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Invited Review-pharmacology across disciplines

DLL4^{+} dendritic cells: Key regulators of Notch Signaling in effector T cell responses

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ABSTRACT

Dendritic cells (DCs) are critical regulators of adaptive immune responses. DCs can elicit primary T cell responses at low DC:T cell ratios through their expression of high levels of antigen-presenting molecules and costimulatory molecules. DCs are important for induction of functionally diverse T cell subsets such as CD4^{+} T helper (Th)1 and Th17 cells and effector CD8^{+} T cells able to reside in epithelial tissues. Recent studies begin illuminating the underlying mechanism by which DCs regulate specialized T cell subsets. DCs are composed of subsets that differ in their phenotype, localization and function. DCs expressing high levels of DLL4 (DLL4^{+} DCs), which is a member of Notch ligand family, are newly discovered cells that have greater ability than DLL4^{-} DCs to promote the generation of Th1 and Th17 CD4^{+} T cells. DLL4 derived from DLL4^{+} DCs is also important for promoting the differentiation and expansion of effector CD8^{+} T cells. Experimental studies have demonstrated that selective deletion of DLL4 in DCs causes impaired antitumor immunity. In contrast, blocking DLL4 leads to dramatic reduction of inflammatory T cell responses and their-mediated tissue damage. We will discuss emerging functional specialization within the DLL4^{+} DC compartment, DLL4^{+} DC biology and the impact of pharmacological modulation of DLL4 to control inflammatory disorders.

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Abbreviation: APC, antigen presenting cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; cDC, conventional dendritic cell; pDC, plasmacytoid dendritic cell; CMP, common myeloid progenitor; HPC, hematopoietic progenitor cell; MDP, macrophage and DC progenitor; HSCT, hematopoietic stem cell transplantation; DLL, delta-like ligand; GVHD, graft-versus-host disease; NICD, Notch intracellular domain; moDC, monocyte-derived dendritic cell; Th, T helper; TLR, toll-like receptor; TCR, T cell receptor.

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1. Introduction

Dendritic cells (DCs) are essential for eliciting primary T cell responses [1–3]. DCs express high levels of antigen presenting molecules, which present antigen peptides to prime naïve T cells by triggering T cell receptor (TCR) signaling, and costimulatory molecules, which are able to amplify TCR signaling to promote proliferation and survival of activated T cells [1–3]. DCs also produce cytokines to direct effector differentiation [4–8], however, DCs can polarize the generation of distinct lineages of effector cells independent of cytokines [9,10]. We now appreciate that Notch ligands expressed on the surface of DCs are crucial for promoting effector differentiation [11–14]. In mammalians, there are five Notch ligands (i.e., Delta-like 1 (DLL1), DLL3, DLL4, Jagged1 and Jagged2) [15–17]. Notch ligands interact with Notch receptors (Notch 1, 2, 3, and 4) [15,17,18], triggering the release of intracellular Notch and the subsequent transcription of Notch target genes [15,17,18]. Among these Notch ligands, DLL4 shows greater capacity than others to promote the generation of T helper (Th)1 and Th17 CD4$^+$ T cells, which are characterized by producing high levels of IFN-γ and IL-17, respectively [14,19–21]. This leads to our discovery of DLL4-positive (DLL4$^+$) DCs that have greater capacity than DLL4-negative (DLL4$^-$) DCs to induce Th1 and Th17 cells [14,19,20]. A recent study reports that DC-derived DLL4 was able to regulate CD4$^+$ T cell metabolism and proliferation through potentiating T cell receptor (TCR)/CD28 signaling [22]. Thus, DLL4 activation of Notch may represent a ‘fourth’ signal that is crucial for instructing effector development [11,12,14,19,20,23,24]. This review will focus on discussing our current understanding of biology of DLL4$^+$ DCs and their-derived DLL4 in the generation of specialized effector T cells and their-mediated inflammatory disorders.

2. Induction of DLL4$^+$ DCS and lineage-specific effector T Cells

Early studies revealed that DLL4 was highly and selectively expressed within vascular endothelium and crucial for the control of endothelial cell development [25]. In 2004, studies by

Amsen and colleagues suggested that DLL4 was induced in lipopolysaccharides (LPS)-stimulated bone marrow (BM) cells that contained antigen-presenting cells (APCs). Ectopic expression of DLL4 in IE^k-expressing L cell lines enhanced the production IFN-γ by naïve CD4$^+$ T cells of AND TCR transgenic T cells [12]. In 2007, Skokos and colleagues reported that CD8$^-$ DCs induced IL-12-independent Th1 differentiation through DLL4 activation of Notch [10]. Subsequent studies showed that DLL4 regulated pathogenesis of inflammatory diseases in experimental mice, including respiratory viral (RSV) infection [26,27], experimental allergic conjunctivitis [28], experimental autoimmune encephalomyelitis[29] and mycobacteria-elicited pulmonary granulomatous [30]. These studies open the perspective to explore the importance of DLL4 and DLL4$^+$ DCs in inflammatory T cell responses. However, under steady state conditions, DLL4 was barely detected on the surface of DCs and only a small numbers of DLL4$^+$ DCs could be recovered from normal mice [10,26–28,30,31], which limited our capacity to investigate the biological properties of these DLL4$^+$ DCs. By 2013, we discovered that DLL4 was dramatically upregulated on the surface of approximately 40% of host DCs from the spleen of mice undergoing preparative conditioning for allogeneic hematopoietic stem cell transplantation (HSCT). This finding allowed us to characterize these DLL4$^+$ DCs [14]. Most recently, we have established a novel culture system that can produce large amount of DLL4+ DCs from murine BM, providing a unique opportunity to investigate their biology and clinical implications [19].

2.1. DC expression of DLL4 under inflammatory conditions

DCs are heterogeneous cell populations [32]. Based on their surface phenotype, anatomical location and function, murine DCs at the steady state condition are broadly categorized into conventional DCs (cDCs, CD11c$^+$PDCA-1$^-$B220$^-$) and plasmacytoid DCs (pDCs, CD11c$^+$PDCA-1$^+$B220$^+$) [32,33]. Under inflammatory conditions, immature DCs profoundly change their phenotype, acquire enhanced antigen-presenting capacity and alter migration capability [33–37]. To define how inflammatory DCs induce specialized effector T cells, we used murine models of allogeneic HSCT that cause graft-versus-host disease (GVHD). In the GVHD model, recipient mice were pre-conditioned using lethal irradiation, followed by transfer of BM with or without T cells from allogeneic donors. Lethal irradiation would cause tissue injury and gastrointestinal (GI) dysfunction, leading to the release of danger signals and entry of LPS. Within three days after transplantation, DCs were all of host origin and expressed high levels of MHC class II molecule Ia and costimulatory molecules CD80 and CD86 [14]. Thus, DCs generated in hosts undergoing preparative conditioning resemble the phenotype of inflammatory DCs [33,34,36,37].

The expression of DLL4 is induced in immature DCs upon inflammatory stimulation. Data from our studies and others indicate that under steady state condition in mice, only a small fraction of pDCs expressed low levels of DLL4, whereas cDCs did not produce DLL4 [14,38]. In contrast, DLL4 was dramatically upregulated on the surface of approximately 40% of murine whole DC population from the spleen of allogeneic HSCT recipients. Notably, while approximately 10% cDCs derived from mice undergoing HSCT also upregulated the expression of DLL4, as many as 80% of murine DLL4$^+$ DCs derived from mice undergoing HSCT were PDCA-1$^+$B220$^+$ cells, resembling to pDCs under steady state conditions. However, these DLL4$^+$ pDC-like cells expressed CD11b, which is normally not seen in steady state pDCs [32]. Upon inflammatory stimulation, immature DCs may alter their phenotype and functionality [33–35,39]. Indeed, our subsequent studies showed that while immature pDCs derived from BM cells cultured in the presence of Flt3 ligand (referred to as FL) did not express high level of DLL4, they rapidly upregulated DLL4 transcript and protein upon activation of TLR signaling, accompanied with their increase of CD11b and other costimulatory molecules (e.g., CD40, CD80 and CD86) [19]. These observations suggest that DLL4$^+$ pDC-like cells may be derived from immature pDCs upon inflammatory stimulation. Thus, both murine DLL4$^+$ pDCs and DLL4$^+$ cDCs occurred in mice under the allogeneic HSCT condition, with the former being a major subset. Notably, these DLL4$^+$cDCs did not express CD8 [14,19].

Our understanding of human DCs derived predominantly from studies of cells isolated from peripheral blood [40]. Under steady state conditions, human peripheral blood (PB) DCs lack lineage (Lin) markers (i.e., CD3, CD15, CD19, CD14, CD20 and CD56) and constitutively express HLA-DR (DR$^+$), and can be broadly

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