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Achieving Tolerance with Perforin-Secreting Dendritic Cells

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Abstract

Dendritic cells (DCs) regulate the generation of effector adaptive immunity and enforce peripheral tolerance. In the October 2015 issue of *Immunity*, Zlotnikov-Klionsky *et al.* present exciting data describing a population of perforin-expressing CD11c⁺DCs that limit obesity as well as metabolic and autoimmune inflammation in mice.

Dendritic cells (DCs) are specialized antigen-presenting cells that play an important role in the regulation of immunity and tolerance [1]. DCs can be classified into different populations according to their origin, location, activation status and function. In response to their physiological context, DCs promote immunity or enforce tolerance. In the context of inflammation or pathogen infections, DCs are activated via pattern recognition receptors. This activation results in the expression of co-stimulatory molecules and cytokines that promote effector T-cell responses, such as interleukins IL-12p70 and IL-23, which are important for the differentiation of Th1 and Th17 cells, respectively. DCs can also establish and maintain immune tolerance by inducing anergy and the deletion of effector T cells, while promoting the differentiation of regulatory T cells (Tregs) [1]. This tolerogenic phenotype was initially associated with immature DCs, associated with unresponsiveness and T cell deletion following activation [2]. However, increasing evidence suggests that mature DCs can also perform tolerogenic functions following, for example, activation with IL-27, IL-10 or ligands of the aryl hydrocarbon receptor [3–5]. Whether specific tolerogenic DC lineages exist or whether they represent stages during the life cycle of DCs is still unknown.

In a recent article published in *Immunity*, a group led by Yair Reisner at the Weizmann Institute of Science shed new light on this issue [6]. This group had previously suggested that conventional CD11c⁺DCs expressing perforin (perf-DCs) could enforce peripheral tolerance through the release of perforin in a MHC-dependent manner [7]. In their new study, Zlotnikov-Klionsky and colleagues addressed the role of perf-DCs in the control of inflammation *in vivo* using chimeric mice in which perforin expression was selectively impaired in CD11c⁺DCs [6]. Five months after bone-marrow transplantation, chimeric mice

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lacking perf-DCs began to gain weight spontaneously and exhibited features of metabolic syndrome such as dyslipidemia, gain of body fat and increased glucose, TNF- α and leptin levels. This phenotype was associated with an oligoclonal expansion of T cells in adipose tissue [6]. CD8⁺ T cells residing in adipose tissue have been previously shown to initiate and maintain adipose tissue inflammation by promoting macrophage recruitment and differentiation [8]. In agreement with these findings, Zlotnikov-Klionsky *et al* showed that depletion of T cells with anti-CD4 and -CD8 antibodies in fat tissue prevented the development of metabolic syndrome and obesity associated with perf-DC deficiency (Figure 1) [6]. This suggested that the loss of T cells prevented adiposity. Interestingly, the study also identified a role for perf-DCs in the enforcement of peripheral tolerance. Using the well-established mouse model of autoimmunity experimental autoimmune encephalomyelitis disease (EAE), the authors showed that perf-DC deficiency resulted in exacerbated symptoms of disease in association with higher frequencies of Th1 and Th17 effector cells in the central nervous system (Figure 1) [6]. Collectively, these data indicate that perf-DCs play an important anti-inflammatory role *in vivo*.

Cytolysis mediated by perforin or granzyme has long been considered the effector mechanism used by natural killer (NK) cells and CD8⁺ cytotoxic T lymphocytes (CTLs) to kill virus-infected cells and tumor cells. Tregs, however, have also been shown to use this mechanism to mediate their suppressive activity [9, 10]. Indeed, Foxp3⁺ Treg cells kill NK cells and CTLs and interfere with tumor-specific immunity in a granzyme B- and perforin-dependent manner [9]. Tregs also display perforin-dependent cytotoxicity against autologous activated CD4⁺ and CD8⁺ T cells, monocytes and DCs [10]. As such, results from the Reisner study reinforce the importance of perforin- and granzyme-mediated cytolysis in the immunoregulatory mechanisms balancing health and disease. The data demonstrate that in this context, this type of immunoregulatory control is coopted by a small population of physiologically critical tolerogenic perf-DCs.

The identification of this specific population of DCs allows the investigation of additional questions. Do perf-DCs represent a specific lineage associated to a unique transcriptional program, or do they simply represent a maturation DC stage? Which signals regulate the interaction between perf-DCs and target cells and how is adiposity limited? What are the antigens involved? Are perf-DCs dysfunctional in human inflammatory disorders and are perf-DCs dysregulated in the context of tumors? Indeed, could perf-DCs provide a potential therapeutic target to boost the success of cancer immunotherapies, for instance, by removing perf-DCs from DC-vaccine preparations, or would this be detrimental? Answers to these questions will certainly deepen our understanding of various regulatory mechanisms in immunity and metabolism, and might well illuminate a path towards the development of new therapeutic approaches against various diseases.

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Figure 1. Perf-DCs Control Metabolic Syndrome and Autoimmune Disease in Mice

Perf-DCs arrest the development of metabolic syndrome and limit pathogenic T cell responses in EAE. Open questions with regards to the biology of perf-DCs are related to the origin of this tolerogenic population of DCs, the regulation of their interactions with T cells and their role in tumor-specific immunity.