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Review

Emerging Roles for MicroRNAs in T Follicular Helper Cell Differentiation

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T follicular helper (Tfh) cells are essential for the formation of germinal centers (GCs) and the development of long-lived humoral immunity. Tfh cell differentiation is a multistep process driven by the balanced expression of key transcription factors that form a regulatory network in which small changes in gene expression determine the Tfh cell fate decision. Here, we review recent findings that have revealed that certain microRNAs act as important mediators within this network, with roles in tuning gene expression. We integrate these findings into the current understanding of the mechanisms governing T helper cell differentiation, and propose a model in which the establishment of Tfh cell identity is dependent on the differential expression and concerted action of distinct microRNAs and transcription factors.

Introduction

Tfh cells, a subset of $CD4^+$ T helper (Th) cells, mediate GC formation and maintenance and provide help to antigen-specific B cells during infection and vaccination [1]. Through secretion of cytokines and interactions via costimulatory molecules, Tfh cells promote the viability and proliferation of GC B cells, which reciprocally regulate the maintenance of Tfh cells. Due to the crucial role of Tfh cells in humoral immunity, it is not surprising that dysregulation of Tfh cells can lead to immune pathology [1,2]. For instance, elevated numbers of Tfh cells have been linked to autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis [3]. In contrast to other Th cell subsets, differentiation of Tfh cells is a multistage, multifactorial process that depends on the abundance of several regulatory factors at different time points after T cell activation [1]. Tfh cell differentiation is orchestrated by the transcriptional repressor Bcl6 [4–6], which is upregulated in response to dendritic cell (DC)-mediated T cell activation [7,8]. Primarily acting as a repressor in Tfh cells, Bcl6 promotes the expression of proteins essential for Tfh cell differentiation while at the same time repressing alternative effector T cell gene programs [1]. Basic leucine zipper transcription factor, ATF-like (BATF) is also required for Tfh cell differentiation as it promotes expression of Bcl6 and c-Maf, which regulates Tfh cell homeostasis by induction of IL-21 [9,10]. Other transcription factors with a role in Tfh cell differentiation are the signal transducer and activator of transcription (STAT) proteins. Among these, STAT5 has been reported to inhibit Tfh cell differentiation [11] whereas STAT3 promotes the formation of Tfh cells in mice [4] and humans [12]. Interestingly, it has been shown that STAT3 functionally cooperates with interferon regulatory factor 4 (IRF4) and mice with a T cell-restricted deletion of IRF4 display a defect in Tfh cell differentiation [13,14]. Bcl6 is reciprocally regulated by Blimp-1, a transcriptional repressor highly expressed in $CD4^+$ effector T cells. Thus, it is believed that on activation of naïve $CD4^+$ T cells, a bimodal fate decision drives the cell to differentiate into either a Tfh or a non-Tfh cell based on the graded expression of Bcl6 or Blimp-1 [15]. More recently, T follicular regulatory (Tfr) cells have been described to regulate humoral immune responses in GCs [16–18]. Interestingly, as Tfr cells mainly develop from thymus-derived regulatory T (Treg) cells, Tfr cells share properties of both Treg cells and Tfh cells [19].

Trends

T follicular helper (Tfh) cell differentiation is a complex multistep process that involves sequential interactions with dendritic cells (DCs) and B cells.

Small changes in gene expression can have an extensive impact on T helper (Th) cell fate decisions and miRNAs critically modulate these processes.

Compared with other effector Th cell subsets (e.g., Th1, Th2, Th17), Tfh cells are particularly responsive to regulation by miRNAs, as global miRNA deficiency in $CD4^+$ T cells prevents Tfh cell differentiation.

While most miRNAs are downregulated in activated $CD4^+$ T cells, some miRNAs (e.g., the miR-17∼92 cluster, miR-155) are rapidly induced in these cells and contribute to shaping Th cell identity.

miR-17∼92 promotes Tfh cell differentiation while at the same time repressing Tfh subset-inappropriate genes.

miR-146a is upregulated at later stages during Tfh cell differentiation, acting as a potent inhibitor of Tfh cells.

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Fate decisions and plasticity of $CD4^+$ T cells are governed by the balanced expression of transcription factors and small changes in gene expression can have a big impact on the outcome of these processes [20]. Thus, better knowledge of the molecular mechanisms that regulate gene expression in activated T cells should be key to deciphering the requirements for the individual differentiation pathways taken by these cells. miRNAs are small, endogenously expressed RNAs with a length of about 22 nucleotides that have important roles in the post-transcriptional regulation of gene expression [21,22]. The maturation of miRNAs starts within the nucleus, where long primary miRNAs (pri-miRNAs) are bound by DiGeorge syndrome critical region 8 homolog (DGCR8) and cleaved by the RNase III enzyme Drosha into precursor miRNAs (pre-miRNAs). These hairpin structures, with a length of 60–70 nucleotides, are exported to the cytoplasm where they are further processed into mature miRNAs by a complex comprising the RNase III enzyme Dicer and TRBP. After unwinding and dissociation of the single strands from each other, one of the miRNA strands forms the miRNA-induced silencing complex (miRISC) together with other components such as Argonaute (AGO), GW182, and FXR1 proteins [21,22]. The RISC-bound miRNA is able to bind to the 3′ untranslated region (UTR) of certain target mRNAs based on sequence complementarity, leading to induction of translational repression or deadenylation and subsequent degradation of the targeted mRNA [21,22].

How miRNAs exert their specific functions on gene expression has been a matter of intense debate. In general, each miRNA can regulate hundreds of different target genes and many different miRNAs are able to regulate the same target gene. Until recently it was believed that miRNA targeting of a single mRNA has only a minor impact on gene expression whereas the network activity of miRNAs targeting hundreds of genes simultaneously can dramatically affect cellular behavior [23,24]. However, genetic studies have now demonstrated that individual miRNA–mRNA interactions can also play important roles in mediating the function of a miRNA in a cell- and context-dependent manner [25–27]. For example, mice with a mutation in the PU.1 3′ UTR binding site for miR-155 were used to study the causative relation between miR-155 and PU.1 mRNA. Interestingly, this single miRNA–mRNA interaction has been found to be essential for the initiation of plasma cell differentiation [27]. In a different study, mutation of the 3′ UTR of the miR-155 target gene *suppressor of cytokine signaling 1* (*SOCS1*) revealed that some immunological functions of miR-155 were fully or largely attributable to the regulation of *SOCS1* whereas other functions could be accounted for only partially or not at all by this interaction, thus emphasizing a cell type- and context-dependent role for such a single miRNA–mRNA interaction [26]. Together, these studies support the concept that miRNAs exert their function primarily by targeting key cellular proteins that may be part of individual or larger functional pathways [28].

In the past few years, miRNAs have emerged as critical modulators of the immune system and miRNA dysregulation has been associated with immune pathology [28–30]. The first evidence for a role of miRNAs in Th cells was provided by two studies in which conditional T cell-specific knockout of Dicer, which results in miRNA deficiency, significantly impaired the proliferation, survival, and differentiation of $CD4^+$ T cells in mice [31,32]. Another study revealed that mice lacking miRNAs as a result of Dicer deficiency in T cells displayed impaired thymic differentiation of Tregs and induced immune pathology affecting the colon, lung, and liver [33]. Surprisingly, Dicer-deficient $CD4^+$ cells produce increased amounts of interferon gamma (IFN-γ) as compared to Dicer-sufficient cells, suggesting a role for miRNAs in the suppression of subset-specific genes during Th cell differentiation [31]. Several miRNAs have now been identified as important regulators of Th cell differentiation and plasticity [29].

Tfh cells have a characteristic miRNA expression profile as compared to other effector Th cells [6,34] and Tfh cell differentiation fails in the absence of miRNAs [35], whereas Th1 or Th2 cells are still able to develop from naïve $CD4^+$ T cells without the requirement for miRNAs [31]. Several