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Review

Epigenetics, autoimmunity and hematologic malignancies: A comprehensive review

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ABSTRACT

The relationships between immunological dysfunction, loss of tolerance and hematologic malignancies have been a focus of attention in attempts to understand the appearance of a higher degree of autoimmune disease and lymphoma in children with congenital immunodeficiency. Although multiple hypotheses have been offered, it is clear that stochastic processes play an important role in the immunopathology of these issues. In particular, accumulating evidence is defining a role of epigenetic mechanisms as being critical in this continuous spectrum between autoimmunity and lymphoma. In this review, we focus attention predominantly on the relationships between T helper 17 (Th17) and T regulatory populations that alter local microenvironments and ultimately the expression or transcription factors involved in cell activation and differentiation. Abnormal expression in any of the molecules involved in Th17 and/or Treg development alter immune homeostasis and in genetically susceptible hosts may lead to the appearance of autoimmunity and/or lymphoma. These observations have clinical significance in explaining the discordance of autoimmunity in identical twins. They are also particularly important in the relationships between primary immune deficiency syndromes, immune dysregulation and an increased risk of lymphoma. Indeed, defining the factors that determine epigenetic alterations and their relationships to immune homeostasis will be a challenge greater or even equal to the human genome project.

1. Introduction

The mechanisms that lead to loss of tolerance include both genetic and environmental factors. Indeed, the understanding that environment plays a critical role in the development of autoimmunity was based in part on studies of concordance of specific autoimmune diseases in identical twins. Although identical twins share genetic elements, they differ in epigenetic alterations. Indeed, a recent symposium has highlighted the multiple environmental features that predispose to autoimmune disease. Interestingly, a number of these factors lead to changes at the epigenetic level which can result in immune dysregulation. It is such stochastic processes that lead to loss of tolerance in the genetically susceptible host. In contrast, hematologic malignancies are thought to arise from chromosomal translocations that are often associated with missing or extra copy of genes and thereby with altered expression of specific molecules. Patients with autoimmune disease often have a higher incidence of lymphoma and indeed children with immune deficiency syndromes may likewise have an increased incidence of autoimmunity and lymphoma. The mechanisms that lead to these associations are diverse but likely include the relationships between T regulatory (Tregs) and T helper 17 (Th17) cells.

Regulatory T cells (Tregs) and T helper 17 (Th17) cells, two reciprocally related T cell subsets, are generally considered to play essential but opposing roles in modulating the immune response. Tregs, which express the transcription factor forkhead box P3 (Foxp3), are pivotal in the maintenance of self tolerance and immune homeostasis, while Th17 cells usually promote inflammatory conditions. In both autoimmune diseases and hematological malignancies, inherited or acquired changes at the genetic or epigenetic level can affect the expression of several cytokines and transcription factors, eventually leading to an imbalance in the ratio of Treg to Th17 cells that will in turn favor a particular disease condition. It has been observed that Treg number and function are both reduced in autoimmune diseases, whereas the opposite occurs

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in several hematological malignant conditions. On the other hand, Th17 cells are generally increased in number and function in most autoimmune diseases. In hematological malignancies, these cells may have a dual role where they either enhance anti-tumor immunity as expected or promote malignant disease by producing pro-oncogenic factors. In this review, we discuss the interplay between Tregs and Th17 cells in the development of autoimmune diseases and hematological malignancies, with a particular focus on the epigenetic mechanisms known to be involved.

2. Epigenetic mechanisms

Epigenetics is the study of inherited changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. Such mechanisms include altering the levels of DNA and histone methylation and of histone acetylation, which leads to changes in the chromatin structure that can either activate or silence gene expression. Epigenetic modifications affect the degree of DNA compaction and the accessibility of the transcription machinery to the DNA strand, thus altering gene expression, phenotype and disease susceptibility [1]. The study of epigenetic mechanisms has provided new insights into how environmental changes contribute to the pathogenesis of autoimmune diseases and hematological malignancy, and has helped justify the rising prevalence of these conditions. The major processes that establish the epigenetic memory through modulation of the chromatin architecture operate by recruiting various histone modifier proteins as well as DNA methyltransferases. Histone deacetylases (HDAC) remove acetyl groups, which leads to gene silencing; whereas histone acetyl transferases (HAT) add acetyl groups, creating a more open chromatin structure for enhanced gene expression. Histone methylation by histone methyltransferases (HMT) affects the interaction of nucleosomes with other proteins and can lead to either activation or repression of transcription depending on the context. DNA methyltransferases (DNMT) add methyl groups to CpG islands in DNA promoter regions. High levels of DNA methylation silence transcription, while hypomethylation of gene promoter regions is associated with increased transcriptional activity [2,3].

3. T helper 17 and regulatory T cells

T helper 17 (Th17) cells are a proinflammatory subset of T helper cells that produce IL-17 cytokines (mainly IL-17A and IL-17F), as well as IL-21 and IL-22. They protect mucosal and epithelial surfaces against extracellular microbes by mediating the recruitment of neutrophils and macrophages to infected tissues. They are developmentally distinct from Th1 and Th2 cells, and excessive amounts of Th17 cells have been linked to the development of various autoimmune diseases [4]. The cytokines produced by Th17 cells stimulate the production of anti-microbial proteins by epithelial cells, which help combat certain types of microbes. They also express the transcription factor retinoic acid-related orphan receptor (ROR) γt, whose expression is required for the transcription of IL-17 and for regulating its production. The transcription factor nuclear factor of activated T cells (NFAT) is another important regulator of IL-17 production. Cytokines such as IL-6, IL-21 and IL-23 activate the transcription factor STAT3, which has been shown to play an essential role in multiple aspects of Th17 cell biology [5,6].

Regulatory T cells (Tregs) are a subpopulation of T cells that suppress immune system activation and maintain self-antigen tolerance. They are involved in shutting down immune responses after the successful eradication of invading organisms, and also in regulating those immune responses that may potentially attack one's own tissues. Evidence from experimental mouse models suggests that the immunosuppressive potential of Tregs can be used to treat autoimmune diseases [7] and manipulated to facilitate organ transplantation and cancer immunotherapy.

Mature Tregs can arise naturally from the thymus (natural Tregs – nTregs), or from the differentiation of CD4+ T cells in the peripheral circulation (induced Tregs – iTregs). Upon cytokine stimulation, peripheral naïve CD4+ T cells can differentiate into either iTregs or Th17 cells (Fig. 1). The transcription factor Foxp3 (forkhead box p3) acts as a master switch governing the development of CD4+ regulatory T cells into iTregs, while RORγt is responsible for Th17 development. Recent studies have demonstrated that the specific induction of RORγt or Foxp3 is dependent on TGFβ signaling and that the two transcription factors can directly interact, establishing a competitive antagonism that determines Th17 versus iTreg lineage specification [8,9].

4. Foxp3 epigenetics in Treg development

Several cytokines are involved in the regulation of Foxp3. For example, IL-2 signaling activates STAT (signal transducer and activator of transcription) proteins, which bind to evolutionarily conserved regions in the *Foxp3* locus and induce Foxp3 expression. TGFβ plays a role in maintaining Foxp3 expression and levels in nTregs. It has also been shown that TGFβ-inducible early gene 1 (TIEG1) can bind to the *Foxp3* promoter and cooperate with itchy E3 ubiquitin protein ligase homolog (ITCH) to induce Foxp3 expression. In addition, retinoic acid has been found to indirectly enhance

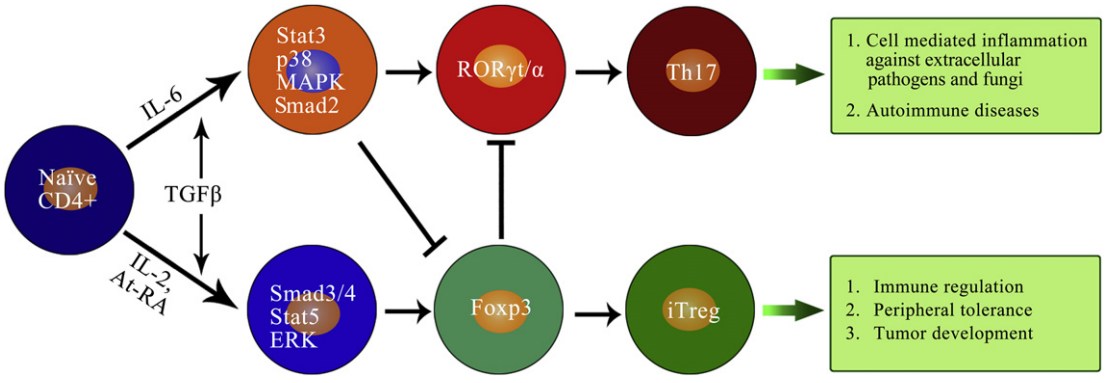

Fig. 1. Schematic diagram showing the developmental relationship between iTreg and Th17 lineages, highlighting some of the main components and stages involved. Inhibition at any of the stages will lead to reduced or no production of that particular cell type and favor differentiation of the other.