Autoinflammatory Diseases

Summer AAD 2019 Handout

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Outline

• What is autoinflammation?
• Classical/Monogenic Autoinflammatory Diseases
• Common Dermatologic Conditions featuring Autoinflammation
What is autoinflammation?

• Autoinflammatory syndromes are conditions characterized by:
  – Exaggerated **innate** immune system response
  – **Episodes** of spontaneous inflammation affecting multiple organ systems
  – Primarily **neutrophil**-mediated response
  – Usually involving **IL-1** pathways
## Autoinflammation vs Autoimmunity

<table>
<thead>
<tr>
<th>Autoinflammation</th>
<th>Autoimmunity</th>
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</thead>
<tbody>
<tr>
<td>Innate immune system</td>
<td>Adaptive immune system</td>
</tr>
<tr>
<td>Neutrophil-mediated</td>
<td>Lymphocyte-mediated</td>
</tr>
<tr>
<td>No detectable autoantibodies</td>
<td>Characteristic autoantibodies in serum</td>
</tr>
<tr>
<td>Linked to inflammasome activation</td>
<td>Less clear link to inflammasomes</td>
</tr>
<tr>
<td>Classically IL-1 mediated</td>
<td>Mediated by T- and B- cells, with variable interleukin activation (including IL-1)</td>
</tr>
<tr>
<td>Host vs. Danger signals</td>
<td>Self vs. Non-self</td>
</tr>
</tbody>
</table>
IL-1β and IL-18

- Both activated by **inflammasome** activation, central to autoinflammation
- Both released as precursors and require activation
IL-1β

- IL-1β – discovery first started in 1948
  - Substance from rabbit leukocytes able to cause fever, later identified in 1970’s as IL-1
  - Secreted by immune cells
    - Monocytes/macrophages, dendritic cells, neutrophils, NK cells, lymphocytes
    - Also secreted by keratinocytes
- Acute phase reactant and pyrogen
- Upregulates secretion of COX-2, IL-6, TNF-α, and IL-1
  - Activation of NFκB and subsequent expression of COX-2 leads to fever
- Multiple types of receptors, including soluble receptors
Medications Targeting IL-1β

• Anakinra - competitive inhibitor of IL-1; binds to IL-1R
  – Short half-life necessitates daily SQ injections
  – FDA approved for RA, CAPS
• Rilonacept - fusion protein of IL-1R which binds IL-1 (soluble decoy),
  – Stronger binding to IL-1β than IL-1α; FDA approved for CAPS
  – Weekly injections
• Canakinumab - anti-IL-1β monoclonal antibody
  – Half life of ~25 days allows for injection q2mo
  – FDA approved for CAPS, systemic JIA, TRAPS, FMF
• Gevokizumab (anti-IL-1β mAb), LY2189102 were in development but not progressing
• P2D7KK - similar to Canakinumab but 11x more potent; still in preclinical trials
IL-18

• Induces interferon-γ
  – Requires IL-12 or IL-15 also
• Not a strong pyrogen (less activation of NFκB)
• Possible role in inflammation of IBD, heart disease, metabolic syndrome
• Blocking IL-18 reduces metastasis in a mouse model of melanoma
The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL-β

Fabio Martinon, Kimberly Burns, Jürg Tschopp

Abstract

Generation of Interleukin (IL)-1β via cleavage of its proform requires the activity of caspase-1 (and caspase-11 in mice), but the mechanism involved in the activation of the proinflammatory caspases remains elusive. Here we report the identification of a caspase-activating complex that we call the inflammasome. The inflammasome comprises caspase-1, caspase-5, Pycard/Asc, and NALP1, a Pyrin domain-containing protein sharing structural homology with NODs. Using a cell-free system, we show that proinflammatory caspase activation and proIL-1β processing is lost upon prior immunodepletion of Pycard. Moreover, expression of a dominant-negative form of Pycard in differentiated THP-1 cells blocks proIL-1β maturation and activation of inflammatory caspases induced by LPS in vivo. Thus, the inflammasome constitutes an important arm of the innate immunity.
Inflammasomes

- Regulates immunologic response to either exogenous stimuli (pathogens) or endogenous stimuli (neoplasia)
- Intracellular multi-protein complexes
  - Molecular pattern recognition receptor (PRR)
  - Apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) adaptor protein
  - Caspase-1 enzyme

[Image: Inflammasome multiprotein complex diagram]

http://www.invivogen.com/review-inflammasome
Inflammasome

PRR recognizes stimuli → ASC linked to procaspase-1 which is cleaved → caspase-1 activation → pro-IL-1β and pro-IL-18 cleaved to active forms
Autoinflammation as Aberrant Host Defense

- Pathogen-associated molecular patterns (PAMPs) activate inflammasomes
- Prototype of PAMP is Lipopolysaccharide, an endotoxin found on gram-negative bacterial cell walls
- Also flagellin, lipoteichoic acid (Gram+), peptidoglycan, dsRNA (viruses)
- Necessary for innate immune response to microbial invaders
Autoinflammation as Aberrant Host Defense

• Danger-associated molecular patterns (DAMPs) part of host response to non-pathogenic danger signals
• During cell death, some nuclear/cytosolic proteins are broken down → activate inflammasome to clear away cellular debris or react to possible neoplasia
• Examples include DNA/RNA, Heat Shock Protein, ATP, adenosine, S100
• Complicated relationship with tumorigenesis
Outline

• What is autoinflammation?

• Classical/Monogenic Autoinflammatory Diseases

• Common Dermatologic Conditions featuring Autoinflammation

• Case Discussions
## Categories of Autoinflammatory Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean Fever (FMF)</td>
<td>MEFV (AR)</td>
<td>Erysipelas-like lesions on lower extremities, vasculitis</td>
<td>Colchicine, Anakinra, TNF inhibitors</td>
</tr>
<tr>
<td>Cryopyrin-Associated Periodic Syndromes (CAPS)</td>
<td>CIAS/NLRP3 (AD)</td>
<td>Urticarial lesions</td>
<td>Anakinra, Rilonacept, Canakinumab, Thalidomide</td>
</tr>
<tr>
<td>Hyper-IgD Syndrome (HIDS)</td>
<td>MVK (AR)</td>
<td>Erythematous macules/patches and urticaria</td>
<td>Prednisone, Colchicine, IVIG, Cys, Anakinra, TNF inhibitors</td>
</tr>
<tr>
<td>TNF Receptor Associated Periodic Syndrome (TRAPS)</td>
<td>TNFRSF1A (AD, sporadic)</td>
<td>Erythematous patches/plaques, sometimes figurate</td>
<td>TNF inhibitors, prednisone, anakinra</td>
</tr>
<tr>
<td>Juvenile Autoinflammatory Diseases</td>
<td>Various</td>
<td>Various, including severe acne, HS, PG, pustular psoriasis</td>
<td>Various</td>
</tr>
</tbody>
</table>
Familial Mediterranean Fever

• Most common systemic autoinflammatory disease
  – Primarily affects patients with Jewish, Arab, Armenian, Turkish, and Italian lineage
  – AR; Carrier frequency in Middle Eastern populations as high as 1:3
  – Almost all have at least one episode by age 20
  – Fever 6 hours – 3 days, erysipelas-like lesions of lower extremities, monoarthritis, abdominal pain, pleurisy
Familial Mediterranean Fever

• Mutation in MEFV which encodes for pyrin
• Distinguishing clinical finding is erysipelas-like lesions of lower extremities in up to half of patients
  – Warm, erythematous, edematous, well-demarcated
  – Below knee, dorsal foot, anterior leg
  – Symmetric or unilateral
  – Generally less than 15cm in size
• Histology shows dermal infiltrate of neutrophils and nuclear dust
• Higher likelihood of vasculitis such as HSP (5%), PAN
Familial Mediterranean Fever

- Systemic manifestations common and may vary between episodes
  - Most common – abdominal pain (95%)
  - Monoarthritis (75%) with effusions – knee, ankle, hips
  - Pleuritic chest pain (30%)
  - Scrotal pain/swelling in boys
  - Amyloidosis in untreated
Familial Mediterranean Fever

- Treatment of choice – colchicine
- Reduces frequency/severity of attacks
- Remission in up to \( \frac{3}{4} \)
  - Prevents development of amyloidosis
- Reports of anakinra and TNF inhibitors also helping
  - RCT in 2016 from Israel – anakinra reduced frequency of attacks, especially helpful in joints
Colchicine and Inflammasomes

(A) NLRP3 inflammasome

(B) Microtubules mediate NLRP3 inflammasome formation by bringing the mitochondrially-based ASC into apposition with NLRP3, located on the surface of the endoplasmic reticulum.

(C) Colchicine blocks NLRP3 inflammasome formation and activation by inhibiting microtubule polymerization, thereby disallowing formation of the ASC-PRR complex and thus the inflammasome.
Cryopyrin Associated Periodic Syndromes

• Encompasses a *spectrum* of severity and diseases previously classified separately

• Collectively referred to as CAPS or cryopyrinopathies
  – Familial Cold-Associated Syndrome (FCAS)
  – Muckle-Wells Syndrome (MWS)
  – Neonatal-onset multisystem inflammatory disease (NOMID)/Chronic infantile neurologic cutaneous articular syndrome (CINCA)
Cryopyrin Associated Periodic Syndromes

- FCAS and MWS found in 2001 to share the same mutation – susceptibility gene is CIAS1 which encodes for cryopyrin
  - Later found to also underlie NOMID/CINCA
  - Mutations mostly localized to exon 3
  - Some mutations can lead to different manifestations and severity
Cryopyrin Associated Periodic Syndromes

• NOMID/CINCA – earlier onset, most severe end of the spectrum
  – Triad of disabling arthropathy, skin eruption, CNS inflammation
  – 2/3 with urticaria-like eruptions at birth, most of the rest have it by 6 months
    • Biopsy showing dermal infiltrate of neutrophils, lymphocytes, occasional eosinophils but no mast cells as in true urticaria
  – Neurologic manifestations and arthropathy common and variable; also conjunctivitis and hearing loss
  – Treatment of choice is now anakinra (steroids, Cys much less effective)
Cryopyrin Associated Periodic Syndromes

• FCAS (aka familial cold urticaria) least severe – cold-induced bouts of fever, urticaria, and arthralgia
• MWS – fever, urticaria, and limb pain; also associated with amyloidosis and deafness
• Urticarial lesions provoked by generalized exposure to cold in FCAS; delay of 2-3 hours, lasting up to 12 hours
• Urticarial lesions in MWS persist for longer (up to 3 days)
• Dermal edema, infiltrate of neutrophils on histology
• In MWS, progressive sensorineural hearing loss in adolescence in 2/3 to 3/4; nephropathy due to amyloid in up to 1/4
Cryopyrin Associated Periodic Syndromes

- For FCAS/MWS, NSAIDs and systemic steroids can be used during attacks to attenuate them and help with joint pain
- IL-1 blockade can limit number of attacks and prevent amyloidosis so should be considered especially in MWS
  - Treatment may help or reverse the hearing loss but not yet clear whether this is consistent
Treatment of Muckle-Wells syndrome: analysis of two IL-1-blocking regimens

Jasmin B Kuemmerle-Deschner1†, Helmut Wittkowski2†, Pascal N Tyrrell3, Ina Koetter4, Peter Lohse5, Katharina Ummenhofer1, Fabian Reess1, Sandra Hansmann1, Assen Koitschew6, Christoph Deuter7, Anja Bialkowski1, Dirk Foell8† and Susanne M Benseler3†

Disease activity and inflammatory markers. At last follow-up, 75% of anakinra-treated and 93% of canakinumab-treated patients achieved remission. During follow-up, S100A12 levels mirrored recurrence of disease activity. Both treatment regimens had favorable safety profiles.

Conclusions: IL-1 blockade is an effective and safe treatment in MWS patients. MWS-DAS in combination with MWS inflammatory markers provides an excellent monitoring tool set. Canakinumab led to a sustained control of disease activity even after secondary failure of anakinra therapy. S100A12 may be a sensitive marker to detect subclinical disease activity.
Hyper-IgD Syndrome

- Mutation in Mevalonate Kinase (MVK) gene leading to reduced enzyme function
- Recurrent fevers, cervical lymphadenopathy, arthralgias, abdominal pain, rash
- Can have amyloidosis (AA) – kidney dysfunction
- At least 2 IgD levels above 100mg/L one month apart
  - Can also be seen in FMF, TRAPS, others
  - Genetic testing also available; mevalonic acid in urine elevated during attacks
Hyper-IgD Syndrome

- Skin eruption usually consists of erythematous macular eruption; biopsy may show vasculitic lesions
- Attacks up to 1 wk of lymphadenopathy, abdominal pain, rash, splenomegaly
- Treatment with steroids, IVIG, cyclosporine, statins
- Anakinra works well; from 1 to 5 mg/Kg per day
- Canakinumab 4mg/Kg q4-6 wk
- Newer reports of TNF inhibitors successfully treating HIDS
TNF-Receptor Associated Periodic Syndrome

- Mutation in TNF-Receptor superfamily 1A (TNFRSF1A) gene which encodes for the TNF receptor
- Skin lesions consist of erythematous macules/papules which then expand and coalesce into serpiginous or annular patches and plaques associated with deep pain beneath these areas (not usually seen in CAPS)  
  — “painful erythemas”
- Upper extremities most commonly affected, migrates proximal to distally
TNF-Receptor Associated Periodic Syndrome

- Skin lesions may resolve with ecchymoses
- Attacks can last for weeks, with fever persisting for days to weeks
- Steroids can help during attacks
- TNF inhibitors (etanercept) may work however patients might lose efficacy over time
- IL-1 inhibitors (anakinra, canakinumab) more effective
- IL-6 inhibitor also reported effective (tocilizumab)
Juvenile Autoinflammatory Diseases

- Many described with more being reported frequently in the literature (often with just a few cases)
- Blau, PAPA, PASH, SAPHO, CANDLE, DIRA
- Blau syndrome – mutation in NOD2/CARD15
  - Granulomatous arthritis, uveitis, skin lesions: “Tapioca grain-like papules”
  - Tx with steroids, MTX, Cys, anakinra, TNF inhibitors
Juvenile Autoinflammatory Diseases

• PAPA/PASH
  – PAPA = PG, Acne, Pyogenic Arthritis
  – PASH = PG, Acne, HS (suppurative hidradenitis)
  – Mutation in PSTPIP1 for the former (possibly for the latter)
  – PAPA more periodic, a/w fever, flares of joint pain, starting in childhood and improving into adulthood
  – PASH starts with HS/acne in adolescence with PG coming later in life, less episodic/fevers
  – Treatment with TNF inhibitors (helps more with cutaneous manifestations) or IL-1 inhibitors (help more with joint pain)
  – Recalcitrant cases of PASH responded to infliximab + dapsone + cyclosporine
Juvenile Autoinflammatory Diseases

- SAPHO – Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis
  - Clinically on a spectrum with CRMO (Chronic Recurrent Multifocal Osteomyelitis)
  - May present with bone pain, worse at night, associated with fevers
  - No specific cause identified
  - Often coincides with other inflammatory skin diseases (Psoriasis/Palmoplantar Pustulosis, Sweet’s Syndrome, Vasculitis) or IBD
  - Treat with acitretin/isotretinoin, biologics, DMARD’s
Juvenile Autoinflammatory Diseases

• **Deficiency of the IL-1 Receptor Antagonist (DIRA)**
  – Mutation in IL1RN (AR)
  – Neonatal onset; osteomyelitis; pustular eruptions; treat with anakinra

• **Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE)**
  – Annular purpuric plaques, periorbital edema, partial lipodystrophy; typical facies
  – Mutation in PSMB8, involved in proteasome formation
  – Aberrant IFN signaling
    • Possible benefit of IFN inhibition

Summary: Monogenic Systemic Autoinflammatory Diseases

- Numerous autoinflammatory diseases
  - Multiple types and variations
- Treatments with IL-1 inhibitors tend to be effective as steroid-sparing agents
- Colchicine only consistently effective against FMF
- Genetic testing important to establish diagnosis
- Early treatment may prevent later sequelae such as amyloidosis
Outline

• What is autoinflammation?
• Classical/Monogenic Autoinflammatory Diseases
• Common Dermatologic Conditions featuring Autoinflammation
• Case Discussions
More common conditions featuring autoinflammation

- Numerous conditions also feature autoinflammation as a major cause of disease pathogenesis
- HS, PG, Psoriasis, Acne
Hidradenitis Suppurativa

- Recent studies show increase in IL-1β and IL-17 in lesional skin of HS
- Lesional DAMPs (S100A8/A9) are upregulated and the NLRP3 inflammasome is activated
- Early lesions show increased IL-17+ cells which in turn promotes release of IL-1β from keratinocytes
Biologics in HS

- Widespread evidence of good treatment results with both infliximab and adalimumab (now FDA-approved to treat HS)
- No such evidence for etanercept
  - Randomized double-blind trial showed no difference from control
- Newer reports and studies with ustekinumab
- 12 patients completed protocol, half achieved HS Clinical Response 50 (corollary to PASI-50)
Hidradenitis Suppurativa

Acta Derm Venereol 2012; 92: 320-335

LETTERS TO THE EDITOR

Management of Recalcitrant Hidradenitis Suppurativa with Ustekinumab

Victoria R. Sharou¹, Miki Shirakawa Garcia², Sepideh Bagheri², Heidi Goodarzi¹, Clara Yang¹, Yoko Uno³ and Emmanuel Maverakis¹*
Anakinra and HS

- Anakinra may be a treatment option in recalcitrant HS
- Successful treatment in a patient who failed oral antibiotics, azathioprine, cyclosporine, adalimumab, and infliximab

Apremilast and HS

• Two small trials: one randomized controlled trial from the Netherlands and one open-label trial from Miami
• Both showed benefit in using Apremilast
Apremilast and HS

- Open-label trial with 20 patients
- Mild-moderate HS
- Sartorius score, PGA, VAS pain, DLQI scores all significantly better
Apremilast and HS

- RCT with 20 patients with moderate HS
- Almost all white race, mostly women, most active smokers, previous tx with biologic in 27-40%

Fig 2. Percentage of patients in both treatment groups reaching the Hidradenitis Suppurativa Clinical Response (HiSCR) relative to baseline during the treatment period. Fisher’s exact test was performed at week 4 ($P = .033$) and at week 16 ($P = .055$). †Last observation carried forward for 1 HiSCR nonachiever as a result of dropping out. ‡Last observation carried forward for 1 HiSCR achiever as a result of dropping out.
Apremilast and HS

Fig 3. Example of a patient in the apremilast treatment group: baseline (left), at week 4 (early response) (middle), and at week 16 (end of study) (right). Arrows indicate index lesions (ie, inflammatory nodules that were larger than 10 mm in diameter and painful by palpation at baseline. Note that all the deep-seated lesions have resolved. Erythematous lesions seen at week 16 are scars and superficial folliculitis.
Pyoderma Gangrenosum

• IL-1β recently shown to be elevated in lesional skin
  – In the context of normal levels of TNF-α and IFN-γ

• Numerous autoinflammatory syndromes feature PG (PAPA, PASH, SAPHO – which can be a/w PG as well)

• Unclear etiology – could be that a persistent activation of inflammatory cascade (DAMP/PAMP, i.e. autoinflammation) may lead to the prolonged and unproductive inflammation in PG
## Pyoderma Gangrenosum

<table>
<thead>
<tr>
<th>Systemics</th>
<th>Local</th>
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<tbody>
<tr>
<td>Corticosteroids (60-80mg daily)</td>
<td>Topicals (steroids, cyclosporine, tacrolimus)</td>
</tr>
<tr>
<td>Immunosuppressants (MTX, cyclophosphamide, immunoglobulin, cyclosporine, colchicine)</td>
<td>Wet compresses</td>
</tr>
<tr>
<td>Antimicrobials (dapsone, clofazimine, minocycline)</td>
<td>Hydrophilic occlusive dressing</td>
</tr>
<tr>
<td>Biologics (infliximab, other TNF-α inhibitors)</td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>IVIG</td>
<td>Skin graft/flap</td>
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<tr>
<td>Thalidomide</td>
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IL-1 Inhibitors ????
Canakinumab in adults with steroid-refractory pyoderma gangrenosum

A.G.A. Kolios,1,2 I.-T. Maul,3 B. Meier,4 K. Kerl,1 C. Traidl-Hoffmann,5 M. Herti,6 D. Zillikens,5 M. Röcken,6 J. Ring,3 A. Facchiano,7 C. Mondino,8 N. Yawalkar,9 E. Contassot,1 A.A. Navarini1 and L.E. French1

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8Department of Dermatology, Bern University Hospital, Bern, Switzerland

Linked Comment: Costanzo, Br J Dermatol 2015; 173: 1174

What does this study add?

- The proinflammatory cytokine interleukin (IL)-1β is abundant in its active form in human pyoderma gangrenosum skin lesions.
- Blockade of IL-1β with the monoclonal antibody canakinumab can improve steroid-resistant pyoderma gangrenosum.
- This provides novel evidence that IL-1β plays a role in the pathogenesis of pyoderma gangrenosum.
Canakinumab for PG

• Dosed once, with optional doses at week 2 and week 8 depending on response
  – All patients received at least 2 doses
• 3/5 complete clearance, 1 partial response
• Previous treatments included steroids in all, and cyclosporine, azathioprine, cyclophosphamide, dapsone, IVIG, infliximab
• Sfx fatigue in 1, worsening of a lesion in 1
Canakinumab for PG

- Canakinumab dosed 150mg once monthly for 3 months in a patient with PG refractory to systemic steroids, cyclosporine, infliximab, and adalimumab

Traditional Biologics for PG

• Many case reports of successful treatment with infliximab and one randomized, double-blind, placebo-controlled trial
  – Several reports in populations with IBD
Biologics in PG

• Etanercept and adalimumab – results are more mixed
  – Case reports of success with either
  – Case reports of failure with both
  – One report of failure with etanercept but successful treatment upon switching to adalimumab

• Rituximab weekly shown to have benefit in a particularly recalcitrant case on the face

• Apremilast used in one reported case
Biologics in PG

• One study found increased IL-23 expression in PG and successful treatment with ustekinumab

Ustekinumab for PG

Biologics in PG

• Need a balanced approach considering risk of infection (and immunosuppression) and area/severity of disease
  – Should take into account underlying conditions (such as IBD) as well
  – Relapse is common, loss of effect is common
  – Keep in mind that ustekinumab has a slower onset of action than infliximab, systemic steroids, or cyclosporine
  – IL-1 inhibitors may represent a good therapeutic option in challenging cases
Autoinflammation in Psoriasis

- Increased levels of Caspase-1 in psoriasis lesional skin
- Polymorphisms of NLRP1/3 and CARD8 associated with susceptibility towards psoriasis
  - CARDs are Caspase Recruitment Domains
Autoinflammation in Psoriasis

- Mutations in CARD14 recently shown to be involved in the pathogenesis of psoriasis in multiple studies
  - Familial and sporadic
  - Found to be the locus for PSOR2
- IL-1 inhibitors not consistently effective in psoriasis
- May be better for pustular psoriasis
IL-1β Drives Inflammatory Responses to Propionibacterium acnes In Vitro and In Vivo

Magdalena Kistowska1,4, Samuel Gehrke1,4, Dragana Jankovic1, Katrin Kerl1, Antonia Fettelschoss1, Laurence Feldmeyer1, Gabriele Fenini1, Antonios Kolios1, Alexander Navarini1, Ruta Gancevicienė2, Jürgen Schauber3, Emmanuel Contassot1,5 and Lars E. French1,5

Acne vulgaris is potentially a severe skin disease associated with colonization of the pilo-sebaceous unit by the commensal bacterium Propionibacterium acnes and inflammation. P. acnes is considered to contribute to inflammation in acne, but the pathways involved are unclear. Here we reveal a mechanism that regulates inflammatory responses to P. acnes. We show that IL-1β mRNA and the active processed form of IL-1β are abundant in inflammatory acne lesions. Moreover, we identify P. acnes as a trigger of monocyte–macrophage NLRP3-inflammasome activation, IL-1β processing and secretion that is dependent on phagocytosis, lysosomal destabilization, reactive oxygen species, and cellular K+ efflux. In mice, inflammation induced by P. acnes is critically dependent on IL-1β and the NLRP3 inflammasome of myeloid cells. These findings show that the commensal P. acnes—by activating the inflammasome—can trigger an innate immune response in the skin, thus establishing the NLRP3-inflammasome and IL-1β as possible therapeutic targets in acne.

Autoinflammation in Acne

New Insights into Acne Pathogenesis: 
*Propionibacterium Acnes* Activates the Inflammasome

Emmanuel Contassot¹ and Lars E. French¹

The precise contribution of the commensal bacterium *Propionibacterium acnes* (*P. acnes*) in the inflammatory response associated with acne vulgaris remains controversial. In this issue Qin et al. show that *P. acnes* induces robust IL-1β secretion in monocyctic cells by triggering the activation of the NLRP3 inflammasome. In *vivo*, the encounter of *P. acnes* and macrophages in the peri-follicular dermis could locally result in the release of substantial amounts of IL-1β and therefore exacerbate inflammation. Such findings suggest that molecules targeting IL-1β and/or the NLRP3 inflammasome may constitute new treatment possibilities for acne vulgaris.

Autoinflammation in Dermatology

• HS, PG, and other neutrophilic dermatoses (including Sweet’s Syndrome) clearly linked to autoinflammation
• Emerging evidence that acne is linked to autoinflammation
• Psoriasis also characterized by some degree of autoinflammation
• Other entities reported to feature autoinflammation include Schnitzler’s Syndrome, Behçet’s Disease, generalized vitiligo, SLE, systemic sclerosis, acne, rosacea, and atopic dermatitis
Suggested References

• Fenini G, Contassot E, French LE. Potential of IL-1, IL-18, and Inflammasome Inhibition for the Treatment of Inflammatory Skin Diseases. Front Pharmacol. 2017; 8: 278.