The immune system fights pathogens using innate and adaptive immune mechanisms. The innate immune system is comprised of cellular receptors, called PRRs, that detect PAMPs present on invading pathogens, including viruses [1]. PRRs include sensors, such as TLRs, NLRs, RLRs, and ALRs, to name just a few. The initial innate immune response produces type I and type III IFNs, in addition to proinflammatory cytokines and chemokines that function to recruit immune cells to the site of viral infection. Recruited NK cells, macrophages, and dendritic cells help control the spread of the virus and also initiate the adaptive immune responses to the virus. PRRs are also able to sense endogenous danger-associated molecular patterns, including ATP, monosodium urate, and calcium pyrophosphate dehydrate, which can be biomarkers of trauma and tissue damage [2].

NLRs are cytosolic PRRs that have been linked to autoimmune disease, metabolic disorders, and cancer, in addition to antiviral responses [3]. NLRs contain an N-terminal effector, which is typically a CARD or a PYD [4]. All NLRs also have an NBD and a LRR domain. Many NLRs form an integral part of a large protein complex, called the inflammasome. Activation of inflammasomes results in the induction and secretion of IL-1β and IL-18. Inflammasomes are most often comprised of an NLR, a caspase-1, and ASC, although other inflammasomes comprised of ALR and RLR family members also exist. Several NLR family members have been demonstrated to form inflammasomes, including nucleotide-binding domain and leucine-rich repeat, pyrin domain containing 1 (NLRP1), nucleotide-binding domain and leucine-rich repeat, CARD domain containing 4 (NLRC4) and nucleotide-binding domain and leucine-rich repeat, pyrin domain containing 3 (NLRP3).

The NLRP3 protein is comprised of an N-terminal PYD, a central NBD region, and a C-terminal LRR domain. Although it lacks a CARD, by interacting with ASC via its PYD, NLRP3 can recruit pro-caspase-1 to form the inflammasome complex [5] (Fig. 1A). Activation of the NLRP3 inflammasome by viral infection results in the activation of caspase-1 from procaspase-1, which in turn, results in the caspase-1-dependent cleavage of pro-IL-1β and pro-IL-18 to active IL-1β and IL-18 (Fig. 1A).

NLRP3 can be activated upon RNA virus infection, such as infection with influenza A, Sendai virus, respiratory syncytial virus, vesicular stomatitis virus, measles virus, HIV, and hepatitis C virus [6]. NLRP3 is also activated in response to DNA viruses, such as modified vaccinia ankara, adenovirus, varicella-zoster virus, HSV, and Kaposi’s sarcoma-associated herpesvirus [6-9].

HSV-1 and -2 are members of the herpesviridae family. Infection with these viruses is associated with recurrent sores affecting the skin, eyes, mouth, and genitals, as well as more serious conditions, such as herpes encephalitis and meningitis. HSV-1 infection can lead to a condition called herpetic SK, which is a potentially blinding disease caused by HSV-1 corneal infection [10]. HSV-1-induced SK is driven by inflammation that is often accompanied by angiogenesis and neovascularization. Destruction of the cornea by both viral replication and immune-mediated damage has been implicated in necrotizing SK, whereas non-necrotizing SK pathology is primarily driven by the host immune response [10].

In this issue of JLB, Gimenez et al. [11] report that NLRP3−/− mice display an early onset and more severe HSV-1-mediated SK than WT mice. SK was visible 3 d earlier in the HSV-1-infected NLRP3−/− mice compared with WT mice. Surprisingly, the NLRP3−/− mice displayed increased IL-1β cytokine and increased neutrophil and T cell infiltration into the corneas. In particular, IL-1β levels, but not IL-18, were increased at all time points postinfection of the corneas of NLRP3−/− mice compared with WT mice. However, caspase-1 activity was similar in both groups. In addition to IL-1β, other cytokines, including IL-6, IL-12, IL-10, MIP2, and TNF-α, were all increased in NLRP3−/− mice. As noted above, SK is associated with angiogenesis and neovascularization, and Gimenez et al. [11] also described increased angiogenesis and neovascularization in NLRP3−/− mice compared with WT mice.

Abbreviations: ALR = absent in melanoma 2-like receptor, ASC = apoptotic-associated speck-like protein containing a caspase-activation and recruitment domain, CARD = caspase-activation and recruitment domain, LRR = leucine-rich repeat, NBD = nucleotide-binding domain, NLR = nucleotide-binding domain and leucine-rich repeat, NLRP = nucleotide-binding domain and leucine-rich repeat protein, NLRP3−/− = nucleotide-binding domain and leucine-rich repeat protein, NLRP3−/− knock out, NSP = neutrophil serine protease, PAMP = pathogen-associated molecular pattern, PRR = pattern recognition receptor, PYD = pyrin domain, RL = retinoic acid-like receptor, SK = stromal keratitis, WT = wild-type
expression of the angiogenic factor, vascular endothelial growth factor, in the corneas of the HSV-1-infected NLRP3−/− mice compared with WT mice. Viral titers were slightly higher in the NLRP3−/− mice, but both groups appeared to clear the virus by 7 d postinfection, suggesting that increased viral replication was not responsible for the early onset of SK in the NLRP3−/− mice.

Furthermore, neutrophils, as well as CD4+ and CD4+ Th1+ cell infiltration into the corneas of HSV-1-infected NLRP3−/− mice, were significantly higher compared with WT mice, implying that SK in the NLRP5−/− mice was related to increased immune cell infiltrates. Moreover, the increased CD4+ T cell infiltrate in the corneas of the HSV-1-infected NLRP3−/− mice suggests that mice lacking NLRP3 develop a greater adaptive immune response to HSV-1 infection compared with WT mice. This is in contrast to a parasitic infection model, where NLRP3−/− mice develop a down-regulated Th1, Th2, and Th17 adaptive immune response to helminth infection [12].

NSPs, including cathepsin G, neutrophil elastase, and PR3, are enzymes that modulate inflammation. NSPs can cleave pro-IL-1β and pro-IL-18 into active IL-1β and IL-18 in a caspase-1-independent fashion (Fig. 1B) [13]. The authors found that 2 of these NSPs, PR3 and cathepsin G, were increased at the gene-expression level in HSV-1-infected NLRP3−/− mice compared with WT, suggesting that the increased IL-1β expression in the corneas is likely mediated by NSP-dependent cleavage of pro-IL-1β rather than NLRP3. To prove this, the authors injected NLRP3−/− mice with either anti-Ly6G to deplete neutrophils or isotype control antibody. The mice injected with anti-Ly6 antibody did not display early onset of SK or increased IL-1β expression compared with the NLRP3−/− mice injected with isotype control antibody. This suggests that the increased IL-1β and early onset of SK in the HSV-1-infected NLRP3−/− mice are neutrophil dependent.

There is also a small possibility that the IL-1β production seen in the NLRP3−/− mice could be generated by a different non-NLRP3 inflammasome (e.g., NLRP1 or absent in melanoma 2) that is triggered when NLRP3 is not operational in the cornea. This could be investigated using caspase 1/11-deficient animals.

The fact that IL-1β levels were increased at all time points postinfection in the corneas of HSV-1-infected NLRP3−/− mice also suggests a novel role for NLRP3 in playing an immunomodulatory role in the development of HSV-1-induced SK through an as-yet unknown mechanism and that the presence of NLRP3 in the cornea of HSV-1-infected mice reduces inflammation and severity of the disease. Interestingly, Madouri et al. [14] recently reported that in an allergic lung inflammation model, the NLRP3 inflammasome complex modulates IL-33 levels, as well as Th2 cytokine and chemokine levels. In their house dust mite-induced lung inflammation model, the NLRP3−/− mice displayed increased Th2 cytokine and chemokine levels.

The effects reported by Gimenez et al. [11] could also represent an inflammasome-independent role for NLRP3 in the cornea, as other reports have...
alluded to inflammasome-independent functions of NLRP3, such as its ability to act as a transcription factor in Th2 differentiation and induce transcription of a number of anti-inflammatory genes [15].

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REFERENCES


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