

Mechanisms of Pain in Degenerative and Inflammatory Joint Disease

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Joint Pain

- Synovial joints are richly supplied with sensory nerve fibres, the terminals of which express multiple receptors, the most important of which are nociceptors & those for proprioception
- The quality or nature of the pain in osteoarthritis and in other rheumatologic disorders (eg RA) often overlap and discrimination is problematic.

- Notwithstanding

Inflammatory pain is worse in am and relieved by activity and associated with stiffness and swelling.

Degenerative joint pain is better at/with rest and aggravated by activity, without much stiffness or swelling

- Most research now indicates the importance of soluble mediators released from synovium or bone as being important in aetiology of symptoms

Pain in Osteoarthritis (1 in 3 adults)

- Usually a strong mechanical component
- Minor response to paracetamol and moderate response to NSAIDs and opiates (recent reviews of RCTs show opiates no better than NSAIDs)
- Poor correlation with structural evidence of joint damage
- Knee pain correlates with MRI findings of
 - Moderate to large effusions
 - Synovial hypertrophy
 - bone marrow lesions
- No correlation with articular cartilage damage, in fact articular cartilage is aneural and avascular
- Changes in bone marrow lesions and synovitis correlate with fluctuations in knee pain

Osteoarthritis pain (continued)

- Potential peripheral mediators/targets for OA pain are inflammatory mediators and receptors including
 - prostanoids
 - kinins
 - chemokines
 - growth factors, eg nerve growth factor
 - cytokines, esp IL-1, TNF & IL-6 (although less than in Rheumatoid)
- Sensitivity of receptors (primary sensory nociceptors) is governed by
 - interaction with local microenvironment
 - prior stimuli, ie modified response properties to subsequent stimuli
- Sensitisation of receptors to stimulation, both peripheral and central, is very important concept.

Sensitization of Receptors

- Peripheral sensitization

Early post-translational changes with lowered threshold for activation
(mediators include PGE2-activate kinases to phosphorylate receptor-ion channels).

Later gene induction transcription-dependent cell phenotype changes
(mediators include growth factors including NGF)

- Central sensitization

at spinal level (dorsal horn neurons)

exaggerated responses to (non) painful stimuli

pain threshold

allodynia

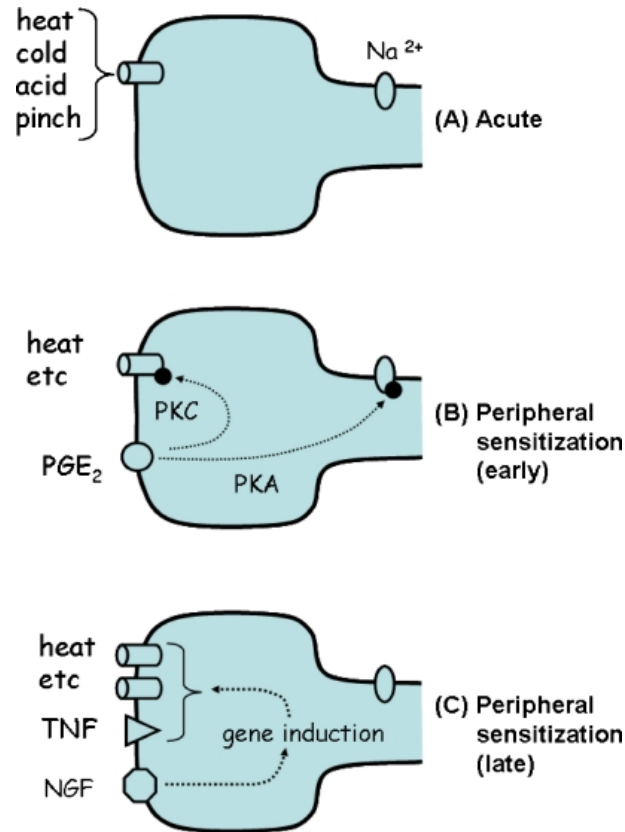
hyperalgesia

expansion of receptive field with strengthening of synapses

loss of descending inhibitory mechanisms

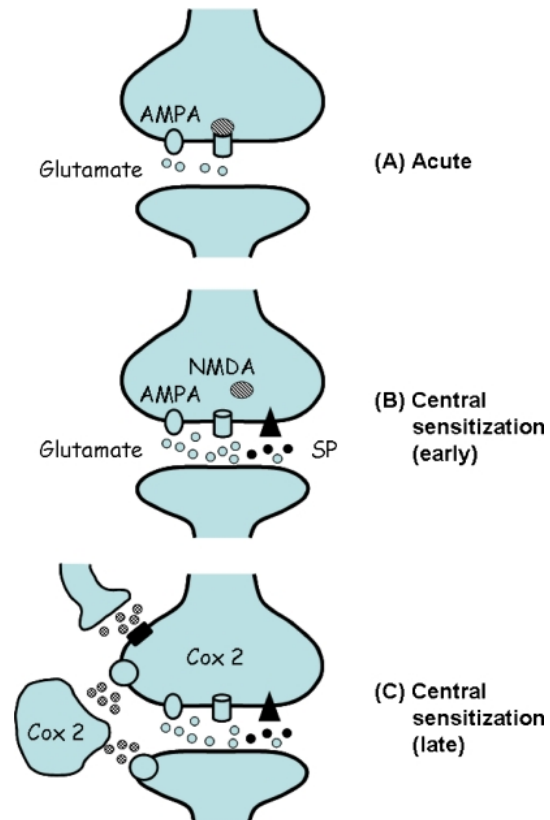
at cortical level

Peripheral Sensitization in OA Pain

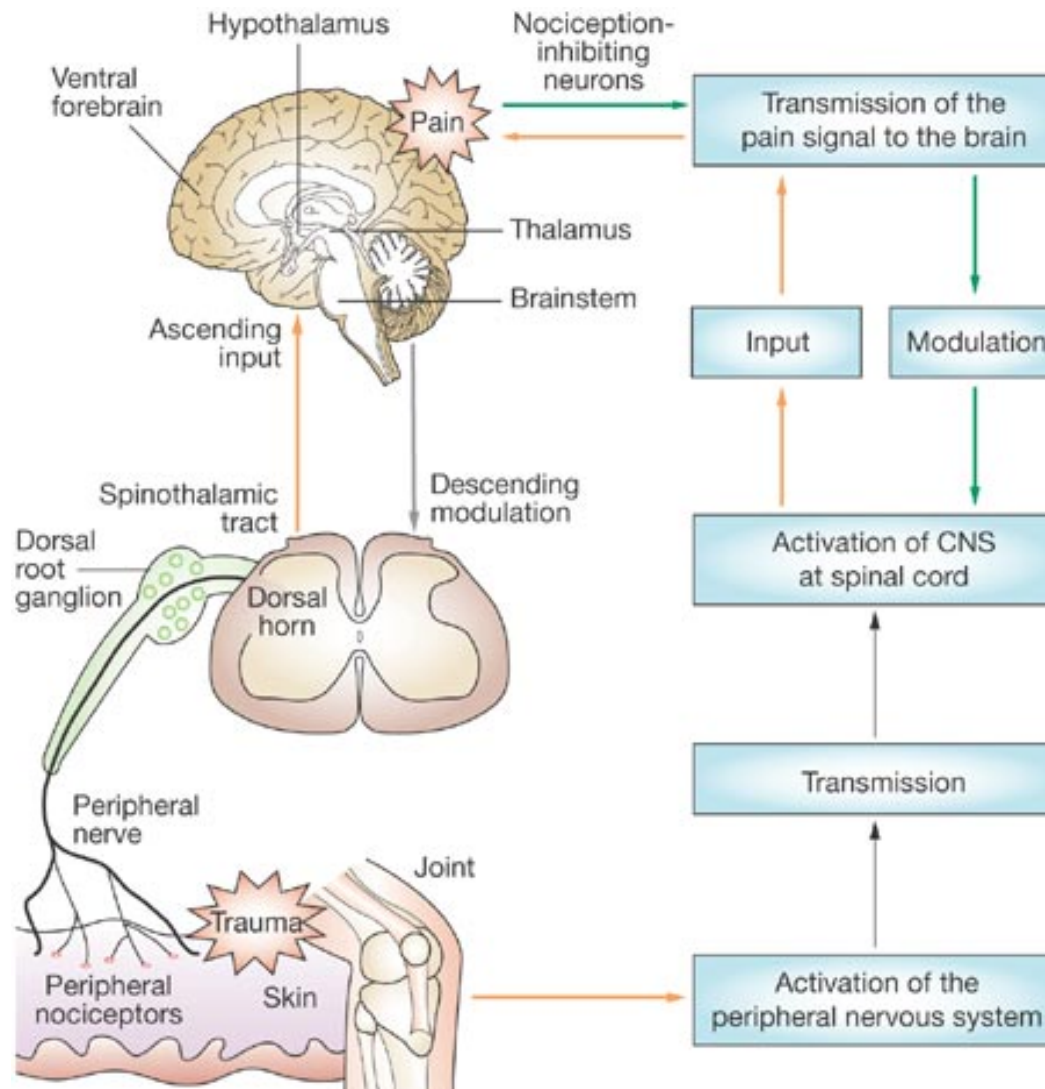


Central Sensitization in OA Pain

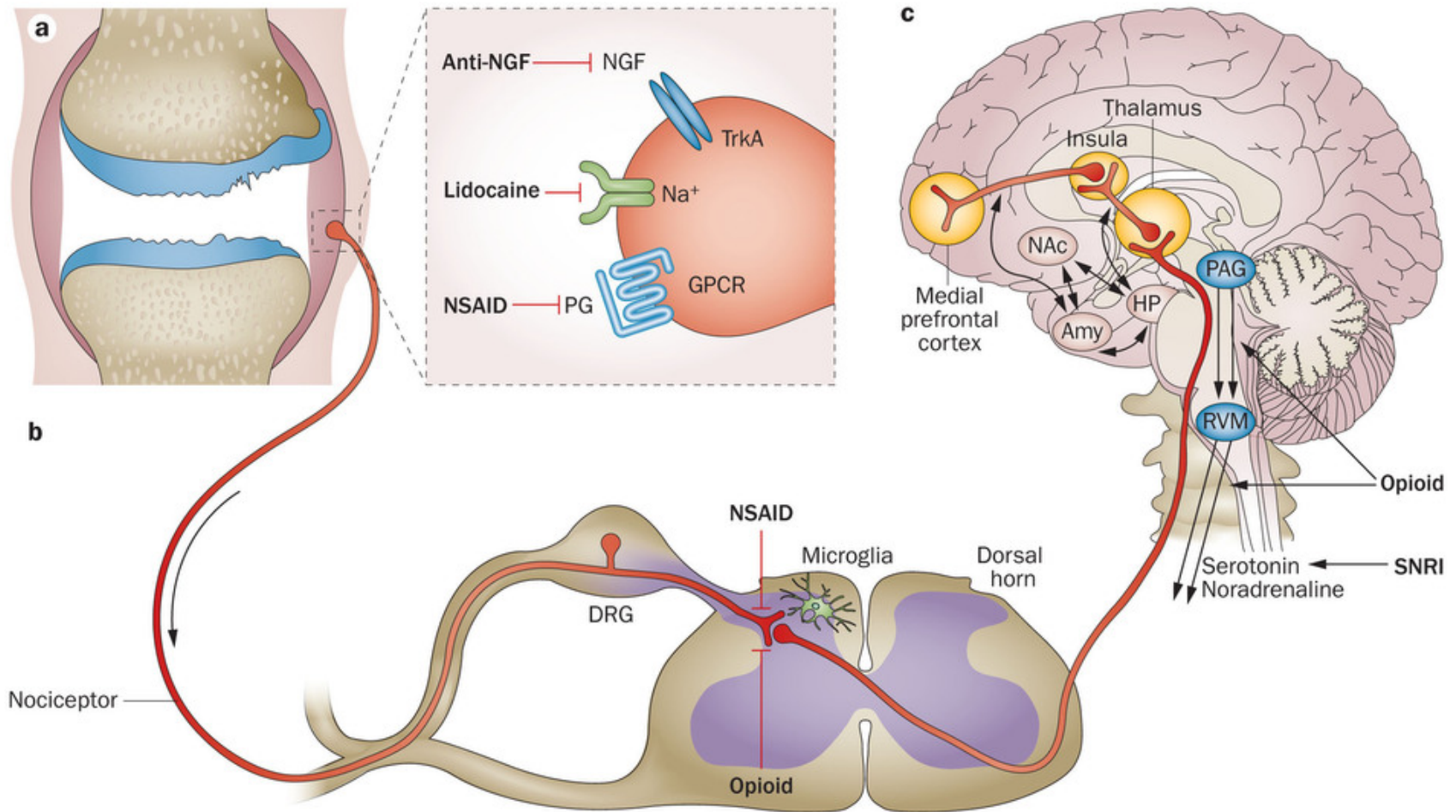
Spinal cord neurons



Pain pathways to and from the cortex



Pain pathways to and from the cortex



Neuropathic pain

- Pain generated by the nervous system resulting directly from action on nerves, eg nerve damage by trauma to nerves or metabolic damage, for instance diabetic neuropathy
- In a significant subset of OA (and other arthritides) first- and second-line analgesics, such as NSAIDs and opiates, are ineffective
- For these patients source of pain may not be nociceptive or inflammatory but from an alternative mechanism

Neuropathic pain (2)

- Examination of nerves innervating a degenerate or inflamed joint (eg knee) often reveal damage including truncation and varicosity consistent with a peripheral neuropathy
- These abnormal nerve endings are rich in algogenic neurotransmitters such as substance P and calcitonin gene-related peptide
- In addition to nociceptors, other receptors are also involved and knee OA can be associated with a loss of proprioception which, in some studies, is correlated with pain severity
- Thus the origin of some arthritis pain may involve activity of damaged nerves opening new therapeutic options

Obesity and Joint disease

- Age, genes, prior joint damage and excessive joint loading due to obesity are considered key risk factors for OA
- Traditionally it is believed that obesity affects joints through loading, however there must be additional mechanisms as, for example, hand arthritis is also strongly correlated with obesity
- Furthermore recent work using MR imaging has shown that obesity is associated with joint damage well before symptoms develop, indicating that obesity is not a secondary event
- Now recognized that body fat is not inert but is metabolically active releasing pro-inflammatory molecules including cytokines and adipokines that can damage joints
- In addition to osteoarthritis, rheumatoid arthritis and psoriatic arthritis are also associated with obesity

Inflammatory Joint Disease

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing Spondylitis/Spondyloarthropathy
- Reactive arthritis
- Crystal arthritis
 - Gout
 - Pseudogout

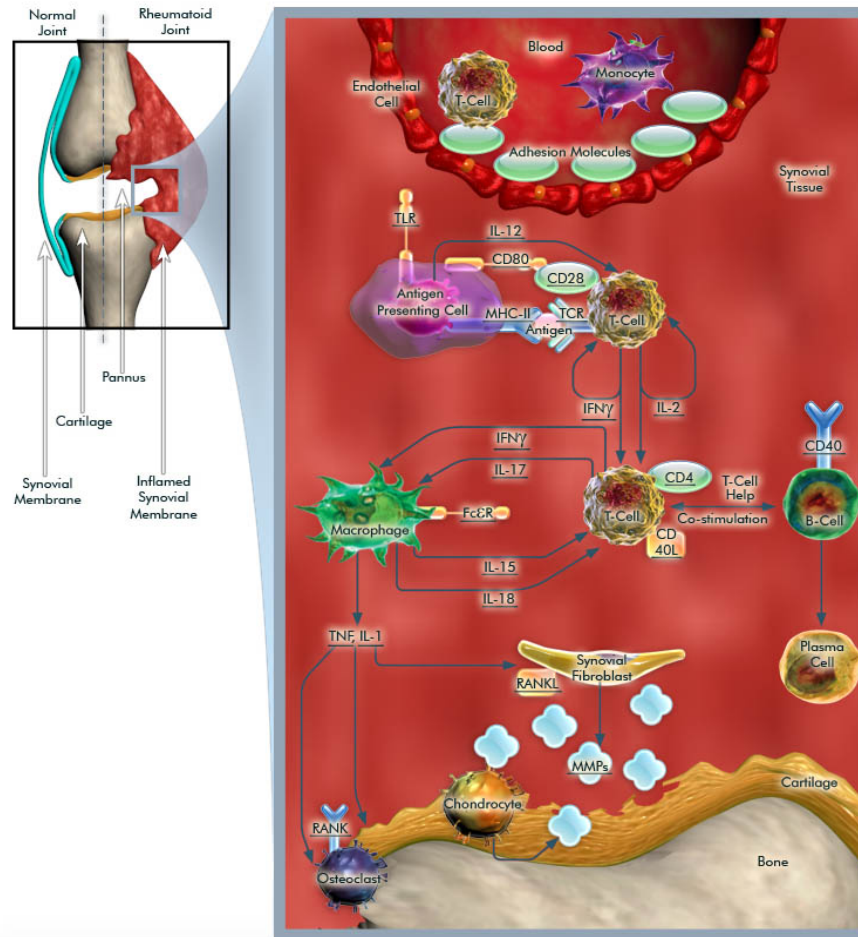
Rheumatoid Arthritis

- RA is the prototypical inflammatory autoimmune joint disease
- Affects 2% women and 0.5% men, overall 1% population
- Onset most often young to middle age, prime working years
- Classically peripheral and symmetrical
- Knees often involved
- Patients commonly highlight pain as the most important issue
- Pain may remain problematic despite good control of inflammation
- Fatigue, stiffness and psychological distress/low mood modulate and are part of the pain experience

Rheumatoid Arthritis-pathogenesis

- Autoimmune disease with antibodies directed against self tissues.
- An important group of auto-antigens are citrullinated proteins/peptides
- During inflammation, and sometimes for unknown reasons, arginine amino acid residues are enzymatically converted into citrulline residues in proteins such as vimentin
- These altered proteins may be seen as antigens by the immune system, allowing the generation of an immune response
- In fact the test for antibodies to citrullinated peptides has now become a diagnostic test for RA (ACPA) more specific than Rh F
- Th1 mediated disorder with T cells producing inflammatory cytokines such as IL-2, IFN γ & TNF along with autoantibodies (P.C.)

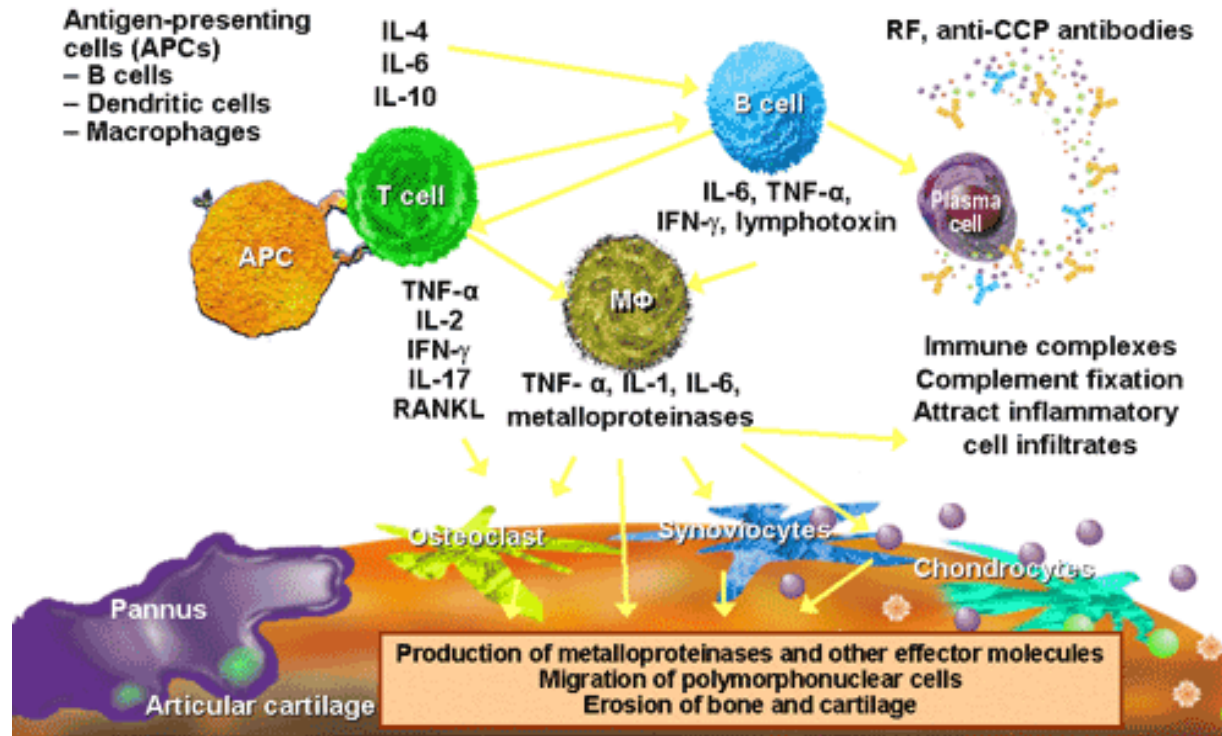
Pathogenesis of RA



Pathogenesis of RA (2)

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1. Adapted from: Smolen JS, et al. *Nat Rev Drug Discov.* 2003;2:473-488.
2. Choy EH, et al. *N Engl J Med.* 2001;344:907-916.
3. Silverman GJ, et al. *Arthritis Res Ther.* 2003;5(suppl4):S1-S6.

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Peripheral Mechanisms of RA Pain

- Pain occurs either on
 - Mechanical stimulation of joint, eg weight bearing or movement
 - Spontaneously at rest
- Numerous algogens (pain producing agents) have been identified in the RA joint (synovium or synovial fluid) and these can either activate or sensitize peripheral nociceptors
- Algogens include
 - cytokines, eg IL-1, IL-6, IL-8, TNF & GM CSF
 - growth factors, eg β NGF & VEGF
 - chemokines, eg CCL2 or MCP-1
- Algogens above can either excite or sensitize
 - Uncertain whether act directly or indirectly via another mediator

RA pain (continued)

- Fatigue in RA can be as disabling as pain
- Fatigue variously attributed to
 - inflammatory disease activity
 - pain itself, in fact improves with control of pain
- Pain, impaired sleep & fatigue may alter central pain processing, in part by blunting descending analgesic mechanisms
- In fact 10 to 20% of patients with RA satisfy diagnostic criteria for fibromyalgia
- Thus in RA both peripheral and central mechanisms of pain are involved

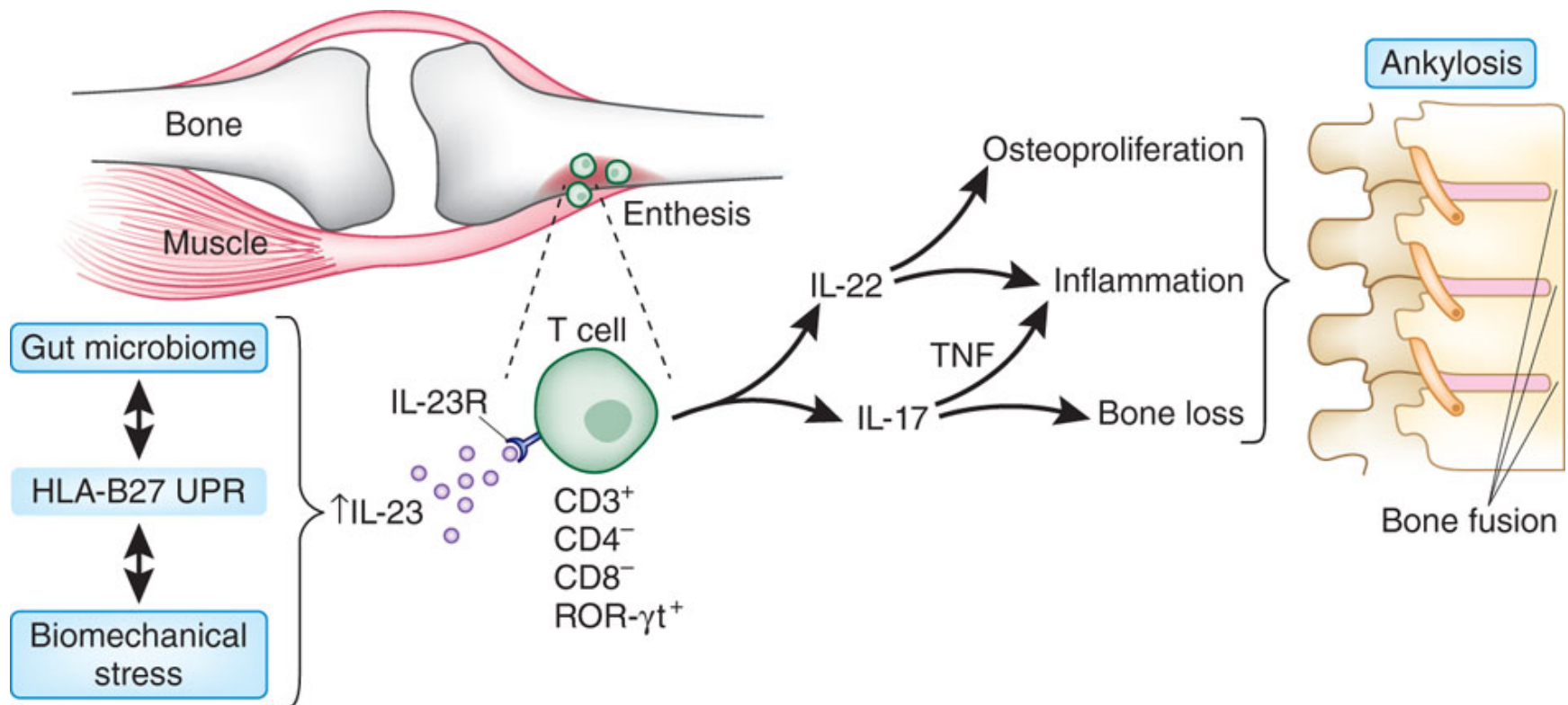
Psoriatic Arthritis

- 3 to 5% of population have psoriasis and up to 1/3 of these may have psoriatic arthritis, ie 1 to 2% of the population, thus maybe more prevalent than rheumatoid arthritis
- Peak age of onset is 30 to 50 yrs, can occur at any age, M=F
- In 80% of patients the psoriasis precedes the arthritis, average of 10 yrs
- Most typical pattern is asymmetric, large joint, lower limb oligoarthritis, commonly knee
- Less common forms are pseudo rheumatoid, DIP predominant, atypical spondyloarthropathy and arthritis mutilans

Psoriatic Arthritis-Mechanisms

- TH 17 (CD 4/CD8 neg) are key cells-prominent in joint
stimulated by IL-23
release IL-17/21/22 & some IL-23
downstream generation of IL-1, IL-6 and TNF
- Dendritic cells and macrophages release IL-23 when triggered in joint and skin
- Inflammation probably commences in the enthesis (where tendon or ligament connect to bone via fibrocartilage) and is affected by mechanical strain
- Enthesis is functionally integrated with synovium and inflammation involves the synovio-entheseal complex (SEC)
- There are in fact 32 entheses in the knee joint

Immunology of Psoriatic Arthritis



Features of psoriatic arthritis (2)

- Enthesitis can include plantar fasciitis, Achilles, patellar, supraspinatus and quadriceps tendonitis and at insertion of gluteus medius along iliac crest
- Dactylitis can occur with swelling of an entire digit
- Ray diversity: mutilans in one, dactylitis in another, ankylosis and synovitis in others
- Nail disease in 80%, vs 50% in psoriasis alone
- Uveitis and retinal inflammation 15 to 20%
- Clinical bowel disease in 15 to 20%. Up to 30% on biopsy, most like Crohns
- Enthesitis is often subclinical and joint destruction can sometimes progress insidiously

Features of psoriatic arthritis (3)

- Psoriasis is associated with obesity, an increased BMI and the metabolic syndrome and psoriatic arthritis is more strongly associated with these
- Frequently glucose intolerance, diabetes and CV disease
- Hypertension, dyslipidaemia, hepatic steatosis
- RR of AMI 6 to 8 fold increased in young patients

In Summary

- Joint disease is common and, in fact, WHO ranks musculoskeletal disorders as the most frequent cause of disability in the modern world.
- Pain is the predominant symptom but is frequently associated with fatigue, which may be disabling
- Pain is classically nociceptive due to mechanical or inflammatory joint damage but is amplified/modified by both acute and chronic peripheral and central sensitization
- IL-1, IL-6 & TNF α are important final mediators of inflammation and pain, especially but not only in RA and psoriatic arthritis
- In all forms of arthritides it is important to consider that there may be a neuropathic element to the pain which may require a different approach to treatment
- Most arthritides, including OA, RA, PsA and gout are associated with obesity, an obviously important target for prevention/modification/treatment