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Review

Th9 lymphocytes: A recent history from IL-9 to its potential role in rheumatic diseases

Wilmer Gerardo Rojas-Zuleta [a], Gloria Vásquez [b,*]

[a] Rheumatology Fellow, Universidad de Antioquia, Medellin, Colombia
[b] Grupo de Inmunología Celular e Inmunogenética, Instituto de Investigaciones Médicas, Facultad de Medicina, Universidad de Antioquia, Medellin, Colombia

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ABSTRACT

Various subtypes of effector T cells have been described up to date, and each one has its specific immunological function and a defined cytokine secretion profile. Th9 lymphocytes, recently described, are characterized by a high IL-9 expression. Their differentiation requires the integration of IL-4 and TGF-β signaling pathways and the coordinated participation of multiple transcription factors. Their role has been mainly found in immunity against parasites and in allergic inflammatory processes. Nevertheless, they have been implicated in processes as autoimmunity, cancer and recently in rheumatic diseases. The objective of this review is to describe the discovery of this cellular subtype, its differentiation, expression regulation and its potential role in rheumatic diseases.

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1. Introduction

Since 1996, the year when Mosmann et al. [1] characterized two different subpopulations of $CD4^+$ murine effector lymphocytes which were determined by the response to their activation with specific antigen, the cytokine expression profile and particular effector functions. Type 1 T-helper lymphocytes (Th1 cells) produce interferon gamma

* Corresponding author at: Grupo de Inmunología Celular e Inmunogenética, Instituto de Investigaciones Médicas, Facultad de Medicina, Universidad de Antioquia, Kr 53 61-30 Laboratory 510, Colombia.
E-mail addresses: wgrojasz@gmail.com (W.G. Rojas-Zuleta), glomavas@gmail.com (G. Vásquez).

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(IFN-γ) and IL-2 and Type 2 T-helper lymphocytes (Th2 cells) produce IL-4 and IL-10 [2]. They recognized that the differentiation towards a particular type of T effector lymphocytes is intimately related to the microenvironment to which a naive T cell is exposed.

Furthermore, it is necessary to integrate signals given by the type and amount of antigen, co-stimulation molecules and exposure to certain cytokines [3]. The latter are the most potent inducers of T lymphocyte differentiation, for Th1, exposure to IL-12 and for Th2, exposure to IL-4 and IL-2 [4,5].

Nevertheless, in a microenvironment, lymphocytes are not only exposed to one cytokine; therefore, the interaction between the signaling pathways of different cytokines, a balance among them, time of exposure and the order in which they are exposed establish the differentiation towards a determined subpopulation of induction specific lineage transcription factors [6]. Hence, there is a specificity of these different cellular phenotypes and the intricate interactions they may establish.

Currently, various specialized types of effector T lymphocytes have been described including regulatory T lymphocytes, Type 17 T helper lymphocytes (Th17) and recently Type 9 T helper lymphocytes (Th9) [7]. The latter which have been recently described are characterized by the expression and secretion of great amounts of interleukin 9 (IL-9) and they are implicated in inflammatory and allergic processes, autoimmunity and cancer [8]. The objective of this review is to describe the discovery of this cellular subtype, its differentiation, its regulation expression, and its potential role in rheumatic diseases.

2. Discovery

The discovery of interleukin 9 preceded several years of descriptions of Th9 cells. IL-9 was described in 1989 [9]. It was originally called P 40, T lymphocyte growth factor (TCGFIII) or MEA (mast cell growth-enhancing activity). At first, it was thought that it was part of a cytokine repertoire produced by Th2 cells [10]. Nevertheless, it was not known if they were produced by IL-4-producing Th2 Cells [10] or if it referred to another cell phenotype [11]. In 1994, Schmidt et al. [12] for the first time described the IL-9 production by naïve $CD4^+$ murine effector lymphocytes in the presence of IL-2 under the stimulus of TGF-β. Likewise, they found that adding IL-4 enhanced this effect. All this suggested that these cytokines acted synergically and had an effect which was dose-dependent to induce IL-9 production. On the other hand, if IFN-γ was added to the medium with TGF-β, IL-9 secretion was inhibited. Schmidt also proposed that the enabling effect of IL-4 in IL-9 production was secondary to its capacity to inhibit IFN-γ production. Thus, the inhibiting effect it had on the IL-9 expression was neutralized.

However, it was not until 15 years later, when in 2008, Veldhoen et al. [13] discovered a different lymphocyte T subpopulation based on cultivating $CD4^+$ murine lymphocytes under different groups of inductor cytokines which polarized the differentiation towards Th1, Th2, Th17, Treg and $CD4^+$ $IL\text{-}9^+$. There was evidence that these cells, which acquired the IL-9 phenotype lost expression of other characteristic cytokine of T effector lymphocytes including IL-4, IL-5, IL-13 of Th2, IL-17-α for Th17 or IFN-γ for Th1, and they did not express the specific transcription factors T-bet for Th1 [14], GATA 3 for Th2 [15] FOXP3 for T reg [16] and ROR-γt for Th17 [17]. This confirmed that this subset of lymphocytes is a different T-lymphocyte subpopulation with high IL-9 and IL-10 expressions and they were named Th9 lymphocytes [13].

Concomitantly, Dardalhon et al. [18] confirmed that the combination of IL-4 and TGF- β polarized $CD4^+$ lymphocytes towards a Th9 phenotype since IL-4 suppresses the induction of the FOXP3 transcription factor by TGF-β, inhibiting the differentiation towards Treg and favoring the Th9 phenotype. This demonstrates a delicate balance between these cytokines which favor or inhibit the differentiation towards this particular subtype.

Nonetheless, their stability in vivo is the topic of a broad debate. It is worth noting that under optimal polarization conditions Th9-cell frequency is relatively low, close to 5–15% in published studies [19–21]. However, Th9 cells increase in allergic patients' peripheral blood and their presence correlates IgE titers [22]. Likewise, in the peripheral blood of children with atopy, an increase in IL-9 production was demonstrated independent of Th2 cytokines [23], which suggests that IL-9 secretion is not related to a Th2 expansion.

Nevertheless, they present flexibility towards other cell phenotypes. Tan et al. [24] demonstrated the plasticity of Th9 cells especially towards the Th2 phenotype. After they are polarized towards Th9, if they are placed in a medium with specific cytokines to differentiate Th2, Th1 and Th17, a greater change towards the Th2 phenotype is observed. Likewise, Veldhoen et al. [13] demonstrated at the same time that Th2 lymphocytes cultivated with TGF-β can change the phenotype towards Th9. This suggests a close relation between these two phenotypes which may present plasticity between them depending on the medium and the cytokines to which they are exposed.

3. Development of Th9 lymphocytes

The activation of a T cell with its specific antigen via a T cell receptor (TCR) is a prerequisite for the induction of effector T cells. However, the expression of co-stimulating molecules is also required to intensify the induction of a determined phenotype [25]. Xiao et al. [26] demonstrated that co-stimulation through OX 40 (CD134), a member of the TNF receptor superfamily, with its OX40L ligand leads to a potent increase in Th9 differentiation and L-9 production, and at the same time, it inhibits polarization towards Th17 mediated by IL-6 and TGF-β or Treg mediated by IL-2 and TGF-β (Fig. 1), which suggests that the effect of OX40 is specific for Th9. This effect was demonstrated in vivo on transgenic mice for OX40, a potent inflammatory effect of the airways was evidenced and the IL-9 and IL-13 expressions increased.

Another signal that can stimulate polarization towards Th9 is a signaling pathway through Notch-type receptors. These transmembrane receptors recognize the ligands of a family similar to Delta (Dll1 Dll3, Dll4,) and Jagged ligands (Jagged 1 and 2) and participate in effector T lymphocyte differentiation functions [27]. Elyaman et al. [28] demonstrated that T lymphocytes of mice with a deletion of Notch 1 and 2 receptors were affected in their polarization towards Th9. Furthermore, they demonstrated that a Th9 phenotype induction under TGF-β stimulation depends on the Jagged 2 ligand and not on Dll1. Likewise, the interaction of a notch intracellular domain (NICD) with SMAD3 on the IL-9 promoter suggests a cooperation of signaling through Notch and TGF-β in the IL-9 expression.

Up to date, a vast variety of stimuli have been described which contribute to Th9 differentiation, such as IL-2 [12], IL-25 [29], the peptide related to the calcitonin gene [30] and Thymic Stromal Lymphopoietin [31], among others. This redundancy suggests cell function diversity and heterogeneity.

4. Th9 regulation

The differentiation towards Th9 indicates the participation of numerous cytokines, and the interaction of their signal transduction pathways. It requires signaling through IL-4 and TGF-β, acting in a coordinated balanced manner, because the signaling for TGF-β promotes a Treg differentiation in the absence of IL-4. On the other hand, a lack of TGF-β would lead to a Th2 differentiation for IL-4 [32].

With a differentiation towards a polarized response, T lymphocytes express transcription factors, which are specific for their cellular phenotype and regulate current cytokine expressions specific to their lineage. Nevertheless, for Th9 cells, there is no one transcription factor which directs its expression, and a coordinated participation of numerous transcription factors is required; some are specific of other T effector lymphocyte subpopulation and others are shared (Fig. 1).

Stimulation with IL-2 is required for a Th9 phenotype induction. This was demonstrated on the T lymphocytes of knockout mice for IL-2, which were unable to induce a Th9 phenotype. Nevertheless, their