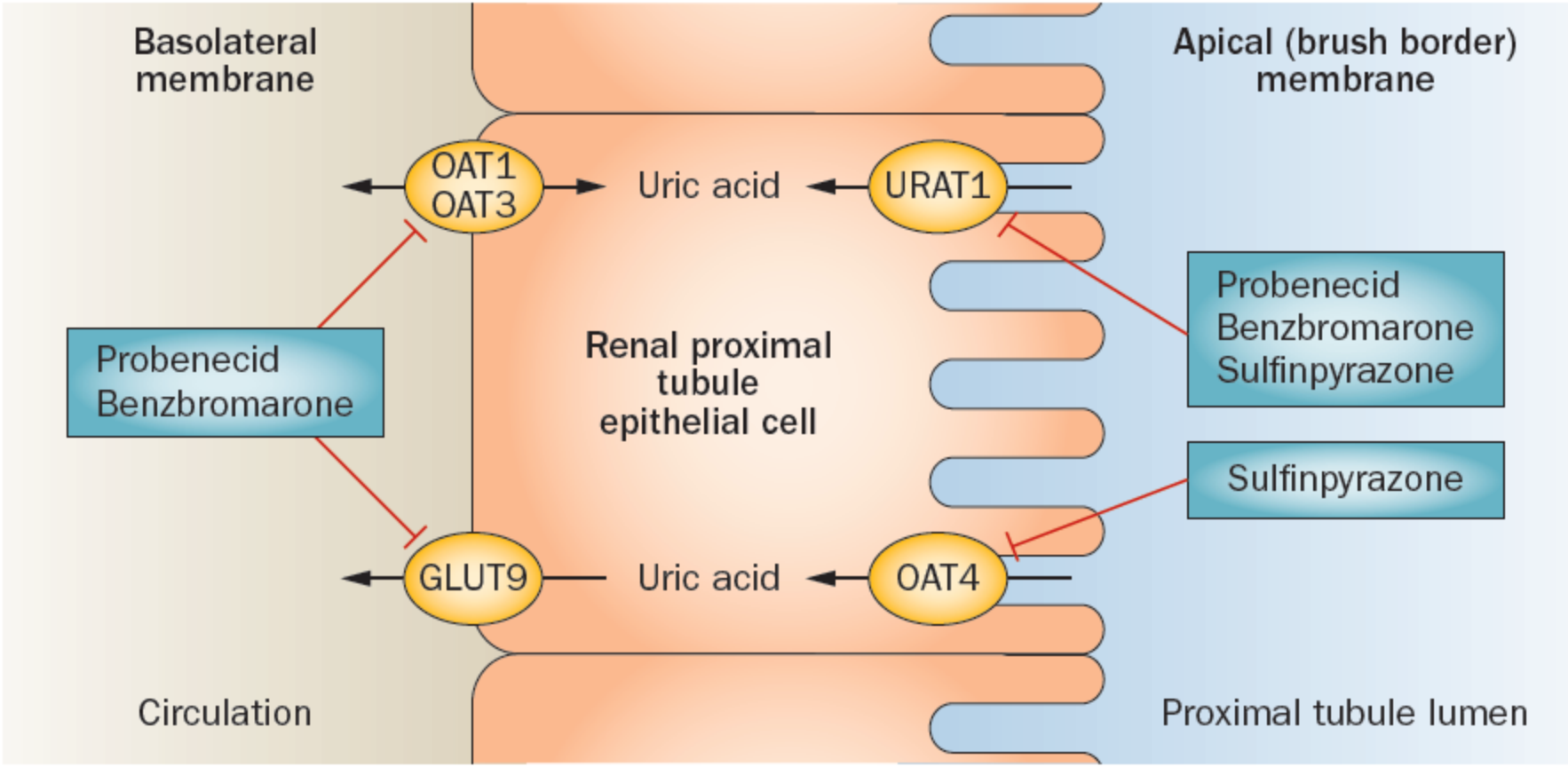
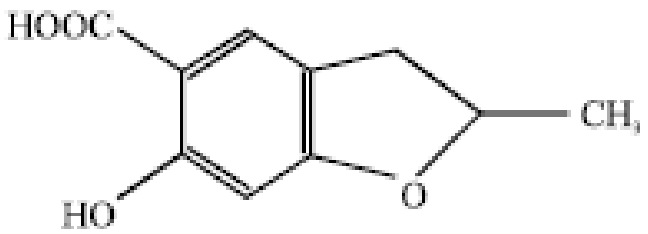


Figure 5 | Mechanism of action of uricosuric drugs at the proximal renal tubule. Uricosuric drugs licenced for gout (shown in blue boxes) act on URAT1 to prevent re-uptake of uric acid and thus increase its renal excretion. As this is a simplified schema, not all transporters are shown. Abbreviations: OAT, organic anion transporter; GLUT9, glucose transporter type 9; URAT1, urate anion exchanger 1.

Celery (*Apium graviolens*)



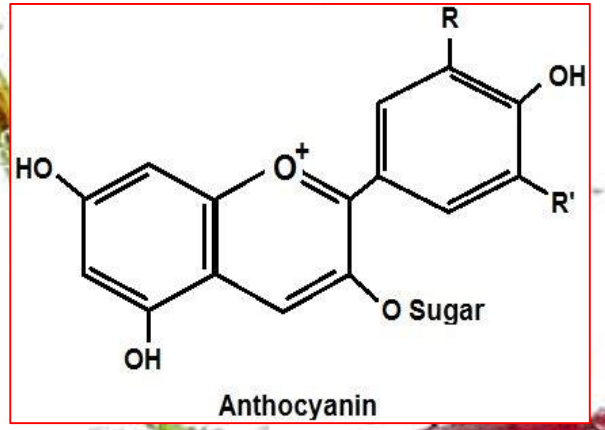
2, 3-dihydro-6-hydroxy-5-benzofurane carboxylic acid

MoA

Inhibit xanthine oxidase

Cherry (*Prunus sp.*)

Grade B: Good scientific evidence for arthritis, gout



Anthocyanin

Phytochemical compounds

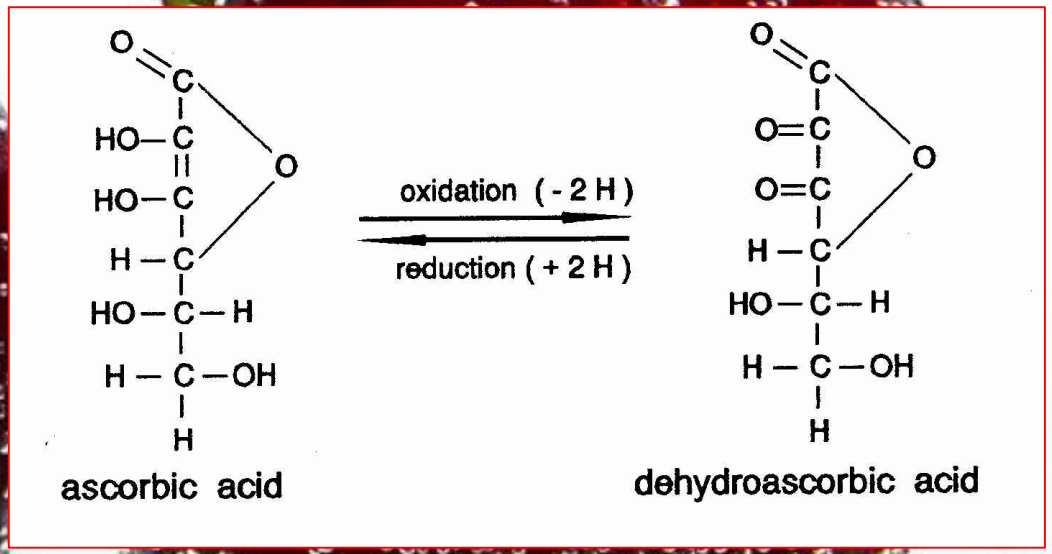
Anthocyanin, hydroxycinnamate, dehydroascorbic acid (DHA)

MoA

Lower plasma urate concentrations, increase plasma elimination in the urine

Dose

Clinical trial → 227 g of cherry products daily for 3 days to 3 months



ascorbic acid — dehydroascorbic acid

Vit C

Integrative Therapy Plan

Know the symptoms:

- OA → pain in fingers & weight-bearing joints (may only affect one joint)

- RA → swelling, stiffness and pain in hands, wrist, knees (symmetrically) → usually worse in the morning

- Gout → intense pain & redness of single joint (frequently of the big toe), usually begin at night and may resolve within several days

Ask if the px has any allergies of meds (aspirin, NSAIDs)

Rose hip should be avoid on antiplatelet & anticoagulant med

If the px has RA, you might suggest borage oil (should be avoided in the pregnant or immunosuppresses px)

Integrative Therapy Plan

Physical activity for OA → gardening, walking, sport activities (golfing, dancing, yoga, swimming)

Different types of exercises:

- Range of motion exercises → for increaseing flexibility
- Strengthening exercises → for weight training
- Aerobic/endurance exercise → for CS and overall health

Maintaining a proper vody weight will reduce the amount of stress on joints

Healthy dies (gout → low purin)

Avoid aspirin, although high dose can promote the uric acid secretion, low dose are known to increase uric acid retention & worsen gout symptoms

REFERENCES

Optimizing current treatment of gout

Frances Rees, Michelle Hui and Michael Doherty

Abstract | Gout is the most common inflammatory arthritis worldwide. Although effective treatments exist to eliminate sodium urate crystals and to 'cure' the disease, the management of gout is often suboptimal. This article reviews available treatments, recommended best practice and barriers to effective care, and how these barriers might be overcome. To optimize the management of gout, health professionals need to know not only how to treat acute attacks but also how to up-titrate urate-lowering therapy against a specific target level of serum uric acid that is below the saturation point for crystal formation. Current perspectives are changing towards much earlier use of urate-lowering therapy, even at the time of first diagnosis of gout. Holistic assessment and patient education are essential to address patient-specific risk factors and ensuring adherence to individualized therapy. Shared decision-making between a fully informed patient and practitioner greatly increases the likelihood of curing gout.

Rees, F. *et al. Nat. Rev. Rheumatol.* **10**, 271–283 (2014); published online 11 March 2014; doi:10.1038/nrrheum.2014.32

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

Why does the gout attack stop? A roadmap for the immune pathogenesis of gout

Georg Schett, Christine Schauer, Markus Hoffmann, Martin Herrmann

To cite: Schett G, Schauer C, Hoffmann M, *et al*. Why does the gout attack stop? A roadmap for the immune pathogenesis of gout. *RMD Open* 2015;**1**:e000046. doi:10.1136/rmdopen-2015-000046

ABSTRACT
Gout is one of the most severe and frequent rheumatic diseases. Clinical manifestations of gout arise from uric acid crystal deposition in the musculoskeletal tissue. At high concentrations of uric acid in the body (hyperuricaemia), needle-shaped monosodium urate (MSU) crystals are formed. The structures are ingested

Key messages

What is already known about this subject?

- Precipitation of monosodium urate crystals in the tissue leads to an acute gout attack by inducing the inflammasome and releasing interleukin-1.

Gout

Nicola Dalbeth, Tony R Merriman, Lisa K Stamp

Gout is a chronic disease of deposition of monosodium urate crystals, which form in the presence of increased urate concentrations. Although environmental factors contribute to hyperuricaemia, renal and gut excretion of urate is central to regulation of serum urate, and genetic factors are important. Activation of the NLRP3 inflammasome and release of interleukin 1β have key roles in initiation of acute gout flares. A "treat to target serum urate" approach is essential for effective gout management; long-term lowering of serum urate to less than 360 μmol/L leads to crystal dissolution and ultimately to suppression of flares. An allopurinol dose-escalation strategy is frequently effective for achieving treatment targets, and several new urate-lowering drugs are also available. Worldwide, rates of initiation and continuation of urate-lowering therapy are very low, and, consequently, achievement of serum urate targets is infrequent. Strategies to improve quality of gout care are needed.

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Department of Medicine, University of Auckland, Auckland, New Zealand (Prof N Dalbeth FRACP); **Department of Biochemistry, University of Otago, Dunedin, New Zealand**

The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis

Jérémie Sellam and Francis Berenbaum

Abstract | Osteoarthritis (OA), one of the most common rheumatic disorders, is characterized by cartilage breakdown and by synovial inflammation that is directly linked to clinical symptoms such as joint swelling, synovitis and inflammatory pain. The gold-standard method for detecting synovitis is histological analysis of samples obtained by biopsy, but the noninvasive imaging techniques MRI and ultrasonography might also perform well. The inflammation of the synovial membrane that occurs in both the early and late phases of OA is associated with alterations in the adjacent cartilage that are similar to those seen in rheumatoid arthritis. Catabolic and proinflammatory mediators such as cytokines, nitric oxide, prostaglandin E_2 and neuropeptides are produced by the inflamed synovium and alter the balance of cartilage matrix degradation and repair, leading to excess production of the proteolytic enzymes responsible for cartilage breakdown. Cartilage alteration in turn amplifies synovial inflammation, creating a vicious circle. As synovitis is associated with clinical symptoms and also reflects joint degradation in OA, synovium-targeted therapy could help alleviate the symptoms of the disease and perhaps also prevent structural progression.

Sellam, J. & Berenbaum, F. *Nat. Rev. Rheumatol.* **6**, 625–635 (2010); published online 5 October 2010; doi:10.1038/nrrheum.2010.159

Cellular imaging in rheumatic diseases

Robert A. Benson, Iain B. McInnes, James M. Brewer and Paul Garside

Abstract | Developments in cellular imaging now enable the real-time visualization of the choreographed sequence of events that underlie the development of immune responses *in vivo*. The previously unappreciated dynamics and anatomical context of cellular interactions, revealed in these studies, can have profound consequences for the 'decision' by the immune system to induce immunological priming versus immunological tolerance. Importantly, dysregulation of this balance can result in autoimmune diseases such as rheumatoid arthritis (RA). By further developing our understanding of how, where and when cells interact during immune responses, we can further dissect these events to assess how cell interactions might be aberrant in autoimmunity. A better knowledge of the mechanisms involved in cellular interactions by means of cellular imaging can help the development and targeting of therapies to particular disease stages and tissues in patients with RA in efforts to restore immune homeostasis.

Benson, R. A. *et al. Nat. Rev. Rheumatol.* advance online publication 24 March 2015; doi:10.1038/nrrheum.2015.34

Cytokines in the pathogenesis of rheumatoid arthritis

Iain B. McInnes and Georg Schett‡*

Abstract | Cytokines regulate a broad range of inflammatory processes that are implicated in the pathogenesis of rheumatoid arthritis. In rheumatoid joints, it is well known that an imbalance between pro- and anti-inflammatory cytokine activities favours the induction of autoimmunity, chronic inflammation and thereby joint damage. However, it remains less clear how cytokines are organized within a hierarchical regulatory network, and therefore which cytokines may be the best targets for clinical intervention a priori. Here, we discuss the crucial effector function of cytokines in the immunological processes that are central to the pathogenesis of rheumatoid arthritis.

PHYTOTHERAPY RESEARCH
Phytother. Res. (2012)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.4639

A Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis

Binu Chandran[1] and Ajay Goel[2]*

[1]Nirmala Medical Centre, Muvattupuzha, Kerala, India
[2]Baylor Research Institute and Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA

The role of the cartilage matrix in osteoarthritis

Dick Heinegård and Tore Saxne

Abstract | Osteoarthritis (OA) involves all the structures of the joint. How the disease is initiated and what factors trigger the disease process remain unclear, although the mechanical environment seems to have a role. Our understanding of the biology of the disease has been hampered by the lack of access to tissue samples from patients with early stage disease, because clinically recognizable symptoms appear late in the osteoarthritic process. However, new data about the early processes in articular cartilage and new tools to identify the early stages of OA are providing fresh insights into the pathological sequence of events. The progressive destruction of cartilage involves degradation of matrix constituents, and rather active, yet inefficient, repair attempts. The release of fragmented molecules provides opportunities to monitor the disease process in patients, and to investigate whether these fragments are involved in propagating OA, for example, by inducing inflammation. The role of bone has not been fully elucidated, but changes in bone seem to be secondary to alterations in articular cartilage, which change the mechanical environment of the bone cells and induce them, in turn, to modulate tissue structure.

Heinegård, D. & Saxne, T. *Nat. Rev. Rheumatol.* **7**, 50–56 (2011); published online 30 November 2010; doi:10.1038/nrrheum.2010.198

Bone remodelling in osteoarthritis

David B. Burr and Maxime A. Gallant

Abstract | The classical view of the pathogenesis of osteoarthritis (OA) is that subchondral sclerosis is associated with, and perhaps causes, age-related joint degeneration. Recent observations have demonstrated that OA is associated with early loss of bone owing to increased bone remodelling, followed by slow turnover leading to densification of the subchondral plate and complete loss of cartilage. Subchondral densification is a late event in OA that involves only the subchondral plate and calcified cartilage; the subchondral cancellous bone beneath the subchondral plate may remain osteopenic. In experimental models, inducing subchondral sclerosis without allowing the prior stage of increased bone remodelling to occur does not lead to progressive OA. Therefore, both early-stage increased remodelling and bone loss, and the late-stage slow remodelling and subchondral densification are important components of the pathogenetic process that leads to OA. The apparent paradoxical observations that OA is associated with both increased remodelling and osteopenia, as well as decreased remodelling and sclerosis, are consistent with the spatial and temporal separation of these processes during joint degeneration. This Review provides an overview of current knowledge on OA and discusses the role of subchondral bone in the initiation and progression of OA. A hypothetical model of OA pathogenesis is proposed.

Burr, D. B. & Gallant, M. A. *Nat. Rev. Rheumatol.* advance online publication 7 August 2012; doi:10.1038/nrrheum.2012.130

OSTEOARTHRITIS — AN UNTREATABLE DISEASE?

Heike A. Wieland, Martin Michaelis, Bernhard J. Kirschbaum and Karl A. Rudolphi

Abstract | Osteoarthritis is a painful and disabling disease that affects millions of patients. Its aetiology is largely unknown, but is most likely multi-factorial. Osteoarthritis poses a dilemma: it often begins attacking different joint tissues long before middle age, but cannot be diagnosed until it becomes symptomatic decades later, at which point structural alterations are already quite advanced. In this review, osteoarthritis is considered as a disease of the whole joint that may result from multiple pathophysiological mechanisms, one of which is the dysregulation of lipid homeostasis. No proven disease-modifying therapy exists for osteoarthritis and current treatment options for chronic osteoarthritic pain are insufficient, but new pharmacotherapeutic options are emerging.