In This Issue

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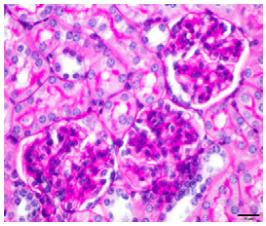
Caspase-8's Tolerance for Autoimmunity



Caspase-8 functions primarily to initiate apoptosis and necrosis; however, recent studies have suggested that this enzyme may have a number of cell death–independent functions. Global or T cell–specific deletion of caspase-8 in mice results in systemic autoimmunity, suggesting that this enzyme may play a role in tolerance. Cuda et al. (p. 5548) sought to determine the role of caspase-8 in dendritic cell (DC)–mediated tolerance and demonstrated that DC-specific deletion of caspase-8 ($Cre^{CD11c}Casp8^{fl/fl}$) in mice resulted in systemic lupus erythematosus–like disease and spontaneous early mortality relative to control mice. Deletion of the receptor-interacting serine-threonine kinase (RIPK)3 can reverse the caspase-8–deficient phenotype in mice; however, RIPK3 deficiency in $Cre^{CD11c}Casp8^{fl/fl}$ mice did not alter the effects of DC-specific caspase-8 ablation. $Cre^{CD11c}Casp8^{fl/fl}$ DCs showed enhanced proinflammatory cytokine production when stimulated with TLR4, 7, and 9 agonists and deletion of the TLR adaptor protein MyD88 reduced cytokine and anti-DNA Ab production and ameliorated kidney disease. $Cre^{CD11c}Casp8^{fl/fl}$ mice exhibited global immune cell dysregulation marked by increased $CD4^+$ T cells and hyperactivated conventional DCs, along with increased B cell Ab production. Together, these data suggest that caspase-8 maintains tolerance by regulating MyD88 signaling in DCs and that unregulated TLR signaling in DCs promotes autoimmunity.

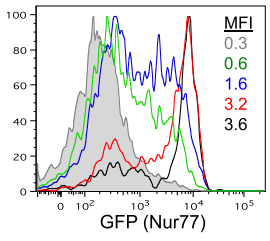
Damaging Protection

Much of what is known about polyomaviruses (PyV), dsDNA viruses that have pathogenic consequences in immunosuppressed hosts, comes from studies of SV40. The large T Ag (LT) of SV40, which promotes host cell transformation, is important for productive viral infection, and a better understanding of how it acts may allow for the development of effective treatments against PyV infection. SV40 LT induces IFN-stimulated genes (ISGs) in mouse embryonic fibroblasts, leading Forero et al. (p. 5933) to assess the ability of this protein to induce ISGs in human fibroblasts. LT expression in the absence of viral infection in human fibroblasts indeed resulted in ISG expression, which protected the cells against infection with a variety of viruses. ISG induction occurred through LT-mediated upregulation of IFN regulatory factor (IRF)1, which triggered IFN-β expression. Signaling through the IFNAR1, in turn, caused activation of IRF7 and IRF9 and subsequent ISG expression. The DNA damage response (DDR), which can be activated by PyV infection and is mediated by two kinases, ataxia-telangiectasia mutated (ATM) and ATM and Rad3-related (ATR), was found to be linked to LT-induced ISG expression. IRF1 upregulation and IFN-β expression required the kinase activity of ATR, but not ATM, and expression of an LT mutant unable to fully induce DDR impaired the induction of ISG and IFN-β expression. Taken together, these data indicate that innate antiviral responses can be activated in the absence of viral infection as a consequence of ATR-dependent DDR induction.

A Fas End to Immune Suppression

Immune suppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are significant impediments to successful antitumor immunotherapy. Previous work showed that treatment of a murine renal adenocarcinoma (Renca) with a combination of IL-2 and agonistic anti-CD40 Ab led to potent antitumor immunity and the loss of Tregs and MDSCs. Because both Tregs and MDSCs can express Fas, a death receptor that triggers apoptosis through caspase activation, Weiss et al. (p. 5821) sought to determine whether a Fas-mediated mechanism caused the loss of these two populations. Elimination of tumor-associated Tregs and MDSCs following IL-2/αCD40 treatment was abrogated when FasL was blocked, either by a neutralizing Ab or in MRL-Fas(lpr) mice, which are deficient in functional Fas. Following IL-2/αCD40 therapy, Tregs and MDSCs upregulated active caspase levels and Tregs decreased Bcl-2 expression when compared with control cells. To determine if the Fas-mediated loss of Tregs and MDSCs was in part responsible for successful immunotherapy, MRL-Fas(lpr) Tregs were adoptively transferred into Treg-depleted wild-type mice prior to Renca challenge, and similar experiments were performed with MDSCs in the 4T1 breast cancer model. The inability of Tregs (Renca model) and MDSCs (4T1 model) to undergo Fas-mediated apoptosis abrogated the efficacy of IL-2/αCD40 therapy, as tumor sizes were similar between mice receiving IL-2/αCD40 and vehicle control therapy. Taken together, these data identify a mechanism by which Fas-mediated apoptosis can alleviate tumor-associated immune suppression and enhance tumor immunotherapy.

Tracking TCR Dependence



Invariant NKT (iNKT) cells recognize glycolipid Ags derived from self or microbial sources in the context of the nonclassical MHC molecule CD1d via their invariant TCRs. These cells can also recognize infectious agents through an indirect process thought to involve TLR stimulation of APCs that results in the presentation of endogenous Ags by CD1d. To better understand

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