of apoptosis that would promote cytokine release by dying inflammasome-competent cells to promote tissue injury-mediated inflammation, or whether the release of oxidized mitochondrial DNA and NLRP3 activation can occur in the absence of apoptosis. Although the mitochondria is emerging as a key organelle that senses cellular insults to promote inflammatory responses, the role of potassium efflux and the mechanisms that drive mitochondrial ROS production and control the release of mitochondrial DNA are still unknown. Finally, it remains to be determined whether release of mitochondrial DNA into the circulation upon tissue injury (Zhang et al., 2010) could contribute to inflammasome activation by recruited phagocytes, thereby contributing to inflammatory responses. Given the important role of the NLRP3 inflammasome in various human pathologies, the answer to these questions will probably provide better overall understanding of the mechanisms that translate cellular stress into an inflammatory reaction. In Choderlos de Laclos’s novel Dangerous Liaisons, relationships are used as weapons in a game of power and revenge that eventually takes a tragic course. By analogy, when mitochondrial DNA encounters and interacts with NLRP3, it initiates a complex cascade of events that start with inflammasome formation and promotes self-defenses or, in a dramatic twist worthy of Laclos, backfires into a dangerous and harmful inflammation.

**REFERENCES**


occur within minutes to a few hours after infection, these studies establish B cells as key regulators of early innate immunity to CMV infection, independent of antibody production.

In the case of vesicular stomatitis virus, a neurotropic member of the Rhabdoviridae family that also includes rabies virus, protection during primary and secondary infections has long been ascribed to early neutralizing natural antibodies followed by induction of VSV-glycoprotein (G)-specific IgM and subsequent class switching leading to IgG production. After intravenous infection, marginal zone macrophages (MMM) in the spleen capture the virus (Ciavarra et al., 2005). This initial line of cellular defense is vital to protection as indicated by the fact that depletion of splenic macrophages results in virus dissemination and lethality (Honke et al., 2012). B cell-derived LTαβ is also required for splenic CD169⁺ macrophage organization (Mebius et al., 2004), further establishing an antibody-independent role for B cells in antiviral immunity.

More recently, the subcapsular sinus (SCS) macrophages located in lymph nodes (LN) have been shown to be essential for protection against subcutaneous VSV infection. Deletion of the SCS macrophages in the popliteal LN via injection of cedronate-loaded liposomes results in loss of early protection against footpad infection with VSV (Iannaccone et al., 2010). These CD169⁺ macrophages are the LN counterparts to the splenic CD169⁺ macrophages. Thus, this macrophage subset represents a critical initial barrier to viral and probably bacterial infection either through hematogenous delivery or through introduction into the skin. But do these cells directly destroy virus or are cooperative efforts needed from other innate and adaptive immune components? In the spleen, CD169⁺ macrophages actually appear to promote viral replication (Honke et al., 2012). Splenic CD169⁺ macrophages selectively express the ubiquitin-specific protease Usp18, which inhibits interferon αβ receptor (IFNAR) signaling. This inhibition specifically in the CD169⁺ macrophages provides a more hospitable environment for VSV replication. In IFNAR-deficient mice, all other splenic macrophage subsets allow VSV replication whereas in normal mice, only the CD169⁺ macrophages support virus growth. Moreover, deletion of Usp18 results in lower splenic virus titers but rapid dissemination of the virus to the central nervous system. Honke et al. (2012) suggest that uncontrolled virus spread is caused by limited neutralizing antibody production resulting from poor initial virus replication in CD169⁺ macrophages, which is necessary to promote adaptive immunity.

Now, in this issue of Immunity, Moseman et al. (2012) further dissect the role of B cells, LT, type I interferons, and CD169⁺ macrophages in the draining LN after subcutaneous VSV infection. First, they show that B cells but not antibodies are essential for protection against subcutaneous VSV infection. Surprisingly, although mice lacking immunoglobulin but harboring B cells die from intravenous VSV infection, such mice are protected from subcutaneous infection. In contrast, mice lacking B cells succumbed to subcutaneous VSV infection through virus entry into the central nervous system via peripheral nerves. Thus, infection via the skin, perhaps mimicking virus transmission by an insect bite, reveals a clear role for B cells in providing protection against a highly cytopathic virus, without a requirement for antibody. Next, the authors demonstrate that B cells but again not antibody are required for macrophage-dependent type I interferon production. In this model, type I interferon is thought to confer protection via its action on intranodal nerves to inhibit viral replication. The precise mechanisms by which type I interferon affords this protection remain to be defined. Moreover, in the absence of B cells, LN macrophages did not allow virus replication. Similar to studies in the spleen with CD169⁺ macrophages, previous work shows that VSV preferentially replicates in SCS macrophages, rather than their medullary counterparts. Indeed, in B cell-replete but immunoglobulin-deficient mice, this is precisely what is observed. Taken together, the implication is that B cells, but not antibody, are indispensable for promoting replication of VSV in SCS macrophages leading to IFN production and protective immunity.

These intriguing data raise a number of important questions especially when considered in light of earlier work indicating that splenic CD169⁺ macrophages allow VSV replication through mechanisms that inhibit IFNAR signaling (Figure 1). Thus, although CD169⁺ macrophages in both spleen and LN preferentially allow VSV replication, whether Usp18 mediates downmodulation of IFNAR signaling in LN SCS macrophages needs to be examined to complete the circuit. In addition, the possibility that LTαβ2 regulates Usp18 gene expression and thus virus replication in CD169⁺

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**Figure 1.** After Subcutaneous Infection with VSV, the Virus Is Initially Captured by CD169⁺ Macrophages in the Draining Lymph Node

The release of LTαβ2 by B cells allows the CD169⁺ macrophages to tolerate increased replication of VSV, possibly by inducing Usp18. This increased VSV replication induces the release of type I IFN by the CD169⁺ macrophages, which in turn prevents the virus from accessing the peripheral nerves and traveling to the CNS by an undefined mechanism. In the absence of B cells there is a lack of LTαβ2 and without this, the virus fails to replicate in the CD169⁺ macrophages and type I IFN secretion is severely diminished. The lack of type I IFN allows the virus to access the peripheral nerves, leading to dissemination of VSV to the CNS.
Proteases are important components of many allergens (Reed and Kita, 2004). For example, papain is a well-known protease that causes occupational asthma, and native papain but not heat-inactivated papain induces lung inflammation in mice. House dust mites also produce a well-known allergen whose allergy-inducing ability is largely dependent on its protease activity. In addition, invasion of host tissues by helminthes occurs via high protease activities and helmynth infection induces rapid activation of Th2 cell-type inflammatory responses. Proteases are thought to disrupt mucosal integrity by digesting cell adhesion molecules and further act on protease-activated receptors to activate airway epithelial cells. The cytokines thymic stroma lymphopoietin (TSLP), IL-25, and IL-33 derived from epithelial cells activated in this way induce rapid Th2 cell-type inflammation. Polymorphisms of IL-33 and its receptor ST2 are associated with allergic diseases, including asthma in humans, demonstrating the importance of epithelial cell-derived cytokines for the onset of Th2 cell-type immune responses.

Papain causes asthma-like symptoms associated with Th2 cell-type reactions such as eosinophilia and goblet cell hyperplasia in Rag-deficient mice. These