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B Cells, Not Just for Antibody Anymore: The Latest Regulators of Innate Immunity

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B cells, not just for antibody anymore: the latest regulators of innate immunity

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Abstract

Antibody production by B cells is believed to be crucial for protection against virus infection. In this issue of *Immunity*, Moseman et al illustrate an antibody-independent role for B cells in macrophage activation that prevents virus dissemination after subcutaneous infection.

The production of neutralizing antibodies by B cells to protect against virus and bacteria infections is a hallmark of immunity and one of the primary goals of vaccination. However, recent reports including a paper in this issue of Immunity have revealed an additional previously unappreciated critical function of B cells, as regulators of innate immunity to virus infection. For some viruses, the very earliest events after infection that lead to virus clearance are not well-defined. Wheras pre-existing 'natural' antibody may in some cases provide some degree of initial protection, the innate immune system including macrophages, NK cells and neutrophils are believed to be central to limiting initial pathogen spread while the adaptive immune response ramps up. Moreover, cytokines, in particular type I interferons are key to early protection against virus infection. Thus, in the absence of type I interferon receptor signaling, mice are exquisitely sensitive to infection with a number of viruses including vesicular stomatitis virus (VSV) and mouse cytomegalovirus (MCMV) (Garcia-Sastre and Biron, 2006), among others. While plasmacytoid dendritic cells (pDC) triggered through pattern recognition receptors, particularly TLRs, produce copious amounts of IFNα in response to virus infection, many other cell types also have the ability to produce and respond to type I interferons. Nevertheless, the precise mechanisms by which IFN is induced, especially with regard to the initial cell types that encounter and potentially harbor virus replication, are unclear.

In addition to TLR mediated IFNα induction, TLR independent pathways for driving IFNα production have also been described(Delale et al., 2005). For example, the IFNβ response after CMV infection has been shown to be regulated by lymphotoxin (LT) produced by hematopoietic cells. In the absence of LTαβ-LTβR signaling mice are highly susceptible to intravenous MCMV infection, due in large part to poor induction of type I interferons (Benedict et al., 2001). Remarkably, the relevant source of LTβ is the splenic B cell(Schneider et al., 2008). Bone marrow chimera reconstitution studies further revealed that the responding cell type is a stromal cell of non-hematopoietic origin. Thus, B cell derived LTβ acting on a potentially infected stromal cell drives IFNβ production that leads to early protection against infection. Additionally, this pathway of IFN production is

independent of TLR signaling. Considering that these events 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 Rhabdoviradae 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 metallophilic macrophages (MMM) in the spleen capture the virus(Ciavarra et al., 2005). This initial line of cellular defense is vital to protection since 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 clodronate loaded liposomes results in loss of early protection against footpad infection with VSV(Iannacone 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 virus and likely 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 (Figure 1). 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 while 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 (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 (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. 1st, they show that B cells but not antibodies are essential for protection against subcutaneous VSV infection. Surprisingly, whereas mice lacking immunoglobulin but harboring B cells die from intravenous VSV infection, the mice are protected from the 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 the 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 LTα1β2 regulates Usp18 gene expression and thus virus replication in CD169+ macrophages warrants analysis. Moseman et al go on to show that B cell derived LTα1β2 is critical for inducing the protective phenotype of the SCS macrophages. When B cells are the only cell type that cannot produce LTα1β2, macrophages are able to capture lymph-borne viral particles but the virus does not replicate and type I IFN secretion is compromised. An outstanding question is what factors allow virus replication to proceed- can the effects all be attributed to the inability of SCS macrophages to respond to autocrine as well as perhaps paracrine type I interferon? The study by Moseman et al along with other available data suggest the fascinating possibility that the immune system has evolved to allow a certain proscribed degree of microbial growth to “prime the pump” in order to promote both rapid innate immunity and provide sufficient antigenic material and inflammatory signals to promote adaptive immunity to prevent entry of pathogens upon secondary encounter. In fact, recent findings indicate that a specialized subset of dendritic cells are permissive for the initial replication of *Listeria monocytogenes* that leads to the induction of a rapid innate response leading to the generation of a protective T cell response(Edelson et al., 2011). Additional research will be needed to determine whether events such as these are more commonplace than previously appreciated.

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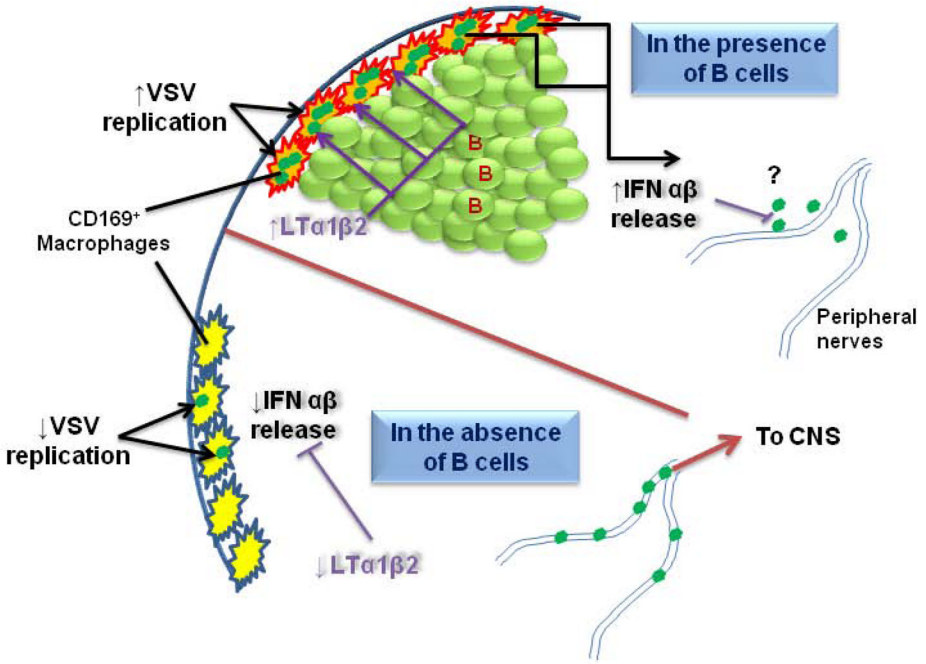

Figure 1.

Following subcutaneous infection with VSV, the virus is initially captured by CD169+ macrophages in the draining lymph node. The release of LTα1β2 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 IFNαβ by the CD169+ macrophages, which in turn prevents the virus from accessing the peripheral nerves and travelling to the CNS by an undefined mechanism. In the absence of B cells there is a lack of LTα1β2 and without this, the virus fails to replicate in the CD169+ macrophages, and IFNαβ secretion id severely diminished. The lack of IFNαβ allows the virus to access the peripheral nerves leading to dissemination of VSV to the CNS.