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Review article

Th9 lymphocytes and functions of interleukin 9 with the focus on IBD pathology

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ABSTRACT

The work presents the newest knowledge on a new phenotype of T helper lymphocytes (Th9) and on Interleukin 9 (IL-9). Processes leading to transformation of naïve T lymphocyte into Th9 lymphocytes are presented, including the role of IL-4 and TGFβ signaling. Involvement of transcription factor network in production of IL-9 is described. Other cells capable of expressing IL-9 and secreting IL-9 are portrayed. Diversity of IL-9 effects caused by activation of IL-9 receptors on various types of cells is presented. Principal effects of the activation of IL-9 receptor on T-cells seem to be antiapoptotic and stimulatory which leads to enhanced defense against parasitic infection and cancer development but, from the other side, it perpetuate chronic inflammation in autoimmune diseases and allergic processes. In the last years the role of IL-9 in autoimmune diseases such as rheumatic diseases and inflammatory bowel disease gained importance since the increased expression of this cytokine has been observed in animal models of intestinal inflammation and in groups of patients with ulcerative colitis. It was also noted that neutralization of IL-9 in animal models of ulcerative colitis leads to amelioration of inflammatory process, what could have significance in the treatment of this disease in humans in the future.

1. Introduction

Under the influence of certain compositions of cytokines naïve T helper lymphocytes are transformed into various functional T helper (Th) cells. After antigen presentation by antigen presenting cell (APC) and activation of T cell receptor in concert with co-stimulation by various cytokines, naïve T helper cell is transformed into either one of T helper cell types, which support inflammatory process or into regulatory T cell which mitigate the process and prevent the development of chronic inflammation [1]. Cytokines which are determining direction of T cell development in intestinal mucosa are secreted by dendritic cells, macrophages, epithelial cells and other immune cells already present in the intestinal wall. Phagocyting cells (macrophages and dendritic cells) are activated by foreign antigens which are detected by pattern recognition receptors (PRR). Antigens are phagocyted, processed and presented to T cells. Professional APC are secreting various sets of cytokines depending on the kind of stimulating antigens, among others, which in turn are influencing T cells to which antigen is presented in various modes [1].

For many years, a search for conditions under which naïve T helper cells are transformed into different types of active T helper cells has been carried out both in animals and in humans (*in vitro* experiments as well as *in vivo* studies). At first, based on the profiles of cytokines secreted, two types of Th lymphocytes have been distinguished: Th1 and Th2. For a long time, based on the presence of these T cells types in various pathological processes or the presence of cytokines secreted by them in the sites of pathology, theories on which type of Th is responsible for a given process have been developed. At present, Th1 is believed to be the major player in ulcerative colitis (UC) and Th2 in Crohn's disease (CD). Along with the development of more precise detection methods for cytokines, transcription factors, and genes encoding these cytokines additional phenotypes of Th have been distinguished: Th17, functional T helper lymphocytes (Tfh), regulatory T lymphocytes (Treg), and some years ago Th9. Combinations of activation factors (cytokines, their receptors, chemokines) which promote the development of naïve T cells into a certain Th type have been precisely determined both *in vitro* and *in vivo*. Detailed sequence of molecular intracellular events (activation of transcription factors, their interplay, epigenetic processes and activation of the genes) are under investigation and in spite of many controversies a picture of naïve T cell differentiation into various types of Th is emerging. It is now known that differentiation into different types is not the final fate of Th cells and, that if the milieu is changing the profile of cytokines secreted by the Th cell may also change. Therefore, a T cell of one phenotype will become

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a T cell of other type − this phenomenon has been named Th cells plasticity [2].

2. Review

2.1. Interleukin-9

Interleukin-9 (IL-9) was first purified in the seventies of the last century and described as possessing a T-cell and mast cell growth factor properties [3]. Later, human IL-9 gene was identified and described. IL-9 gene is located on chromosome 5, in the proximity of the IL-5/IL-13/IL-4 loci [4]. Interleukin IL-9 is a monomeric glycosylated polypeptide, consisting of 144 amino acids with molecular weight of 28–30 kDa and has a secretory signal sequence of 18 amino acids which belongs to the IL-7/IL-9 family of proteins [5,6].

At first IL-9 secretion has been described by Schmitt et al. [6] in activated murine T cells. They found that IL-9 is present in CD4+ T cells activated by IL-2 and its secretion is further enhanced by tumor growth factor-beta (TGFβ) and IL-4. They also found that IFN-gamma inhibits this process [5]. Initially, IL-9 secretion has been associated with Th2 cells phenotype, however, later it turned out that other T helper subsets are also capable of producing IL-9 [6].

Some years later it has been observed that TGF-beta added to T cell culture 'reprograms' the naïve Th cells differentiation into Th2 phenotype to differentiation to other phenotype by suppressing the production of IL-4, IL-5 and IL-13 and promoting production of IL-9, IL-10 and IL-21. Finally, T helper lymphocytes which produced such set of cytokines where named Th9 cells. It has been observed that IL-4 signaling added to TGFβ signaling directed Th cell differentiation towards Th9 instead of Treg by inhibiting the ability of TGFβ to induce the expression of transcription factor FOXP3 (forkhead box P3) connected to Treg [6]. In many, sometimes very sophisticated experiments and observations, a network of cytokine receptors, their transcription factors and genes, which are responsible for transformation of naïve T helper cells into specialized type of T cells have been discovered and described, among them those responsible for Th-9 differentiation [6,7] (Fig. 1).

2.2. Factors promoting the development of Th-9 from Th-naïve cells and expression of IL-9 by T helper lymphocytes

At present there is a great amount of knowledge on the mechanism of action of cytokines which leads to IL-9 production and transformation of naïve Th into Th9 [7]. As in the case of other cytokines specific receptors, their signal traducers and activators of transcription of specific genes which lead to IL-9 expression have been found. The differentiation of T-helper-cell subsets is not only under the influence of specific sets od transcription factors binding to regulatory regions of genes, but is also affected by epigenetic processes [7]. In the last years it has also been found that microRNAs (miRNAs) may regulate the expression of genes that are necessary for the development, persistence and function of Th cells. Expression of IL-9 genes is being suppressed by miRNAs when IL-9 is overexpressed [8].

Transformation of naïve T helper cell into Th9 lymphocyte requires IL-4 and TGF beta are necessary [1,7]. Their signaling through signal transducer and activator of transcription 6 (STAT6), transcription factors PU.1, IRF4, GATA3 and BATF are essential [7,9]. From one side, gene expression which is inherited by progeny cells decides about the fate of the cell but at the same time this fate can be changed by altered environmental signals [9]. The transformation of CD4 naïve T lymphocytes into memory Th9 lymphocytes is associated with post-translational modifications of histones. Modified histones may change the structure of chromatin in such a way that promoter regions of genes involved in Th lymphocyte differentiation and secretion of cytokines are easier accessible [9]. It has been found that Th9-cell differentiation is determined by unique epigenetic modifications in the genes and especially the promoter region of transcription factor PU.1 which is of great importance for IL-9 synthesis [9].

Such complex mechanism of genes activation suggests that the expression of IL-9 depends not only on genes inherited by the individual but also on environmental factors, (intestine content, microbiome, history of nutrition, infections and other environmental factors). As mentioned above IL-4, IL-2 and TGF beta are principal factors in the process of Th9 development.

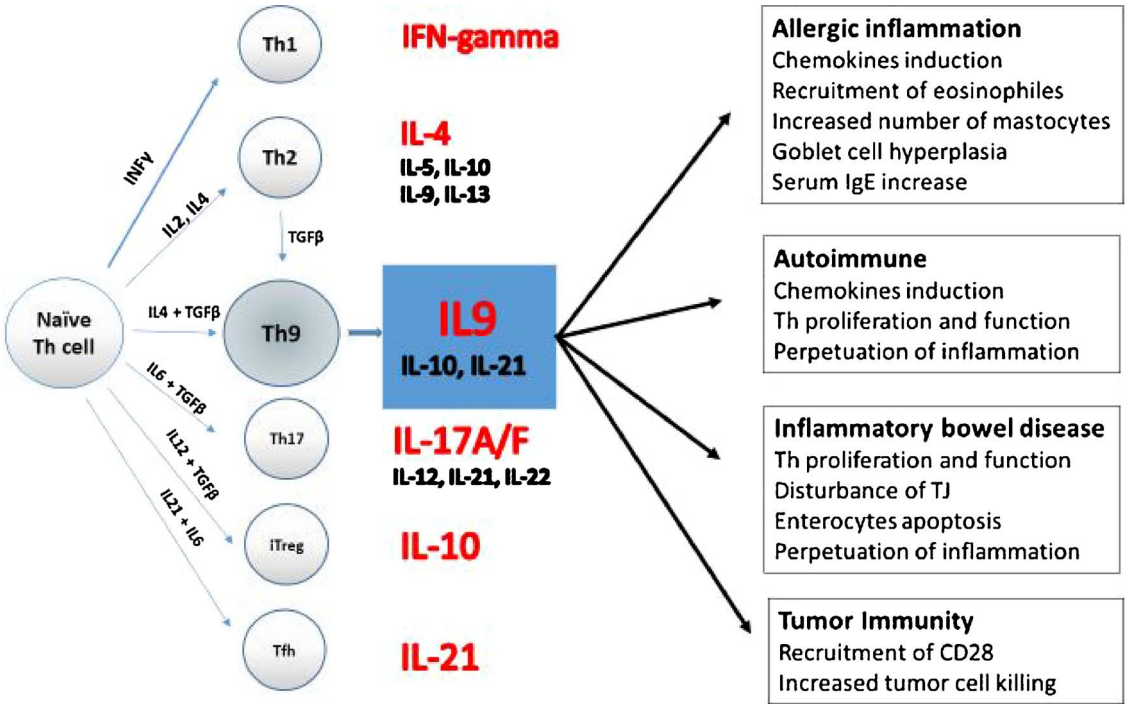

Fig. 1. T cell differentiation and Th9 and IL-9 functions. The development of T helper effector subsets from naive T cells precursors occurs under influence of certain sets of cytokines. IL-2, IL-4 and TGF-β signals promote Th9 development. Each type of Th cell secrets a set of cytokines which act on other cells. IL-9 effect is pluripotent and may influence pathological processes listed in frames. Based on references [6,7,9,11].