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Review

Genetic variations in interleukin-12 related genes in immune-mediated diseases

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ABSTRACT

The interleukin-12 (IL-12) family comprises a group of heterodimeric cytokines and their respective receptors that play key roles in immune responses. A growing number of autoimmune diseases has been found to be associated with genetic variation in these genes. Based on their respective associations with the IL-12 genes, autoimmune diseases appear to cluster in two groups that either show strong associations with the Th1/Th17 pathway (as indicated by genetic association with *IL12B* and *IL23R*) or the *Th1/IL-35* pathway as the consequence of their association with polymorphisms in the *IL12A* gene region. The genetic associations are described in relation to what is known of the functionality of these genes in the various diseases. Comparing association data for gene families in different diseases may lead to better insight in the function of the genes in the onset and course of the disease.

1. Introduction

Autoimmune diseases (AID) are believed to occur as the consequence of a disbalance in the complex interplay between genetic and environmental factors. In the last decade significant progress has been made in the identification of genetic risk factors that underlie these diseases. One recurrent observation is that the known clinical overlap between these diseases has found its counterpart in a considerable genetic overlap [1]. The major challenge lies now in the interpretation of the vast amount of data that have been generated in Genome Wide Association studies (GWAS) and to link these data to the biology of the disease.

A growing number of AID has been found to be associated with genetic variation in the interleukin-12 (IL-12) family of genes. IL-12 related cytokine pathways play a pivotal role in T cell activation and as such these polymorphisms may provide important clues to the mechanisms underlying autoimmune disease.

In the current review we aim to gain insight in the complex role of IL-12 in various immune-mediated diseases. Rather than reviewing the different genetic risk factors associated with a particular disease we here review the different diseases associated with a specific gene cluster. Based on their respective associations with specific IL-12 family members, we demonstrate that AID cluster in two groups. This finding is remarkable since AID clustering within these groups mirror to a certain extent the known clinical relationship between these diseases. Thus, for example, patients with inflammatory bowel disease (IBD) have an increased risk to develop psoriasis, sacroiilitis and spondylitis. As will be discussed here, these diseases show overlapping associations with gene regions within the IL-12/IL-23 gene cluster.

2. Structure and function of the IL-12 cytokine family

The IL-12 cytokine family currently consists of 4 heterodimeric cytokines, interleukin-12 (IL-12), interleukin-23 (IL-23), interleukin-27 (IL-27) and interleukin-35 (IL-35) (Fig. 1).

IL-12 is a heterodimer formed by IL-12p35 (encoded by *IL12A*) and IL-12p40 (encoded by *IL12B*). IL-12 is produced by antigen-presenting cells (APC), phagocytic cells and B-cells in response to infection and favours naïve CD4+ T cells to develop into pro-inflammatory T-helper type 1 (Th1) cells, which secrete the pro-inflammatory cytokine interferon-γ (IFN- γ) (Fig. 2). In addition, it enhances the generation of cytotoxic T lymphocytes and NK cells along with the augmentation of the cytotoxic activity of these cells and concomitantly suppresses differentiation of T-helper type 2 (Th2) cells [2].

Abbreviations: AID, autoimmune disease; AS, ankylosing spondylitis; CeD, celiac disease; CrD, Crohn's disease; GD, Graves disease; GWAS, genome-wide association studies; MS, multiple sclerosis; PBC, primary biliary cirrhosis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

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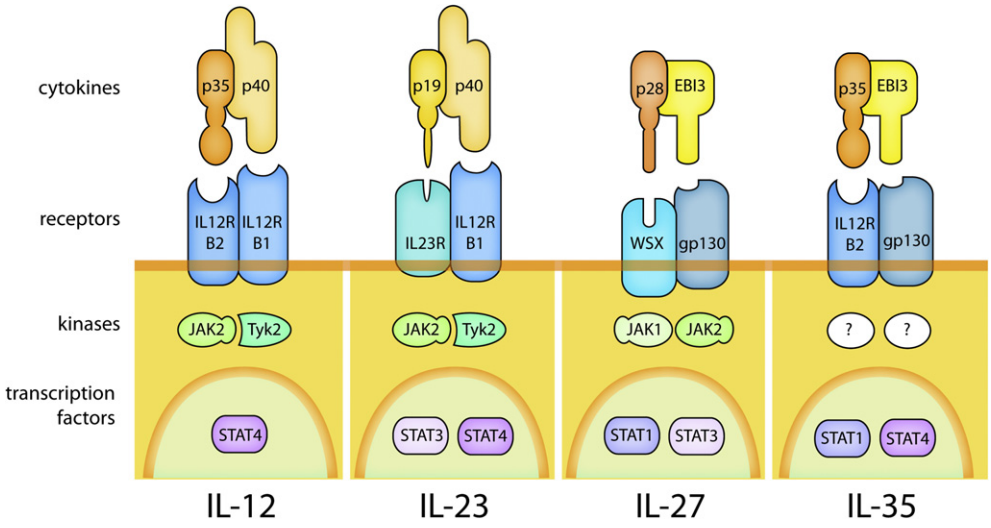

Fig. 1. IL-12 cytokine family. Structure of the IL-12 cytokine family, showing the combination of dimeric molecules that make up the cytokines and their receptors. In addition the kinases and known transcription factors that are crucial for the intracellular signalling are depicted.

In addition to binding to the p35 subunit, IL-12p40 can form the pro-inflammatory cytokine IL-23 when bound to the IL-23p19 chain (encoded by *IL23A*). IL-23 has an important role in amplifying and stabilizing T-helper cells type 17 (Th17 cells), another pro-inflammatory cell population that is involved in combatting a wide range of infections [3], and also plays an important role in autoimmune disease [4]. Th17 cells are characterized by secretion of IL-17A, IL-17F, IL-21 and IL-22 (Fig. 2). Since IL-12 and IL-23 share the IL-12p40 subunit and IL-23 was more recently identified, many activities originally ascribed to IL-12 may in fact have been mediated by IL-23.

Another recently discovered cytokine, IL-27, is formed by Epstein-Barr-Virus induced molecule 3 (EBI3) and IL-27p28. Both proinflammatory (Th1), as well as anti-inflammatory functions (suppression of Th17 cell differentiation) have been ascribed to IL-27 (Fig. 2) [5].

The latest member of the IL-12 family is IL-35, which is composed of IL-12p35 and EBI3. In contrast to the proinflammatory IL-12 family members IL-12 and IL-23, IL-35 is thought to have a role in controlling the immune response during active inflammation. In humans, IL-35 has been shown to suppress the proliferation of conventional T cells as well as the conversion of conventional T cells into T regulatory cells that are named 'iTr35 cells' (Fig. 2) [6,7].

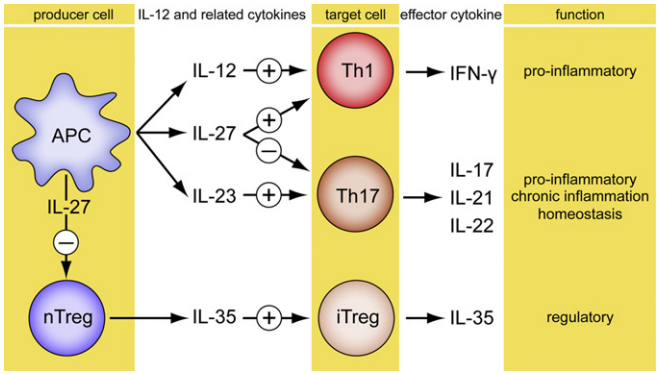

Fig. 2. A schematic view of the members of the IL-12 related cytokines. Antigen presenting cells (APC) are able to produce the majority of IL-12 related cytokines, IL-12, IL-23, and IL-27. All of these affect the differentiation of naïve CD4 T cells into T helper cells of either Th1 or Th17 type. The subsequent production of effector cytokines by the Th1 and Th17 cells leads to profound effects on inflammation and immunity. IL-35 is produced by the naturally occurring Tregs (nTreg) and can lead to the induction of peripheral Tregs (iTreg). They in turn also produce IL-35.

A comparable mixing and matching of heterodimeric molecules is seen for the receptors for IL-12 and IL-23 which share the interleukin-12-receptor- β1 (IL-12Rβ1) chain together with a unique interleukin-12-receptor-β2 (IL-12Rβ2) and IL-23 receptor (IL-23R) chain, respectively (Fig. 1). The receptor for IL-27 consists of a combination of WSX-1 (IL-12Rβ2) and gp130, the latter being a component of several cytokine receptors. The receptors for IL-35 were recently discovered to be composed of the IL-12 family related proteins IL-12Rβ2 and gp130 [8].

3. Genetic associations of autoimmune disease with the IL-12 gene family

When we analyzed studies reporting an association of AID with single nucleotide polymorphisms (SNPs) in any of the gene regions of the IL-12 cytokine family, it became clear that a surprising number of AID are associated with genetic variation in this gene family. This was especially apparent for *IL12p35* and *IL12B*, and for the receptor chains *IL23R*, *IL12Rβ1* and *IL12Rβ2*. In Fig. 3 the positions of the SNPs in these genes and the associations with the different diseases are depicted. For every association the current level of evidence was arbitrarily determined based on the size of the cohorts in which the association was observed as well as replication of the specific association in other study populations. In Table 1 these data are summarized, clearly showing that, based on the association of autoimmune disease with the various IL-12 regions, two major clusters can be distinguished. The first one encompasses Crohn's disease (CrD), ulcerative colitis (UC), psoriasis (Ps), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and rheumatoid arthritis (RA). These diseases all show clear associations with *IL23R*, and the majority is associated with the *IL12B* gene region as well. This indicates an important pathogenic role for the Th17, and possibly the Th1 pathway (Figs. 1 and 2).

The second cluster includes primary biliary cirrhosis (PBC), celiac disease (CeD), multiple sclerosis (MS) and Graves disease (GD), which are all associated with genetic variations in the *IL12A* gene region, suggesting an important pathogenic role for IL-12 and/or IL-35 (Figs. 1 and 2).