

Overview

This module starts with a discussion of IL-1, the cytokine key to the diseases we will be covering in this session and traces the steps required for the production and activation of the form of IL-1 known as IL-1 β . This section is divided into subsections. The first details IL-1 actions in inflammation. The second details the steps regulating the generation of active IL-1 β . We discuss the stimuli required to first induce IL-1 β transcription and second to stimulate activation by cleavage by the enzyme caspase-1. The last subsection covers the inflammasome, the molecular machinery responsible for activating caspase-1 and thus IL-1 β , with a specific focus on the NLRP3 inflammasome that is implicated in the diseases covered in this section.

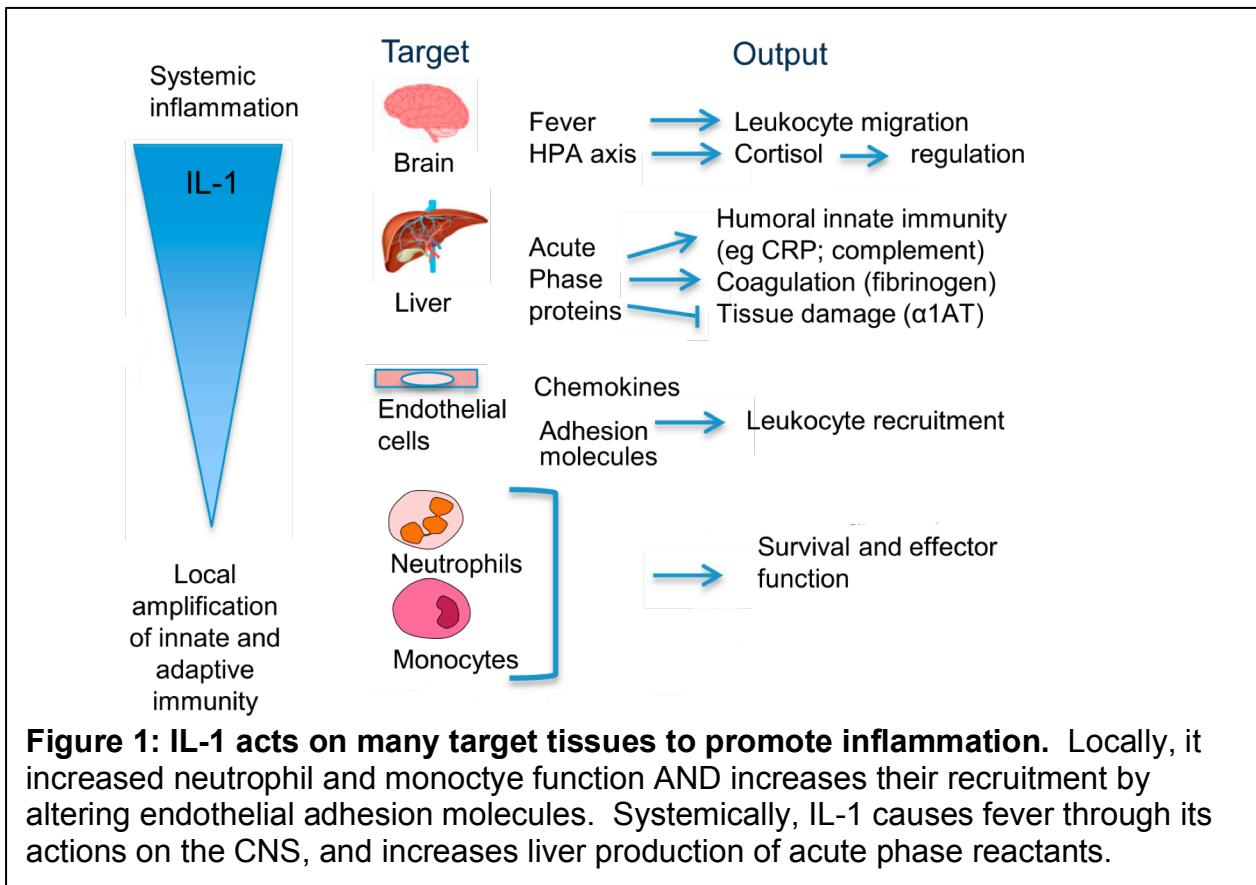
The **second section** covers joint diseases in which activation of the NLRP3 inflammasome is a critical aspect of disease pathophysiology: gout and CPPD (also known as pseudogout).

The **third section** is an optional section. Material in this section is included for fun, buand will not be on your exams or covered by the readiness assessment. The third section discusses other conditions where activation of the NLRP3 inflammasome has been implicated in disease pathology. The **fourth section** briefly discusses genetic diseases linked to mutations in the NLRP3 inflammasome and provides information about drugs that block IL-1 actions.

Section 1: Background on IL-1 activation by the inflammasome

IL-1 is a major mediator of inflammation

IL-1 functions as a mediator of inflammation in multiple ways (Figure 1). It affects the central nervous system to induce fever, which in turn increases leukocyte migration. It induces acute phase proteins including complement that contribute to innate immunity. IL-1 acts on endothelial cells to promote the expression of adhesion molecules and chemokines, which together increase leukocyte recruitment to areas of IL-1 activation (Figure 2). Locally, IL-1 promotes survival and effector function of neutrophils and monocytes.



IL-1 comes in two forms, IL-1 α and IL-1 β . IL-1 α and IL-1 β are encoded by different genes but bind the same receptors and have similar biologic properties. IL-1 α is constitutively present in many cell types. In contrast, IL-1 β is stimulated by activation of toll like receptors (TLR), TNF α and IL-1 itself. **This module will focus on IL-1 β .**

Production of active IL-1 β is stimulated by TLR and inflammatory cytokines

IL-1 β is primarily made by macrophages, monocytes, and dendritic cells (DC). Stimulation of macrophages through TLR activation or by cytokines, including IL-1 as shown in figure 2 and figure 3 below, induces transcription of IL-1 β . Pro-IL-1 β is synthesized but is not biologically active until the pro region is removed by proteolytic cleavage. The primary pathway for activating IL-1 β is cleavage by the protease caspase-1. Caspase-1 is itself synthesized as a zymogen, or inactive enzyme. Pro-caspase-1 is activated by cleavage that occurs only after it is recruited into an inflammasome complex, discussed below. This pathway is depicted in figure 3.

For your information only/not on exam:
Inflammasomes also activate pro-IL-18 by Caspase-1 cleavage in parallel with IL-1 β , but the effects of IL-18 activation are less well studied.

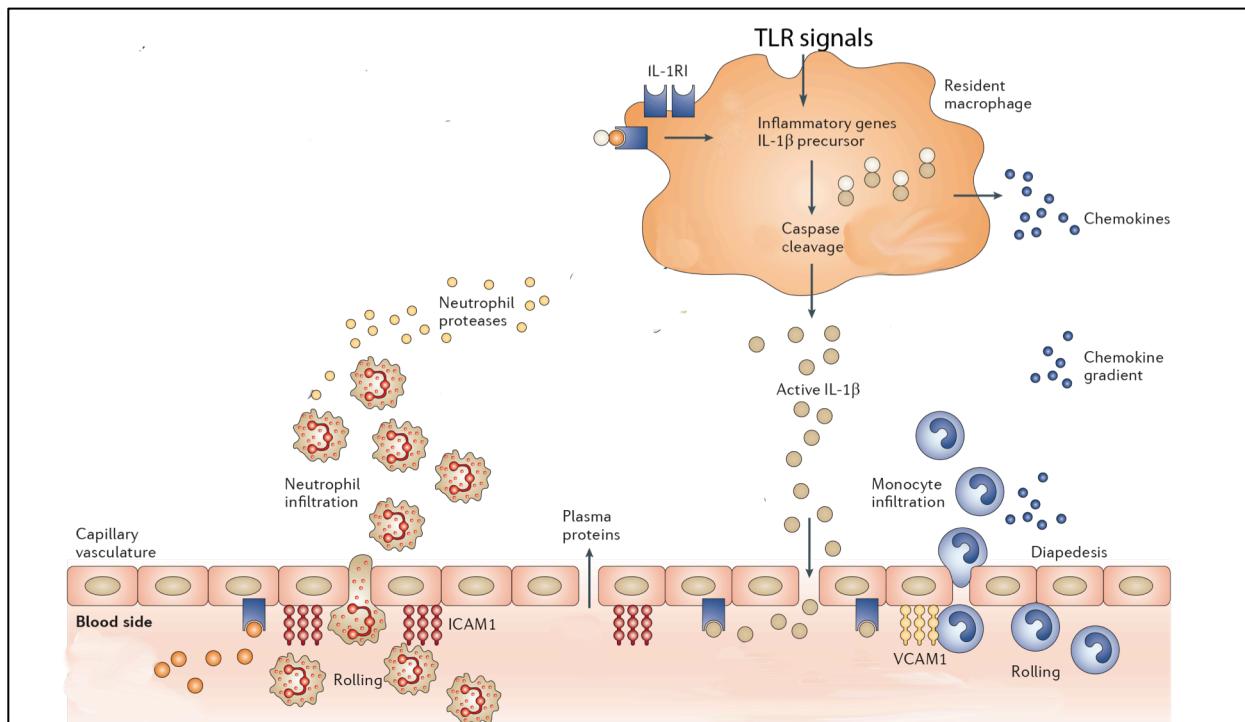
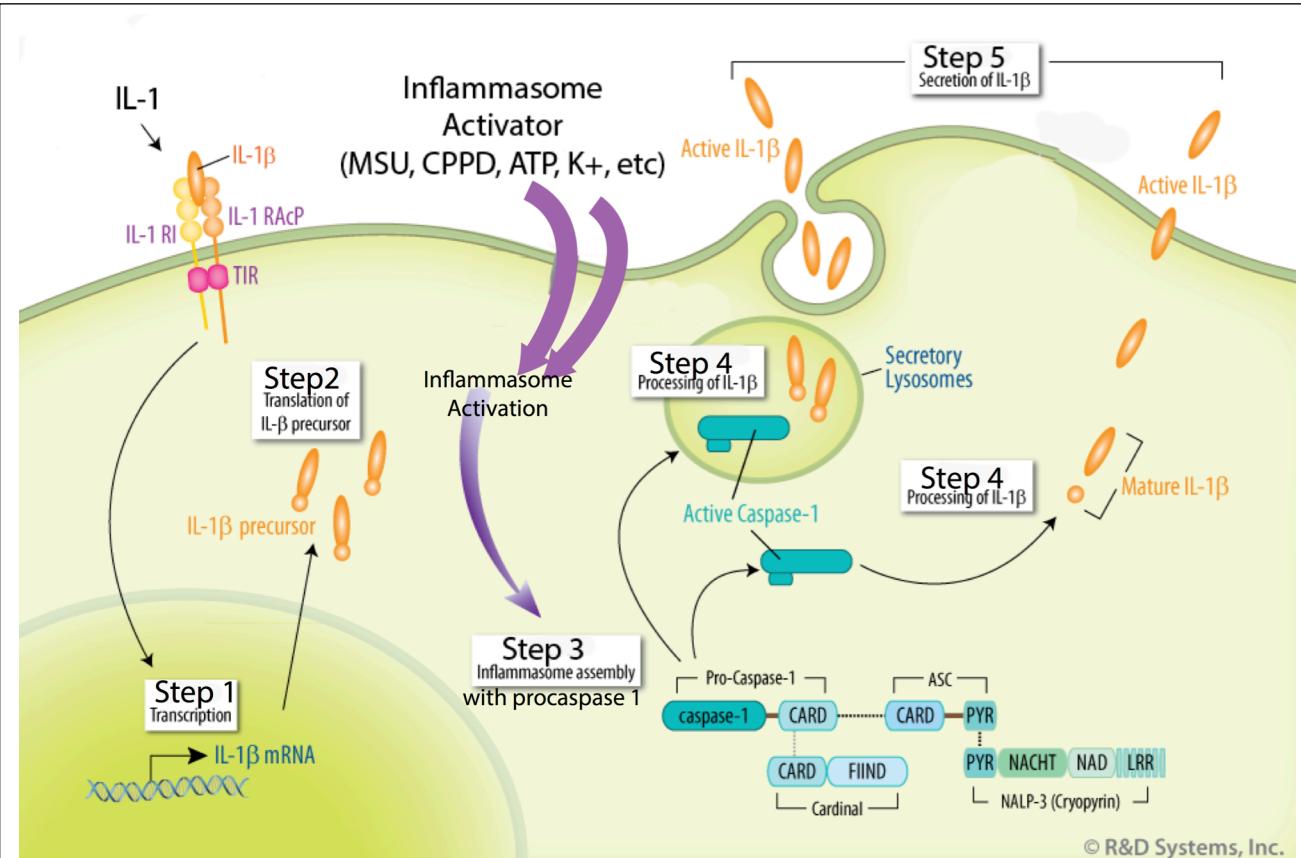


Figure 2. TLR and IL-1 promote production of active IL-1 β by tissue resident macrophages. Transcription of IL-1 β can be induced by multiple inflammatory stimuli, including TLR activation and IL-1 itself, as shown here. Increased IL-1 β transcript levels leads to increased levels of the pro-IL1 β protein. In the presence of activated caspase-1 this results in increased active IL-1 β . Active IL-1 β then acts to promote neutrophil and monocyte migration to the area of inflammation.



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Fig 3. IL-1 β activity is regulated at many levels. Transcription: IL-1 β message is induced by inflammatory stimuli (Step 1), including IL-1 itself, TNF, TLR stimulation. This message is translated into pro-IL-1 β , the precursor of active IL-1 β (Step 2). IL-1 β is activated by cleavage of the propeptide. This activating cleavage is itself highly regulated. A variety of different molecules activate the inflammasome, which causes pro-caspase 1 to associate and become activated by cleavage of its own pro-peptide (Step 3). This schematic shows the NLRP3 inflammasome with activators of the NLRP3 inflammasome, but all inflammasomes similarly activate IL-1 β in response to the stimuli specific to them. After secretion of active IL-1 β (Step 4) the ability of IL-1 β to activate its receptor, IL-1R, is further regulated by competition with IL-1RA (see figure 4 below).

Activated IL-1 β is secreted by an as yet poorly understood mechanism. Once secreted, IL-1 β acts on endothelial cells to induce adhesion molecules and chemokines that contribute to leukocyte and neutrophil influx. It also promotes neutrophil and monocyte function. Neutrophils and monocytes attracted to the area perpetuate inflammation by release of inflammatory cytokines and chemical mediators of inflammation such as the arachidonic acid metabolite prostaglandin E2. Please take a look at the Pathology 2-Acute inflammation module slides 30-34 and 43 on chemical mediators of inflammation to review.

IL-1 β activity is highly regulated

IL-1 activity is regulated at many levels – transcriptionally and post-translationally as discussed and illustrated in figure 3 above, but also by an antagonist of the IL-1 receptor called IL-

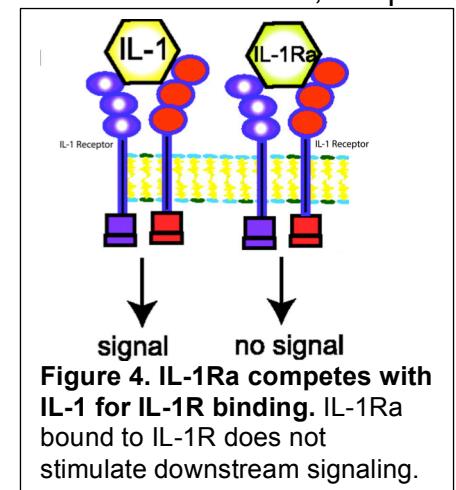


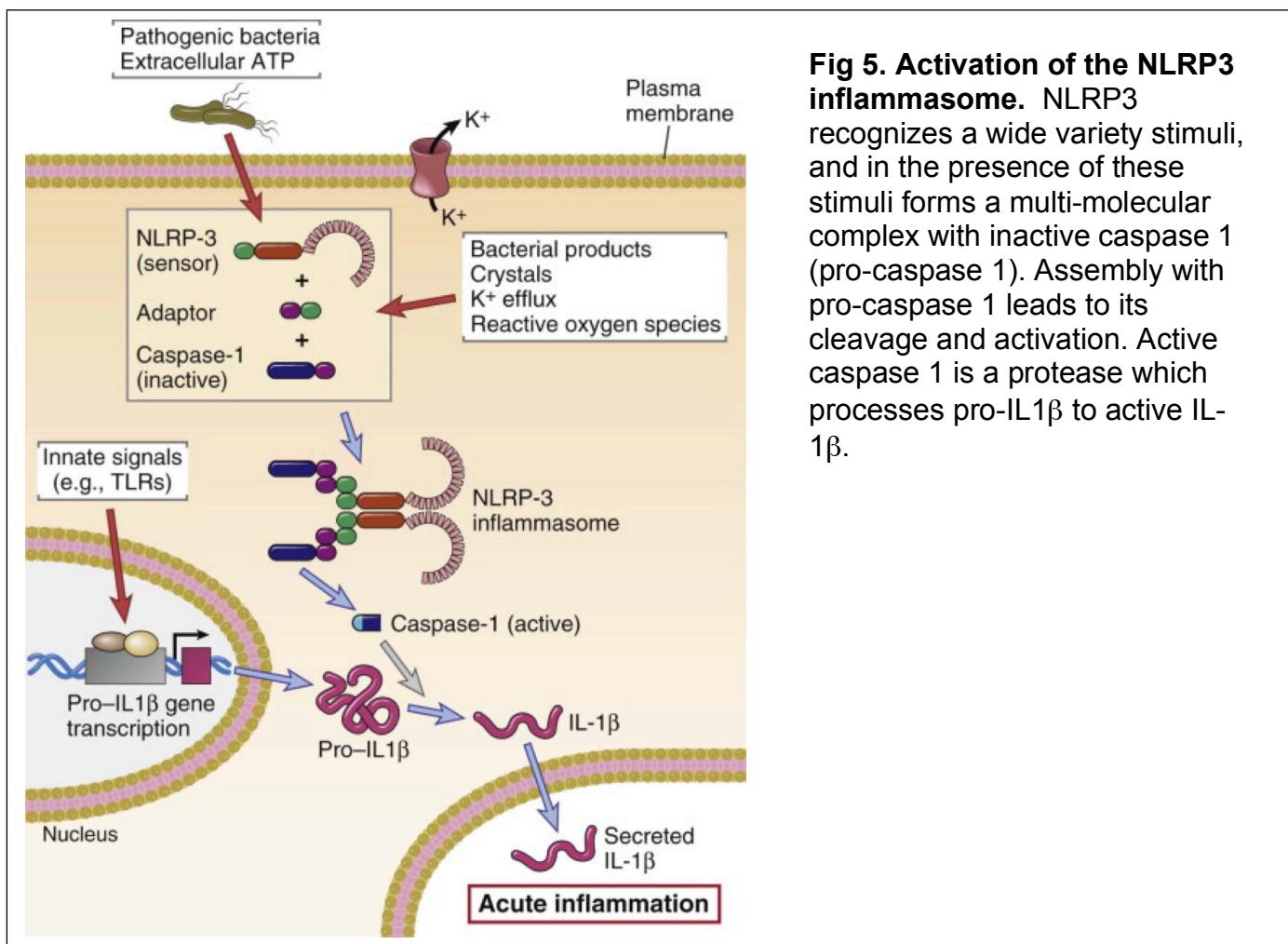
Figure 4. IL-1Ra competes with IL-1 for IL-1R binding. IL-1Ra bound to IL-1R does not stimulate downstream signaling.

1RA. IL-1RA antagonizes IL-1 activity by competing with IL-1 for the IL-1 receptor, as shown in figure 4.

Caspase-1 is activated by the inflammasome

Inflammasomes are complexes that include a sensor, an adaptor protein and caspase-1. Five different sensors have been identified, each responding to a different range of activation signals, resulting in five different types of inflammasomes, all with the function of IL-1 β activation.

The majority of sensors belong to the NOD Like Receptor (NLR) family, and the best characterized sensor is the NLRP3 sensor that we will focus on in this session. The NLRP3 inflammasome is activated by a wide variety of stimuli as depicted in figure 3, and also in figure 5, below. Most relevant for today's discussion are bacterial products and crystals, including monosodium urate (MSU), the crystal responsible for gout.



As you might imagine, inflammasome activity is tightly regulated in order to prevent excess IL-1 production. Basal expression of NLRP3 itself is low but is rapidly induced by microbial products (through TLR stimulation), reactive oxygen species and cytokines.

NLRP3 responds to a wide variety of DAMPs and PAMPs that are structurally dissimilar and thus activation is unlikely to be via direct sensor-ligand interaction, but the mechanism of NLRP3 activation remains to be worked out.

Section 2: Inflammasomes in joint disease

Gout, MSU and the inflammasome

Gout is an acute inflammatory arthritis caused by deposition of monosodium urate (MSU) crystals in tissue. It is almost always associated with hyperuricemia (elevated blood levels of uric acid).

Uric acid is supersaturated at a concentration above 6.8mg/dL and can precipitate into crystals in tissues and joints. These crystals are made up of monosodium urate. Microscopic identification of crystals, as shown in figure 6, is an important test for diagnosing gout.

Monosodium urate crystals are described as needle like and negatively birefringent. This means that when examined with a polarizing microscope they appear yellow when the crystal is oriented parallel to the long axis of the compensator and blue when perpendicular.

(Don't worry about the details of how a polarizing microscope works. Even rheumatologists don't always understand the optics).

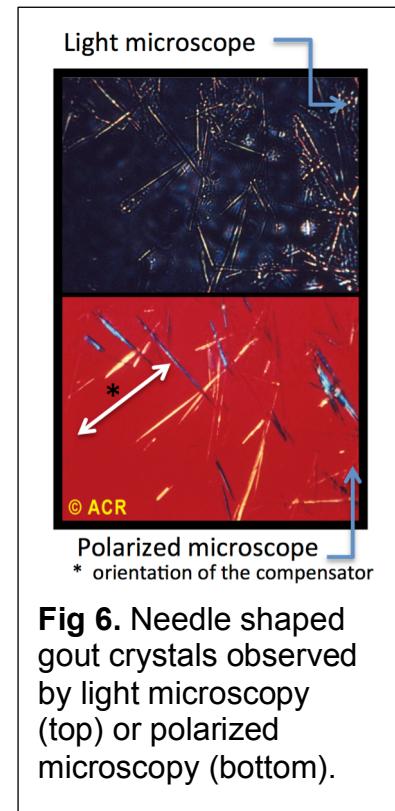


Fig 6. Needle shaped gout crystals observed by light microscopy (top) or polarized microscopy (bottom).

Clinical description of gout

Gout is typically a disease of episodic symptomatic periods, termed "gout attacks." Gout attacks are characterized by rapid onset of exquisite pain associated with warmth, swelling, and erythema of the affected joint. The pain escalates from the faintest twinges to its most intense level over an 8- to 12-hour period. Initial attacks usually affect only one joint, and in half the patients, the first attack involves the first metatarsophalangeal (MTP) joint. Gout of the first MTP is so common that it has its own name: podagra. Other joints commonly involved are the ankle, knee, wrist, finger and elbow.

The intensity of the pain is such that patients cannot stand even the weight of a bed sheet on the affected part and most find it difficult or impossible to walk when the lower extremities are involved in an acute attack. The acute attack may be accompanied by fever (typically only if multiple joints are involved), chills, and malaise. Cutaneous erythema associated with the attack may extend beyond the involved joint and resemble cellulitis. Desquamation of the skin may occur as the attack resolves. Symptoms resolve quickly with appropriate treatment, but even untreated, an acute attack resolves spontaneously over 1–2 weeks.



Fig 7. Acute gout attack of the medial malleolus and first MTP (left image). Acute podagra (right image). Note redness and swelling of involved joints. Gout involving the first MTP is called podagra.

There are 3 stages of gout:

1. asymptomatic hyperuricemia
2. intermittent acute attacks with intervals that are completely symptom free
3. chronic gouty arthritis with constant symptoms with superimposed acute attacks.

Untreated gout can lead to formation of tophi, which are large aggregates of crystals (figure 8. A classic location for tophi is the olecranon bursa (far right image). Tophi can deposit in bone and cause bone erosions (figure 9) and joint destruction. MSU crystals can also deposit in the kidney, causing urate nephropathy.



Fig 8. Three examples of tophi in patients with gout.

Although the reasons why acute gout develops when it does are not clear, attacks tend to be associated with rapid increases, and more often decreases, in the concentration of urate in synovial fluid. These concentrations mirror the fluctuations seen in the serum. Accordingly, a person may experience a sudden drop in the serum urate level leading to an acute attack, and therefore is found to be normouricemic when blood is tested at that time. Trauma, alcohol ingestion, and the use of certain drugs are known to trigger gout attacks as well.



Fig 9. Erosion of the 1st MTP joint caused by gouty tophus deposition in bone. Arrow points to a classic “rat bite” erosion.

Drugs known to precipitate attacks do so by rapidly raising or lowering serum urate levels. Candidate agents include diuretics, salicylates, radiographic contrast agents, and specific urate-lowering drugs (for example allopurinol or febuxostat). It is believed that these fluctuations in urate levels destabilize tophi in the gouty synovium. The sudden addition of urate to them may render them unstable, or the sudden lowering of the urate concentration may cause partial dissolution and instability. As the microtophi break apart, crystals are shed into the synovial fluid and the gouty attack is initiated (see above).

A diagnosis of gout is confirmed by synovial fluid analysis demonstrating MSU crystals or by the presence of tophi.

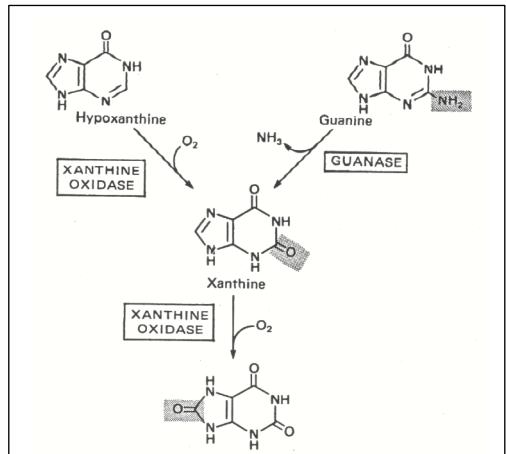


Fig 10. Uric acid is a product of purine metabolism.

Hyperuricemia and gout

Uric acid is a product of the purine salvage pathway. Xanthine oxidase metabolizes xanthine to uric acid (figure 10). Uric acid is cleared by the kidneys and excreted in the urine. Hyperuricemia most commonly results from underexcretion of uric acid due to renal insufficiency or competition for excretion by organic acids (for example, hydrochlorothiazide, low dose aspirin, lactic acid for example in heavy alcohol users). Over production is rare but can be seen with diseases that cause increased nucleic acid turnover, such as myeloproliferative diseases, psoriasis, hemolytic anemia. Rare enzyme deficiencies can also cause

elevated serum uric acid. Alcohol, particularly beer, is a source of purines, in addition to decreasing excretion. Other dietary sources rich in purines include organ meats and shellfish. Dietary change alone, however, is rarely able to control gout. Gout generally affects men over age 30. The incidence of gout increases significantly with rising serum uric acid, as shown in figure 11. Hyperuricemia in the absence of gout is not an indication for treatment, however.

MSU crystals activate the NLRP3 inflammasome

A gout attack is initiated when MSU crystals in the joint are ingested by macrophages or monocytes in the joint. The crystals activate monocytes, which then produce cytokines that stimulate pro-IL-1 β production

Framingham study (12 year observation)	
URATE LEVEL (MG/DL)	OCCURRENCE OF GOUT (%)
<7	2
7-8	17
8-9	25
>9	83

Fig 11. Incidence of clinical gout increases with increasing serum uric acid.

Why does uric acid activate the NLRP3 inflammasome? Uric acid released by dying cells is a DAMP which alerts the body to pathologic cell death.

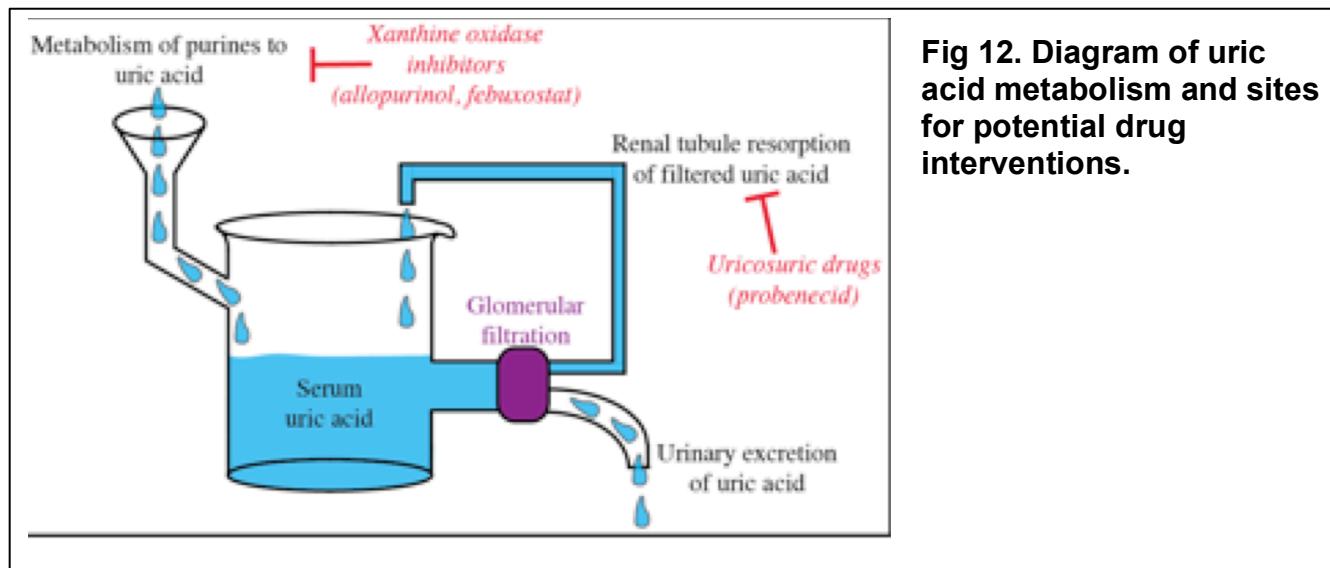
(hit 1). MSU crystals are also sensed by NLRP3 and activate the NLRP3 inflammasome (hit 2), resulting in active Caspase-1 and cleavage of pro-IL-1 β to active IL-1 β . The surge of active IL-1 β then mediates the influx of neutrophils into the joint. In the joint, neutrophils release chemical mediators of inflammation including prostaglandins, as well as proteases and other contents resulting in tissue damage. The appearance of acute gout can be confused with cellulitis. This is not surprising, as both conditions are characterized by acute inflammation.

Treatment of acute gout aka “gout flare”

Treatment of an acute gout attack is aimed at inhibiting chemical mediators of inflammation. NSAIDS and prednisone are the mainstay of treatment. NSAIDS block COX pathways, inhibiting prostaglandin and thromboxane synthesis. Corticosteroids inhibit phospholipase A2 and block both COX pathways and lipoxygenase pathways. Corticosteroids may be given either systemically or locally via injection into the joint. Please review Pathology 2-Acute Inflammation module for more detail regarding the arachadonic acid pathway and inhibitors. Another possible treatment for acute gout is high dose colchicine, which is thought to act via inhibition of the inflammasome. However, side effects (primarily diarrhea) limit its use.

Preventative Treatment of gout

In patients who have had multiple gout attacks, treatment is aimed at decreasing serum uric acid levels as shown in figure 12, below. If kidney function is normal, this can be achieved with probenecid, a drug that increases uric acid excretion (a uricosuric agent). More commonly, xanthine oxidase inhibitors are used. These are allopurinol and febuxostat. These drugs prevent the formation of uric acid, and xanthine is instead shuttled into other metabolic pathways. Lastly, not depicted here, a recombinant form of uricase, an enzyme that metabolizes uric acid to allantoin which is highly soluble and easily excreted, can be given. However, humans do not have uricase and immune reactions to the drug limit its use.

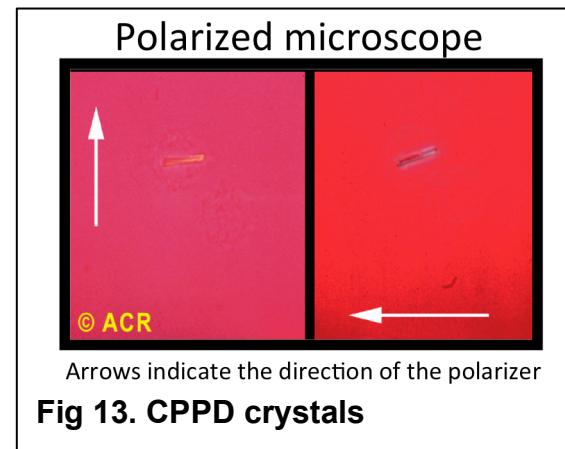


Treatments that inhibit uric acid formation may also precipitate gout flares by rapidly changing serum uric acid. Flares can be prevented by using medications that inhibit the production of inflammatory mediators, typically either NSAIDS or low dose steroids. Another alternative for prophylaxis against flare is colchicine. Colchicine was thought to be beneficial because of its effects on microtubule polymerization and the theory that it decreased neutrophil migration.

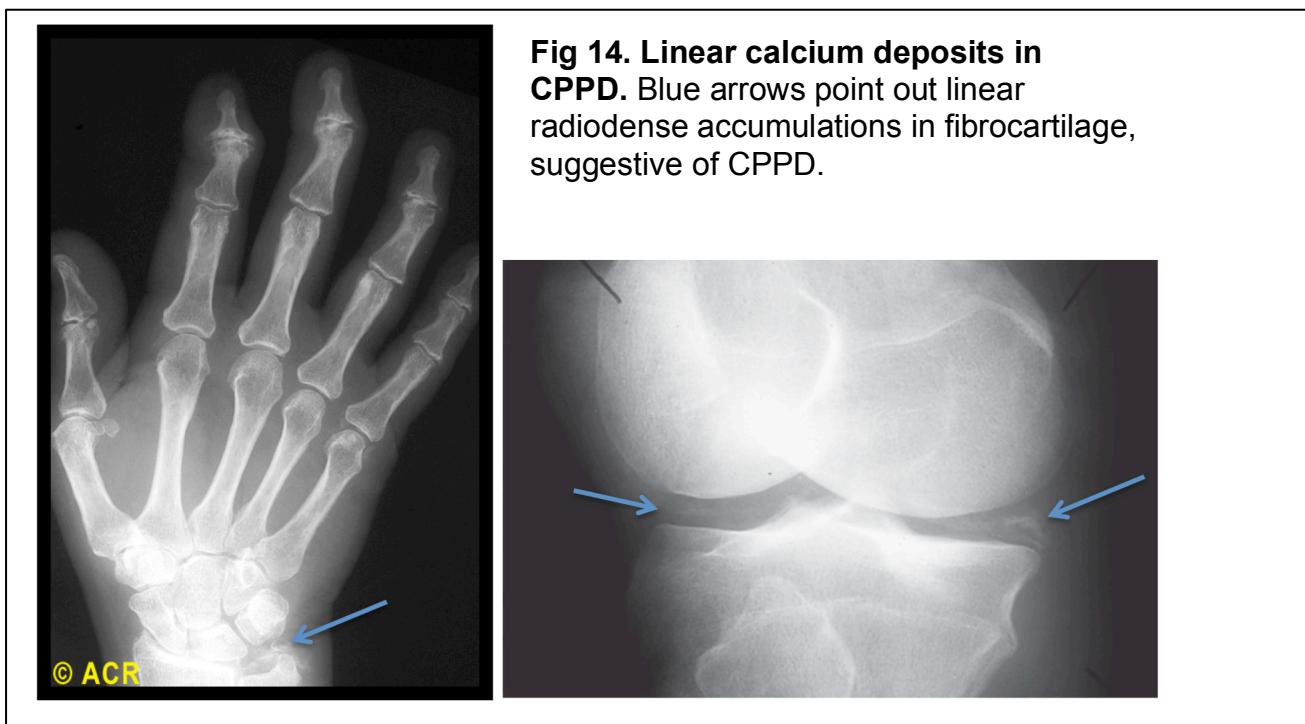
However, more recently, it has emerged that colchicine may inhibit NLRP3 inflammasome activation.

Pseudogout: CPPD crystals activate the NLRP3 inflammasome

As discussed previously, the NLRP3 inflammasome is activated by a number of different stimuli, including several types of crystals. In addition to MSU, the NLRP3 inflammasome is activated by calcium pyrophosphate dihydrate (CPPD) crystals. As with MSU crystals in gout, CPPD crystals can be seen in the synovial fluid during an acute attack of inflammatory arthritis due to CPPD. CPPD crystals are generally rhomboid-shaped and positively birefringent. In contrast to MSU crystals, they appear blue when parallel to the long axis of the compensator and yellow when perpendicular (figure 13).



CPPD crystals deposit in articular cartilage or fibrocartilage. The radiographic findings of punctate and linear densities in hyaline articular cartilage or fibrocartilaginous tissues are diagnostic of CPPD crystal deposition. Radiographs most often demonstrate sites of CPPD crystal deposition in the knees, in the triangular cartilage of the radiocarpal joint of the wrist, and the symphysis pubis.



Not every patient with CPPD crystal deposition develops an acute inflammatory arthritis. Only about 25% of patients with CPPD develop pseudogout, so called because of its clinical similarity to gout. Signs and symptoms are characterized by acute, typically monoarticular inflammatory arthritis lasting for several days to 2 weeks. These self-limited attacks may vary in intensity but can occur just as abruptly as an acute gout attack. Between

episodes, patients are usually asymptomatic. Nearly half of all attacks involve the knees, although pseudogout can affect other joints, including the first metatarsophalangeal joint, which is the most common site of gouty inflammation. Attacks of pseudogout may occur spontaneously or be provoked by trauma, surgery, or severe medical illness. Differentiation of pseudogout from joint infection may be difficult and requires arthrocentesis with examination of synovial fluid for crystals and culture. Without appropriate analysis of synovial fluid, it may be impossible to differentiate pseudogout from septic arthritis.

Although the cause of CPPD crystal deposition is unknown, several risk factors for pseudogout have been identified. Perhaps the most important factor is aging. CPPD deposition will probably occur in everyone if they live long enough. Genetic factors also influence crystal formation, given that numerous familial cases of CPPD deposition have been described in many nationalities. The prevalence of CPPD deposition is greater in people who have suffered orthopedic trauma. Finally, several metabolic and endocrine conditions have been associated with an increased frequency of CPPD disease, the most important of which to consider is hemochromatosis, hypothyroidism and hyperparathyroidism.

Treatment of acute attacks is similar to that for gout. Oral colchicine is useful in the patient with frequent bouts of pseudogout. However, this prophylactic therapy seems less effective in pseudogout than it is in classic gout. Unfortunately, there is no equivalent to allopurinol or a uricosuric agent for the treatment of CPPD deposition disease.

Complications: The development of CPPD crystal deposition disease can lead to progressive degenerative damage of the joint. Findings may be severe with joint collapse and Charcot-like degeneration. Fortunately, abnormalities this severe are unusual.

Section 3: Potential Role of the Inflammasome in Sunburn and Acne

NB: Material from this section is included for interest and will not be on the exams.

Sunburn

Clinical description of sunburn

Sunburn is the normal cutaneous reaction to sunlight in excess of an erythema dose. The minimal amount of a particular wavelength of light capable of inducing erythema on an individual's skin is called the minimal erythema dose. The solar spectrum has been divided into different regions by wavelength. Below 400 nm is the UV spectrum, two components of which, UVA and UVB are responsible for solar erythema. Although the amount of UVA radiation is 100 times greater than UVB radiation during midday hours, UVB is up to 1000 times more erythemogenic than UVA, and so essentially all solar erythema is caused by UVB. UV exposure is an important risk factor for skin cancers, which will be discussed in depth in later sessions.

Sunburn is an example of inflammation, characterized by warmth, erythema, swelling and pain. Thus, it is not surprising that the inflammatory mediators we have learned about may play a role in the pathology of sunburn.



Fig 15. Examples of sunburn.

Mechanism of inflammation in sunburn

As discussed in “Introduction to skin structure and function” earlier in the week, the dermis contains many types of immune cells, including innate immune cells like macrophages and mast cells that can trigger the events of acute inflammation when triggered. However, keratinocytes are increasingly recognized as having immune functions.

Recent work (too recent to be in textbooks!) has demonstrated that keratinocytes contain all the components of the NLRP3 inflammasome, as well as other inflammasomes, and produce pro-IL1 β , as outlined in figure 16. Several groups have shown that UV irradiation activates the NLRP3 in keratinocytes, driving active IL-1 β release and initiating an acute inflammatory response. How does UV irradiation activate the inflammasome in keratinocytes? We don’t have a definitive answer, but it may be through induction of reactive oxygen species, induction of other activators (for example K $^{+}$ flux) or UV radiation (UVR) causing oxidization of sebum components that have been proposed as possible activators of NLRP3.

Acne Vulgaris

Clinical description of acne vulgaris

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles (figure 17). The comedo is the primary lesion of acne. It may be seen as a flat or slightly elevated papule with a dilated central opening filled with blackened keratin (open comedo or blackhead), as seen in figure 18. Closed comedones (whiteheads) are yellowish papules. Erythematous papules and pustules form in response to inflammation (figure 19).

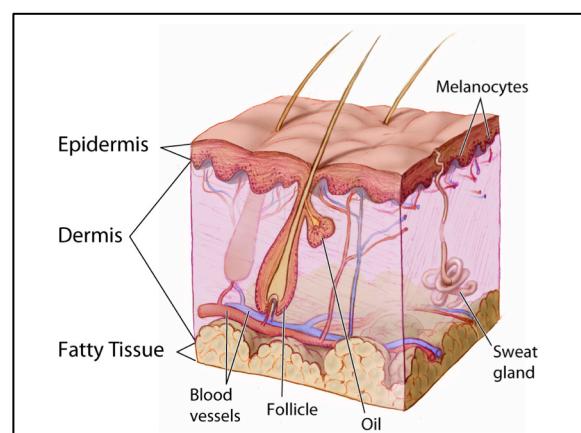


Fig 17. The pilosebaceous follicle.



Fig 18. Example of open comedo (blackhead).



Fig 19. Inflamed pustules of acne vulgaris.

Innate immunity in acne pathogenesis: a work in progress

Acne vulgaris is a follicular disease, in which the follicle is impacted and distended by a keratinous plug. The keratinous plug is caused by hyperproliferation and abnormal differentiation of keratinocytes of unknown causes. Disruption of the follicular epithelium permits discharge of the follicular contents into the dermis. The combination of keratin, sebum, and microorganisms, particularly *Propionibacterium acnes*, leads to the release of proinflammatory mediators and the accumulation of lymphocytes, neutrophils, and foreign body giant cells. This in turn causes the formation of inflammatory papules, pustules, and nodulocystic lesions. Here we have a situation with a microbial pathogen, chemical mediators of inflammation and accumulation of neutrophils and lymphocytes. Is the inflammasome involved in the acute inflammation that initiates acne lesions?

P. acnes activates the NLRP3 inflammasome in **monocytes** in the skin, resulting in release of IL-1 β . It is proposed that *P. acnes* activates macrophage NLRP3 inflammasome, probably in the dermis, causing IL-1 β mediated acute inflammation with influx of neutrophils.

P. acnes also activates TLR2 on **keratinocytes** and drives IL-1 production by keratinocytes in early acne, although it is not known if this is NLRP3 dependent. Thus *P. acnes* likely contributes to inflammation via several mechanisms.

Section 4: Diseases linked to Mutations in Inflammasome Components and IL-1 β excess

Periodic fever syndromes

Hereditary periodic fever syndromes are a group of mainly monogenic disorders characterized by episodes of fever, accompanied by laboratory and clinical signs of inflammation. Laboratory signs of inflammation are characterized elevations in the ESR (erythrocyte sedimentation rate) and the CRP (C reactive protein), two common tests performed on patients' blood samples. The particular feature of clinical inflammation observed in these diseases varies according to the specific genetic defect, and may include some combination of arthralgia or arthritis, myalgia, rash, stomatitis, pharyngitis, conjunctivitis, serositis, and abdominal pain. There are many diseases that fall into this family and the details of each are not important at this stage in your education. Rather, what we hope you will take away is the principle that mutations in innate immune system components can cause autoinflammatory disorders. One subset of these autoinflammatory disorders is

the periodic fever syndromes associated with mutations resulting in aberrant IL-1 β processing.

Mutations in the NLPR3 sensor result in the cryopyrin-associated periodic syndromes (CAPS), all of which are associated with increased/inappropriate elevations of IL-1 β during attacks. Moderately severe CAPS (also known as Muckle-Wells syndrome) presents with fever, rash, arthralgias or arthritis, hearing loss and conjunctivitis. CAPS is treated by inhibition of IL-1.

Inappropriately elevated IL-1 β is also seen in the most common periodic fever syndrome Familial Mediterranean Fever (FMF). In FMF the genetic mutation is in the MEVF gene, encoding pyrin. Pyrin is a component of a distinct inflammasome complex that also activates caspase-1 to generate mature IL-1 β . FMF is characterized by episodic fevers lasting 1-3 days, monoarthritis, rash and severe abdominal pain.

Although a number of periodic fever syndromes share the common pathophysiologic theme of dysregulated inflammasome activation leading to inappropriately elevated IL-1 β , the clinical manifestation of each syndrome are distinct. The molecular basis of the phenotypic heterogeneity of IL-1 mediated diseases is not clear, but the critical role of IL-1 is indisputable based on the response to agents that block IL-1 action.

Therapeutic interventions that can block IL-1 actions

Several therapies have been developed that block IL-1. These therapies were developed for use in inflammatory arthritis, and are effective in some but not all forms of arthritis (they are not effective in RA, for example). In some clinical circumstances, IL-1 blockade has been used to treat severe, acute gout flares.

Anakinra was the first agent developed and its mechanism of action is analogous to IL-1Ra, in that it antagonizes IL-1R function. Rilonacept and canakinumab work by inhibiting IL-1 itself: rilonacept acts as a “trap” to bind circulating IL-1 such that it cannot activate IL-1R, whereas canakinumab is a neutralizing antibody against IL-1. The details of drug names and mechanisms of action are for your information only – they will not be on the exam. The take home message of this section is that there are agents available that block IL-1 action.

Table 1 | Agents available or under study for reducing IL-1 activity

Agent	Availability	Mechanism of action	Company
Anakinra	Approved	Receptor antagonist for IL-1RI	Swedish Orphan BioVitrum (see Supplementary information S1 (table))
Rilonacept*	Approved	Soluble IL-1 receptor that binds IL-1 β >IL-1 α >IL-1Ra	Regeneron
Canakinumab	Approved	Neutralizing anti-IL-1 β IgG1 mAb	Novartis

Thanks for your attention and feel free to email questions to jfcharles@bwh.harvard.edu.

This module was prepared from the following resources. All resources are available online through Countway Library. Schematics and model figures from these references have been modified for the purpose of this session. In some cases, sections of the relevant textbook have been excerpted verbatim.

- Chapter 44: Gout, in Lange Current Diagnosis & Treatment: Rheumatology
- Chapter 45: Pseudogout, in Lange Current Diagnosis & Treatment: Rheumatology
- Section “Actinic Injury” in Chapter 3: “Dermatoses Resulting from Physical Factors” in *Andrews’ Diseases of the Skin*, 12th edition (James, Burger, Elston)
- Chapter 13: “Acne” in *Andrews’ Diseases of the Skin*, 12th edition (James, Burger, Elston)
- Chapter 80: “Acne vulgaris and acneiform eruptions” in Fitzpatrick’s Dermatology in General Medicine.
- Sunburned skin activates inflammasomes. Faustin & Reed, TRENDS in Cell Biology, 2007.
- Sebum, inflammasomes and the skin: current concepts and future perspective. Oyewole and Birch –Machin, Experimental Dermatology, 2015
- Inflammasome activation by Propionibacterium acnes: the story of IL-1 in acne continues to unfold. Thiboutot, JID, 2014.
- The inflammasomes in autoinflammatory diseases with skin involvement. Beer et al, JID, 2014.
- Inflammasomes in health and disease. Strowig et al. Nature, 2012.
- The Interleukin-1 Family: Back to the future. Garlanda et al. Immunity, 2013.
- Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Dinarello et al, Nature Reviews Drug Discovery, 2012.
- The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation. Manthiram et al, Nature Immunology 2017.
- Autoinflammatory Diseases with Periodic Fevers. Sag et al, Curr Rheum Rep, 2017.