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Regulation of Immune Responses by Spontaneous and T cell-mediated Dendritic Cell Death

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Abstract

In response to antigen stimulations, cells in the immune system undergo dynamic activation, differentiation, expansion and turnover. Programmed cell death is important for maintaining homeostasis of different cell types in the immune system. Dendritic cells (DCs) are a heterogeneous population of antigen presenting cells that capture, process and present antigens to stimulate lymphocytes. DCs have also emerged as major regulators of both innate and adaptive immune responses. Conventional myeloid DCs are relatively short-lived compared to lymphocytes in lymphoid organs. Mitochondrion-dependent apoptosis governed by Bcl-2 family members plays a major role in regulating spontaneous DC turnover. Killing of DCs by antigen-specific T cells also provides a negative feedback mechanism to restrict the duration and the scope of immune responses. Defects in cell death in DCs lead to DC accumulation, resulting in overactivation of lymphocytes and the development of autoimmunity in mice. Programmed cell death in DCs may play essential roles in the regulation of the duration and magnitude of immune responses, and in the protection against autoimmunity and uncontrolled inflammation.

Introduction

DCs are the most efficient antigen presenting cells that represent a small population of cells in lymphoid and non-lymphoid organs and tissues. The homeostasis of DCs needs to be strictly regulated to maintain a balanced and functional immune system. It has been reported that disruption of programmed cell death in DCs leads to DC accumulation and systemic autoimmunity [1,2]. Furthermore, immunization with excessive activated DCs can trigger both systemic and tissue-specific autoimmune diseases in mice [3,4]. On the other hand, depletion of DCs by constitutive expression of diphtheria toxin in these cells leads to the onset of lethal inflammatory responses [5]. This suggests that maintenance of a proper number of DC is likely to have major impacts on multiple aspects of immune responses, including the scope of antigen-specific immune responses, inflammation and immune tolerance.

Differential turnover rates for different DC subsets *in vivo*

When DCs were first identified as a distinct cells type, they were found to undergo rapid turnover *in vivo* under steady state conditions [6,7]. Different subsets of DCs have been identified in various organs that display distinct phenotypes and functions [8-11]. These various DC population show different cell surface markers, *in vivo* localization and migration patterns, cytokine productions and other functional properties [8]. The main subtypes of DCs include the conventional DCs and plasmacytoid DCs (pDCs) [11]. Conventional DCs can be further divided into migratory DCs, such as Langerhans cells in epidermal tissues, interstitial DCs and lymphoid-tissue-resident DCs [8-12]. Resident DCs in lymphoid tissues constitute the majority of DCs in the thymus and spleen, and about half of DCs in the lymph node. Lymphoid tissue-resident conventional DCs include $CD8^+$, $CD4^+CD8^-$ and $CD4^-CD8^-$ conventional DCs. Lifespan and functions for residential DCs in different tissues are likely to be influenced by other cell types or soluble factors in their local microenvironment [10,12].

The lifespan of DCs *in vivo* has been determined by the rate of labeling with 5-bromodeoxyuridine (BrdU) [13-16]. Isolated DCs generally do not proliferate *in vitro* [14,16], BrdU-positive DCs therefore represents the DCs newly generated from precursors that have the proliferative potentials [17]. We and others have observed that conventional DCs in lymphoid organs are rapidly labeled by BrdU *in vivo* [14,16,18]. Nearly 50% of $CD11c^+CD11b^+$ DCs in the spleens are labeled by BrdU at 48 h, suggesting that these DCs have a half-life of approximately two days. Interestingly, $CD8^+$ DCs are labeled slightly faster than $CD8^-$ DCs [14,16]. Langerhans cells show a slower rate of BrdU labeling [16]. This suggests that Langerhans cells belong to a distinct lineage with a slower cell death rate. Different from conventional DCs, $CD11c^{low}PDCA\text{-}1^+$ pDCs display significantly slower rates of BrdU labeling *in vivo* with a half-life of eight to nine days [15,18]. Therefore, pDCs are long-lived cells similar to T cells *in vivo*. However, the functional significance for such differences among DC subsets remains to be determined.

Regulation of DC homeostasis

Several lines of evidence suggest that cytokines play important roles in regulating DC homeostasis. It has been reported that Fms-like tyrosine kinase receptor-3 ligand (Flt3-L) promotes both DC survival and differentiation of DC precursors into conventional DCs and pDCs [19-22]. Studies with either DC depletion or Treg ablation indicate that an Flt3-L-dependent feedback mechanism is involved in homeostatic control of DC numbers *in vivo* [17,23]. GM-CSF has been demonstrated to synergize with Flt3-L to maintain the numbers of conventional DCs *in vivo* [24,25]. We have found that withdrawal of GM-CSF leads to up-regulation of pro-apoptotic Bim in bone marrow-

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derived DCs and promoted cell death [26]. This suggests that GM-CSF can inhibit cell death in DCs by suppressing Bim expression. IL-10, on the other hand, has been shown to promote cell death in DCs by down-regulating anti-apoptotic molecules Bcl-2 and Bcl-xL [27]. Although TGF-β1 is known to be required for the development of Langerhans cells [28,29], it has also been shown to induce apoptosis in monocyte-derived DCs [30]. However, the molecular mechanism for TGF- β1-induced DC apoptosis has not been characterized.

Local microenvironment of lymphoid organs may also play an essential role in maintaining the lifespan of DCs. Based on BrdU labeling experiments, we estimate that 40-50% of conventional $CD11c^+CD11b^+$ DCs in the mouse spleen undergo cell death in 48h *in vivo* [18]. However, purified $CD11c^+CD11b^+$ DCs undergo faster cell death *in vitro* [18]. BrdU labeling studies show a relatively slow rate of self-renewal for pDCs *in vivo* with approximately 5% of BrdU labeling over 24 h [18]. Interestingly, nearly 90% of pDCs purified from the mouse spleen undergo cell death after 24 h of *in vitro* culture [18]. It is possible that cytokines or soluble factors secreted by other cell types in the spleen environment help to maintain the survival of DCs *in vivo* (Figure 1). Indeed, it is reported that thymic stromal lymphopoietin (TSLP) produced by non-hematopoietic cells such as fibroblasts and stromal cells can promote the survival of DCs *in vitro* [31]. It remains to be determined whether TSLP protects DC viability *in vivo*.

In addition, direct cell-cell contact between DCs and other cell types in the local microenvironment may also play an important role in the regulation of DC homeostasis. For example, $CD4^+Foxp3^+$ Treg cells may inhibit Flt3-L productions to suppress novel DC generation from their precursors [17,32]. Formation of the immunological synapses between DCs and antigen-specific T cells has been shown to inhibit DC apoptosis [33], while activated T cells can kill antigen loaded DCs during an immune response [34-36]. In addition, interaction with matrix in lymphoid tissues may help to sustain DC survival. Whether adhesion molecules and certain cell surface receptors may induce pro-survival signaling into DCs through interactions with other cell types or matrix remains to be determined.

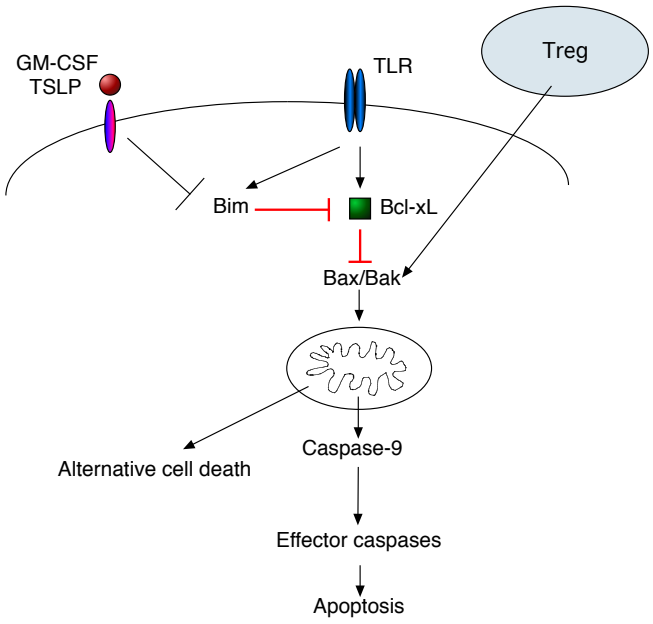

Figure 1: Regulation of mitochondrion-dependent dendritic cells death. Cytokines, such as GM-CSF, can inhibit cell death in DCs by suppressing the expression of Bim. Signaling through TLRs can simultaneously increase the expression of pro-apoptotic Bim and anti-apoptotic Bcl-xL [18]. However, DCs generally survive better after stimulation via TLRs, suggesting a dominant effect for the anti-apoptotic molecules [18]. Treg cells can induce cell death in DCs in a Bax- and Bak-dependent manner [84].

Fas-dependent apoptosis in DCs

Several studies have demonstrated that DCs are sensitive to apoptosis mediated through Fas [37-39]. However, other studies have also shown resistance to Fas-dependent apoptosis in DCs [40-42]. This discrepancy could be due to different sources of DCs or Fas agonists used in the assays. In autoimmune *lpr* mice, both lymphocytes and DCs undergo significant expansion [43], suggesting that Fas regulates apoptosis in both lymphocytes and DCs. We have examined the expression of signaling molecules involved in Fas-dependent apoptosis in DCs [1]. We observed no significant differences between DCs and T cells in terms of the expression of Fas, FADD, caspase-8 and FLIP that are important mediators or regulators of Fas-dependent apoptosis [1], indicating that the Fas signaling pathway is active in DCs.

It has been shown that activated T cells are capable of killing DCs [34,36,37]. We have found that both $CD4^+$ T cells and $CD8^+$ T cells are capable of killing DCs *in vitro* [1]. $Perforin^{-/-}$ T cells showed reduced DC killing when compared to wild type T cells, suggesting that perforin is involved in T cell-mediated killing of DCs [1,44]. Killing of DCs by $perforin^{-/-}$ T cells were completely suppressed in the presence of Fas-Fc, suggesting that Fas is the dominant death receptor employed in T cell-mediated killing of DCs in addition to perforin. These results suggest that T cells kill DCs through a Fas- and perforin-dependent mechanism (Figure 2).

To determine the *in vivo* functions of Fas-mediated apoptosis in DCs, we generated transgenic mice expressing the baculoviral p35, an inhibitor for caspase-8 and several downstream caspases, but not caspase-9, in DCs (DC-p35) [45]. DCs in DC-p35 transgenic mice display reduced Fas-dependent apoptosis. Both conventional DCs and pDCs are accumulated in DC-p35 mice. This supports a role for Fas-mediated apoptosis in regulating DC homeostasis. Consistent with our findings, DC-specific conditional knockout of Fas also leads to significant accumulation of DCs [2]. These data indicate that Fas-mediated apoptosis plays an important role in regulating DC homeostasis *in vivo*. Deficiency in perforin has been shown to exacerbate lymphoproliferation and autoimmunity in Fas-deficient *lpr* mice [46]. We have recently found that perforin and Fas could synergize to maintain DC homeostasis and control inflammation *in vivo* [47].

Bcl-2 family members in the regulation of programmed cell death in DCs

The Bcl-2 family proteins play an important role in regulating mitochondrion-dependent apoptosis [48,49]. Bcl-2 family members share one or more Bcl-2 homology (BH) domains and are divided into three subfamilies. The anti-apoptotic subfamily, the pro-apoptotic Bax- and Bak-like proteins and the pro-apoptotic BH3-only subfamily. Bax and Bak can oligomerize to form pores on the outer mitochondrial membrane to induce mitochondrial membrane permeabilization. The anti-apoptotic Bcl-2 family proteins can bind to pro-apoptotic Bax or

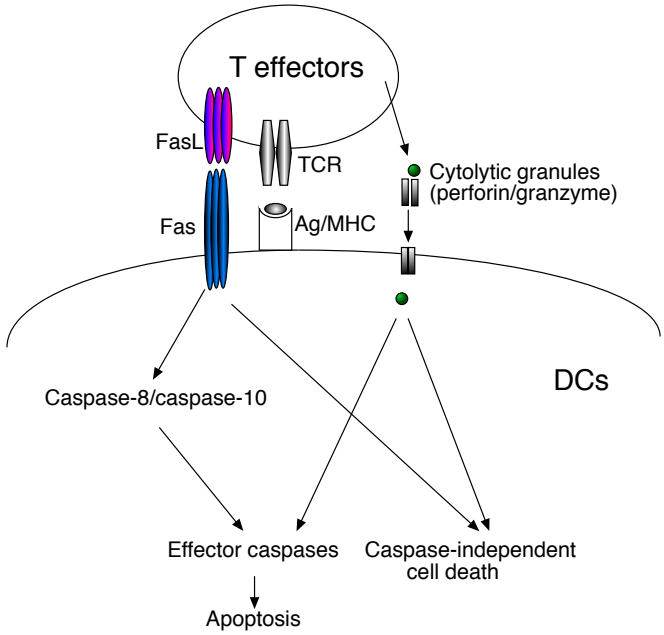

Figure 2: T cell-mediated killing of DCs. Activated T cells express FasL and also secrete cytolytic granules containing perforin and granzyme B. DCs can be killed by activated antigen-specific T cells through Fas- and perforin-dependent mechanisms. Engagement of Fas on DCs by FasL can lead to the activation of caspase-8 and caspase-10 (in humans) and trigger a downstream caspase cascade to induce apoptosis. Cytolytic components secreted by T cells enter DCs through perforin. Granzyme B may directly cleave effector caspases to induce apoptosis. Caspase-independent cell death pathways may also be activated in DCs.

Bak to inhibit their apoptotic potentials [50]. BH3-only proteins can function as "de-repressors" to inhibit the anti-apoptotic molecules, resulting in the aggregation of Bax or Bak. BH3-only proteins may also directly activate pro-apoptotic Bax or Bak to trigger mitochondrial membrane permeabilization. Aggregation of Bax and Bak then leads to the release of cytochrome c from the mitochondrion to the cytosol and activation of caspases [48,49,51]. We have found that knockout of anti-apoptotic Bcl-2 accelerates the rates of renewal of DCs by BrdU labeling [18], while deletion of pro-apoptotic Bcl-2 family member, Bim, inhibits spontaneous DC apoptosis [26]. This suggests that Bcl-2 family members are important for regulating the lifespan of DCs *in vivo*.

Anti-apoptotic Bcl-2 and Bcl-xL

Transgenic mice with DC-specific expression of Bcl-2 show decreased cell death in DCs and increased antigen-specific immune responses [52,53]. We have found that transfection with Bcl-2 increases the survival of bone marrow-derived DCs *in vitro*, knockout of Bcl-2 leads to faster turnover of both conventional DCs and pDCs *in vivo* [18]. We have also observed that Bcl-xL can inhibit spontaneous cell death in DCs [18]. Others have shown that Bcl-xL deficient DCs die rapidly in draining lymph nodes and fail to induce effective immune responses [54]. These data suggest that both Bcl-2 and Bcl-xL help to prolong the lifespan of DCs *in vivo*. Interestingly, DCs only express very limited levels of Bcl-2 [1,18]. Moreover, Bcl-2 is not readily inducible after stimulation via TLRs or CD40 [1,26]. In contrast, Bcl-xL is upregulated in conventional DCs by stimulation of CD40 or TLRs [1,26]. In pDCs expressing TLR9, CpG also leads to significant up-regulation of Bcl-xL [18]. Furthermore, the increased expression of Bcl-xL accompanies the enhanced survival of conventional DCs and pDCs [18]. These data suggest that the limited expression of Bcl-2 contributes to an active intrinsic apoptosis pathway and rapid cell death in DCs, while promotion of DC survival by various TLR stimuli is more likely achieved through the regulated expression of other Bcl-2 family members, such as Bcl-xL, but not Bcl-2.

The differential expression of Bcl-2 family members may play an important role in determining the lifespan of different DC subsets *in vivo*. Interestingly, lower expression of anti-apoptotic Bcl-2 and Bcl-xL were detected in conventional DCs than in pDCs [18]. In addition, conventional DCs express significantly more pro-apoptotic Bax than pDCs [18]. The relatively lower ratios of pro-apoptotic and anti-apoptotic molecules may account for the faster rates of spontaneous turnover of conventional DCs *in vivo*.

BH3-only proteins in DCs

We have observed that the expression of several BH3-only molecules was low in DCs, including Bim, Bad, Nix and PUMA [1]. Interestingly, Bim, Bad and Nix were upregulated after stimulation of TLRs [1,26]. Bad was constitutively phosphorylated at Serine 112 and Serine 136 residues, and TLR stimulation significantly increased the phosphorylation of Bad at serine 155 [26]. Because phosphorylation suppresses the pro-apoptotic activity of Bad by inhibiting its binding to Bcl-xL [55], Bad is potentially inactive in DCs. It will be interesting to test whether signals that promote cell death in DCs can induce dephosphorylation of Bad.

We have also generated Nix-deficient mice to investigate the roles for Nix in regulating DC apoptosis. However, we have not detected any apoptosis defects in DCs nor have we found accumulation of DCs in $Nix^{-/-}$ mice [56,57]. Moreover, $Nix^{-/-}$ mice do not display spontaneous autoimmune or inflammatory symptoms (our unpublished data). Rather, $Nix^{-/-}$ mice show defects in mitochondrial autophagy during terminal erythroid differentiation [57]. However, TLR stimulation can up-regulate Nix expression [1]. Whether Nix might regulate DC functions when it is induced, such as in the scenarios of infections, remains to be examined.

Bim is a pro-apoptotic BH3-only protein that has been demonstrated to regulate apoptosis and homeostasis of lymphocytes [58]. We have found that Bim is also a critical mediator for spontaneous cell death of DCs [26]. Deficiency in Bim inhibits spontaneous cell death in both conventional DCs and pDCs derived from mouse spleens, and in bone marrow-derived conventional DCs [26]. Withdrawal of GM-CSF leads to up-regulation of Bim in DCs [26], suggesting Bim may contribute to increased spontaneous cell death of DCs in the absence of GM-CSF. During the contraction phase of immune responses, similar to T cells, DCs may also undergo spontaneous cell death due to the disappearance of the cytokines that are required to sustain cell survival. It will be interesting to determine whether other cytokines important for prolonging the survival of DCs can also suppress Bim expression in DCs.

CD40 ligation or TLR stimulation leads to up-regulation of Bim in both conventional DCs and pDCs [26]. Simultaneously, however, anti-apoptotic Bcl-xL is also induced in DCs by TLR stimulation [26]. TLR stimulation promotes the survival of DCs during 24 h *in*

vitro culture [26]. Pro-survival Bcl-xL may therefore have a dominant effect to antagonize the action of induced Bim, resulting in enhanced survival of TLR-stimulated DCs. Interestingly, at the later stage of TLR stimulation, pro-apoptotic molecules start to show an advantage over the anti-apoptotic molecules. A recent study has demonstrated that TLR stimulation causes loss of splenic conventional DCs *in vivo* two days following activation [59]. It is possible that TLR stimulation promotes DC survival at the early time point (day 1) but induce DC apoptosis at the later time point (day 2 and after) when pro-apoptotic molecules start to overpower the effects of anti-apoptotic molecules at the later stage. In addition, cytokines produced at the later time point but absent at the early time point may also contribute to DC loss at the later stage. Indeed, type I interferon has been found to be necessary and sufficient for TLR-induced DC apoptosis via induction of BH3-only protein Bim, Bid, Puma, and Noxa in this case [59]. Therefore, the balance between pro-apoptotic (such as Bim) and anti-apoptotic (such as Bcl-xL) proteins, as well as the temporal expression patterns of these molecules, may determine the cell death rate and lifespan of DCs.

$Bim^{-/-}$ DCs survive better than their wild type counterparts after transfer into recipient mice [26], suggesting that $Bim^{-/-}$ DCs undergo reduced spontaneous cell death *in vivo*. It has been reported that DCs are susceptible to killing by antigen-specific T cells [60]. Indeed, we have also observed co-transfer with antigen-specific T cells together with antigen-bearing DCs leads to the loss of DCs in the draining lymph nodes. However, similar reduction of wild type and $Bim^{-/-}$ DCs in the draining lymph nodes were detected in the presence of antigen-specific T cells [26]. Bim therefore possibly regulates spontaneous cell death in DCs, but not the killing by antigen-specific T cells *in vivo*.

DC apoptosis in the regulation of antigen-specific immune responses

Prolonged survival of DCs due to over-expression of Bcl-2 has been shown to enhance antigen-specific T cell activation and antibody production [52,53]. Increased total DC numbers could increase the probability for antigen-presenting DCs to encounter the antigen specific T cells and trigger the activation of T cells. Enhanced DC survival may also prolong the duration for DCs to stimulate T cells for clonal expansion. Conversely, temporary ablation of DCs may result in poor antigen-specific immune responses to infections or even immunosuppression [61]. Cell death in DCs may inhibit the induction of tumor-specific immune responses [62], while suppressing apoptosis in DCs can enhance the potency of DC-based vaccine to trigger tumor-specific immunity [63-66]. These data suggest that the lifespan of DCs indeed affects the magnitude of antigen-specific immune responses.

We have observed that inhibition of apoptosis in DCs leads to DC accumulation, over-activation of lymphocytes and the breakdown of immune tolerance [1]. Consistently, it has been demonstrated that conditional deletion of Fas on DCs induces the development of systemic autoimmune responses [2]. Deficiency in pro-apoptotic Bcl-2 family member Bim has also been shown to contribute to DC accumulation, enhanced T cell activation and the development of autoimmune diseases [26]. Deficiency of perforin has been suggested to cause defective DC killing by $CD8^+$ T cells, contributing to the development of the lethal inflammatory disease hemophagocytic lymphohistiocytosis (HLH) in $perforin^{-/-}$ mice after viral infection [44,67]. Therefore, perturbation of cell death in DCs can have a profound effect in the disruption of antigen-specific immune responses, inflammation, and immune tolerance.

Autoimmunity due to defective Fas-dependent apoptosis in DCs

Immunization with excessive activated DCs can induce systemic and tissue-specific autoimmune responses [3,4]. To examine whether apoptosis in DCs might affect immune tolerance, we generated transgenic mice (DC-p35) expressing a baculoviral caspase inhibitor, p35, under the control of DC-specific CD11c promoter [1]. DC-p35 mice display DC accumulation, increased spontaneous T cell activation, the production of antinuclear autoantibodies and lymphocyte infiltration in multiple organs [1]. Consistent with our studies, Stranger et al. show that conditional knockout of Fas in DCs also induces the development of systemic autoimmunity, including the development of antinuclear antibodies, splenomegaly and leukocytes infiltrations in different tissues [2]. We have observed that negative selection of autoreactive T cells is normal in DC-p35 mice. Therefore, apoptosis deficiency in DCs preferentially affects peripheral tolerance to induce autoimmunity. However, genetic background also plays a role in determining the severity of autoimmunity in DC-p35 mice. Autoimmune responses caused by apoptosis deficiency are more prominent in the autoimmune-prone *MRL* strain than the C57BL/6 background [1]. Therefore, both apoptosis deficiency in DCs and other genetic or environmental risk factors are important for the development of autoimmune diseases.

Deficiency of Bim in DCs in the induction of autoimmunity

Bim deficiency causes significant lymphocyte expansion and the development of autoimmune symptoms in mice [58]. Defective negative selection for autoreactive T cells and B cells has been shown to be involved in the development of autoimmune diseases in $Bim^{-/-}$ mice [68,69]. $Bim^{-/-}$ mice contains slightly increased $CD4^+FoxP3^+$ Treg cells [26], implying that the breakdown of immune tolerance in $Bim^{-/-}$ mice is not due to the loss of Treg cells. We have detected increased number of DCs in $Bim^{-/-}$ mice. $Bim^{-/-}$ DCs are defective in spontaneous cell death [26]. $Bim^{-/-}$ DCs have prolonged survival and are more efficient in inducing the proliferation of antigen-specific T cells *in vitro* and *in vivo* [26]. $Bim^{-/-}$ DCs have also displayed increased propensity for inducing autoantibody production in recipient mice after adoptive transfer [26]. These data suggest that defective apoptosis in Bim-deficient DCs may also contribute to the breakdown of immune tolerance in $Bim^{-/-}$ mice.

T effector cells on DC survival

The activation status of T cells may determine whether T-DC interaction promotes or inhibits cell death in DCs. It has been shown that formation of immunological synapses between DCs and naïve or resting $CD4^+$ T cells promote the survival of DCs *in vitro* or in lymph nodes [31,33]. Immunological synapse formation activates Akt1, thereby activating pro-survival transcription factor NF-κB and inactivating pro-apoptotic transcription factor FOXO1 that controls Bim expression [31,33]. However, DCs are also susceptible to killing by T cells that have been previously activated. DCs form cognate conjugates with antigen-specific T cells in the draining lymph nodes at 24 h after adoptive transfer [60]. However, the majority of these DCs disappear from the lymph nodes 48 h post transfer [60], likely due to cell death induced by T effector cells. Indeed, DCs can be killed by antigen-specific $CD4^+$ T cells *in vitro* [37]. $CD8^+$ T cells can kill DCs during anti-tumor immune responses and viral infections [34,36,70]. Mouse $CD62L^-CCR7^-$ effector memory T cells have also been demonstrated to kill the antigen-loaded DCs in lymph nodes [35].

We have observed that activated T cells can induce cell death in DCs through a Fas- and perforin-dependent manner *in vitro* [1]. Induction of cell death in antigen-specific DCs by antigen-specific T cells may function as a negative feedback mechanism to regulate antigen-specific immune responses (Figure 2).

Treg cells on DC survival

$CD4^+FoxP3^+$ Treg cells can inhibit the activation of T effector cells by multiple mechanisms [71-73]. It has been shown that Treg cells can interact with DCs to inhibit the activation of antigen-specific T cells *in vivo* [74-80]. Treg cells may down-regulate co-stimulatory molecules on DCs to inhibit DC maturation [80-82]. Treg cells may also reduce the lifespan of DCs. Indeed, co-transfer of Treg cells with DCs leads to the disappearance of DCs in the draining lymph nodes [77]. One study shows that human Treg cells can employ a perforin/granzyme-dependent mechanism to kill DCs [83]. Treg cells in tumor tissues have also been reported to kill DCs in a perforin-dependent manner [74]. We have found that activated Treg cells could directly induce cell death in DCs in a Bax and Bak–dependent manner to inhibit DC-dependent immune responses [84]. Therefore, Treg-mediated killing of DCs could provide an alternative mechanism for immunosuppression by Treg cells (Figure 1).

Depletion of Treg cells has been shown to induce an increase in total DCs including the conventional $CD11c^+CD11b^+$ DCs [32]. Treg cells may inhibit DC generation through an action on other cell types. Treg depletion has been shown to induce local Flt3-L production and increased generation of DCs from the precursors of conventional DCs (pre-cDCs) [17]. This suggests that Treg cells may have an inhibitory role in DC generation by suppressing Flt3-L production from an unidentified cell type [32].

Temporary deletion of DCs through injection of diphtheria toxin A (DTA) into CD11c-DTR transgenic mice weakens immune responses [61]. In contrast, constitutive ablation of DCs by DC-specific expression of DTA in CD11c-DTA transgenic mice leads to lethal inflammation [5]. It is possible that DCs are not only essential for activating T cells, but also important for supporting homeostatic expansion of Treg cells in the periphery [85]. We observed a small but reproducible increase of $CD4^+FoxP3^+$ Treg cells in autoimmune mice harboring apoptosis deficiency in DCs [1]. We have also identified that deficiencies in Bax and Bak enable DC to be resistant to killing by Treg cells to over-activate T effector cells [84]. However, other mechanisms by which apoptosis-deficient DCs overcome the inhibition by Treg cells to over-activate T effector cells remain to be elucidated. In addition, what subsets of DCs are critical for the development of immunoregulatory cells, such as Treg cells, in the *in vivo* settings, is an important question for further study.

Deletion of Bax and Bak in mice has shown that Bax and Bak are essential for carrying out all mitochondrion-dependent apoptosis [86,87]. It has been reported that $Bax^{-/-}Bak^{-/-}$ mice are defective in thymic negative selection for autoreactive T cells [88]. We found that DC-specific knockout of Bax and Bak, induced spontaneous T cell activation and autoimmunity in mice [84]. $Bax^{-/-}Bak^{-/-}$ DCs showed a defect in spontaneous cell death and were resistant to killing by $FoxP3^+$ T regulatory cells compared to wild type DCs [84]. Interestingly, Treg cells inhibited the activation of T effector cells induced by wild type, but not $Bax^{-/-}Bak^{-/-}$ DCs [84]. These observations suggest that Bax and Bak not only mediate intrinsic spontaneous cell death in DCs, but also regulate the killing of DCs by Treg cells. Our results suggest that mitochondrion-dependent cell death through Bax and Bak in DCs is important for the suppression of autoimmunity. Although spontaneous autoimmune responses were not identified in CD11c-bcl-2 transgenic mice, bcl-2 transgenic DCs induced diabetes in rat insulin promoter (RIP)-OVA^{low} mice with elevated incidence and severity compared to wild type DCs [52]. This is consistent with an important role of mitochondria-dependent apoptosis in the protection against autoimmunity.

Perforin- and Fas-dependent killing of DCs in the control of inflammation

DCs are susceptible to killing by activated T cells that may involve perforin- and Fas-dependent mechanisms [1]. Although Fas-dependent DC apoptosis helps to limit DC accumulation and prevent the development of autoimmunity, whether perforin plays an important role in the maintenance of DC homeostasis for immune regulation is unclear. We crossed perforin-deficient mice with DC-specific Fas knockout mice. $Perforin^{-/-}DC\text{-}Fas^{-/-}$ mice display DC accumulation, uncontrolled T cell activation and interferon-γ production by $CD8^+$ T cells [47]. $Perforin^{-/-}DC\text{-}Fas^{-/-}$ mice died within 2.5 months, resulting in the development of lethal hemophagocytic lymphohistiocytosis [47]. Neutralization of interferon-γ prevented inflammatory responses and protected the survival of $perforin^{-/-}DC\text{-}Fas^{-/-}$ mice [47]. Although $CD4^+$ T cells and NK cells are capable of killing DCs, $CD8^+$ T cells were essential for the development of lethal inflammation [47]. This study suggests that perforin and Fas synergize in the maintenance of DC homeostasis to limit T cell activation, and prevent the initiation of an inflammatory cascade.

Potential functions for rapid DC turnover *in vivo*

Although the lifespan varies in different DC subsets, conventional DCs are short-lived. Why conventional DCs need to harbor active cell death pathways is not fully understood. DCs are the sentinels that may be constantly undertaking the task of sensing potential antigens that they encounter. DCs may uptake apoptotic cells in the body and the relatively harmless microorganisms. It has been shown that DCs constitutively present self antigens [89]. Most of antigen processing and presentation by DCs would be futile without inducing immune responses. Whether such routine as antigen-presenting cells represents a constant stimulation of DCs that triggers cell death needs to be investigated. In addition, apoptotic DCs could be rapidly engulfed by other neighboring DCs. Engulfment of apoptotic DCs may promote cross presentation of extracellular antigens to the MHC-I pathway for stimulation of cytotoxic T cells. It may also facilitate antigen presentation and amplify the response to intracellular pathogens if apoptotic DCs are infected with pathogens.

Activated T cells can induce Fas- and perforin-dependent cell death in DCs [1]. This represents a negative feedback mechanism to quench the immune responses by inducing cell death in cells that present antigens. T cell mediated DC apoptosis may help to restrict the scope of an immune response by preventing excessive T cell activation. However, excessive or poorly timed elimination of antigen-presenting DCs could lead to defective immune responses. Rapid deletion of DCs by activated viral-specific T cells has been shown to cause immunosuppression after viral infections [34,70]. It will be

interesting to investigate the temporal relation of antigen presentation by DCs and T cell-mediated killing of DCs, and how this regulates the magnitude of immune responses and the effect on T cell memory. Understanding the regulation of cell death in DCs may help to improve the efficacy of DC vaccine against infectious diseases and cancer in human patients [90,91]. Defective apoptosis in DCs was observed in human autoimmune patients harboring caspase-10 mutations [92]. It will be important to investigate the roles for cell death in DCs in human inflammatory or autoimmune diseases.

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