How Opportunistic Agents Benefit from Viral Infections: The Plasmacytoid Dendritic Cell Connection

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Plasmacytoid dendritic cells (pDCs) drive antiviral immunity through their rapid production of type I interferon (IFN-I). In this issue, Zuniga et al. (2008) report that both acute and persistent viral infections dramatically decrease pDC numbers and impair their capacity to produce IFN-I, leading to an enhanced susceptibility to opportunistic viruses.

Chronic viral infections signify the failure of the host’s immune system to eradicate the virus or to efficiently control its replication. It is well established that impairment of adaptive immunity specific to the virus, especially a functional paralysis of cytotoxic CD8 T lymphocytes driven in part by high interleukin-10 (IL-10) production, is involved (Brooks et al., 2006). However, whether innate antiviral immune defenses may be compromised during chronic infections with HIV-I or other viruses, and to which extent this could contribute to enhanced susceptibility to opportunistic agents during the asymptomatic phase of the infection, is not well documented. In the current issue of Cell Host & Microbe, Zuniga et al., 2008 report a well-rounded and captivating study to address this question.

Innate immunity against viral infections is characterized by rapid and robust type I interferon (IFN-I) production. IFN-I displays a wide range of biological properties crucial for the global orchestration of antiviral immunity (Garcia-Sastre and Biron, 2006). IFN-I exerts direct, potent, antiviral effects. It also promotes the cytotoxic functions of innate NK cells and adaptive CD8 T lymphocytes, either directly or through the licensing of conventional dendritic cells. Several in vitro studies have described that many viruses can impair IFN-I production by infected cells. Infections with certain viruses, including HIV-I, have even been shown to generally compromise the ability of the host’s leukocytes to produce IFN-I upon in vitro restimulation with other viruses or stimuli. The present work provides proof that a drastic decrease of IFN-I production upon secondary viral infections does occur in vivo, under physiological conditions of a primary infection with lymphocytic choriomeningitis virus (LCMV) or murine cytomegalovirus (MCMV) in their natural host, the mouse. This impairment of IFN-I responses is observed against a variety of unrelated pathogens, including other viruses. This phenomenon can lead to life-threatening conditions as in the case of infections with human immunodeficiency virus type-I (HIV-I), which induces a progressive and general weakening of adaptive CD4 T cell-dependent immune defenses against a variety of infections with human immunodeficiency virus type-I (HIV-I), which induces a progressive and general weakening of adaptive CD4 T cell-dependent immune defenses against a variety of unrelated pathogens, including other viruses.

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of secondary, heterologous, viral-type challenges, including MCMV, LCMV, VSV, or synthetic ligands for Toll-like receptor (TLR) -3, -7, and -9 which are innate immune recognition receptors that sense viral nucleotides. These results are consistent with those recently published independently by another team (Alsharifi et al., 2006). However, the study by Zuniga et al. (2008) presents a number of other striking observations and brings definitive advances in deciphering the underlying mechanisms.

Zuniga and coworkers demonstrate that the paralysis of innate antiviral immune defenses induced by a primary viral challenge is transient in the case of an acute infection but long lasting in the case of a chronic infection (Figure 1A). Moreover, they demonstrate a striking correlation between this paralysis and the development of quantitative and qualitative defects in plasmacytoid dendritic cells (pDCs). pDCs are believed to be key players in antiviral defense due to their unique capacity to rapidly detect viral particles or infected cells and respond by immediately producing high levels of all subtypes of IFN-I, without the requirement for viral replication within the pDCs themselves. pDC sensing of viral infection occurs mainly through the engagement of TLR-7 or -9 by nucleic acids, in specialized endosomes, which leads to the activation of interferon regulatory factor (IRF) -3 and -7, the major transcription factors driving IFN-I production (Gilliet et al., 2008). The numbers of pDCs and their ability to produce IFN-I are drastically reduced early after an acute viral infection and permanently during a chronic viral infection (Zuniga et al., 2008). In contrast, and remarkably, pDC production of other innate cytokines or chemokines does not seem significantly affected. The identification of pDC as a major target cell type for the general immunosuppression induced by viral infection, and the observation of differential modulation of distinct pDC functions by viral infections paves the way for deciphering the underlying molecular mechanisms.

The authors have made multiple attempts at identifying the mechanisms dampening pDC IFN-I production to secondary heterologous challenges during a primary viral infection. They have examined pathways known to compromise adaptive immunity in the same model, for example the role of IL-10 (Brooks et al., 2006), which can also inhibit pDC IFN-I production in vitro (Contractor et al., 2007). They have also investigated the involvement of T lymphocytes as a major source of TGF-β, another immunomodulatory cytokine known to impair pDC IFN-I production in vitro (Contractor et al., 2007) and to be produced during chronic LCMV infection. They also evaluated IFN-I itself, because it can terminate its own production through a negative feedback loop that involves the upregulation and activation of the TAM protein tyrosine kinases on pDCs and the downstream induction of the suppressors of cytokine signaling (SOCS)-1 and -3 (Rothlin et al., 2007). However, and
unexpectedly, none of these pathways seems to individually bear a significant contribution to the induction of pDC paralysis during viral infections. It is possible that the function of these pathways is largely redundant such that their combined inactivation would be required to restore pDC responsiveness. However, it is also possible that other, yet unexplored, mechanisms are involved.

Several critical steps are involved in the production of IFN-I by pDCs in response to viral challenges, which could be altered early after acute viral infections or permanently in the case of chronic viral infections (Figure 1B). pDCs need to engulf free viral particles or apoptotic bodies from infected cells and direct their trafficking to specialized IRF-7-associated endosomes, which are distinct from endosomes where IL-12 production is initiated in an IRF-5-dependant manner (Gilliet et al., 2008). Since only IFN-I but not IL-12 production by pDCs seems affected in the reported study, it is possible that the trafficking of endocytosed viral components toward IRF-7-associated endosomes is specifically altered after a primary viral infection. Another explanation could be an alteration of the expression or intracellular trafficking of the TLRs themselves, as reported in another study (Schroeder et al., 2005). The activity of components downstream of the TLRs, which are specifically involved in the induction of IFN-I as opposed to IL-12, could be altered—e.g., the availability or activation of IRF-3 or IRF-7. This may result from other inhibitory signals than those driven by the TAM tyrosine kinases, such as the pDC response to glucocorticoids. Indeed, glucocorticoids have been demonstrated to be induced during viral infection in response to the direct stimulation of the adrenal glands by IL-6 and to dampen the production of proinflammatory cytokines (Ruzek et al., 1999). Moreover, steroid hormones can dampen IFN-I production through the inhibition of IRF-3 and IRF-7 activation (O’Neill, 2008). It would therefore be very interesting to test the impact of adrenalectomy on pDC responses to secondary challenges during LCMV infection. However, as the authors underline, the mechanisms modulating pDC responses to secondary challenges during primary viral infections are likely to be highly complex and to involve different pathways that could be partly redundant.

Finally, the authors pinpoint a significant difference in the consequences of damping pDC IFN-I production during primary viral infections depending on the nature of the heterologous virus used for the secondary challenge. Indeed, although a drastic decrease in the systemic levels of IFN-I production is observed in response to all secondary viral infections, this leads to a significant impairment in the ability to control viral replication only in the case where MCMV is used as a challenging agent, and not for LCMV or VSV. This is likely to be relevant to the natural history of opportunistic infections, as severe complications due to uncontrolled reactivation of herpes viruses including human CMV, HHV8, or EBV are most commonly encountered in patients with advanced HIV-I infection. This may result from the impairment of both the direct antiviral activity of pDCs and their priming role for NK cell activation as demonstrated in the present study.

In summary, in this issue of Cell Host & Microbe, Zuniga and colleagues demonstrate that systemic production of IFN-I by pDCs in response to a secondary challenge is severely reduced after a primary viral infection in mice. This occurs significantly in the case of an acute infection but permanently during a chronic infection, and leads to enhanced susceptibility to opportunistic agents such as herpes viruses. The identification of the underlying mechanisms will be an interesting challenge to address in future studies in order to be able to design novel therapeutic strategies to fight opportunistic infections.

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REFERENCES


