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Anti-leukemic properties of IL-12, IL-23 and IL-27: Differences and similarities in the control of pediatric B acute lymphoblastic leukemia

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Contents

Abstract

B acute lymphoblastic leukemia (ALL) is the most common pediatric hematologic malignancy. Although patient cure has reached an excellent rate, a minority of cases relapse and need novel therapies.

IL-12, IL-23 and IL-27 belong to the IL-12 superfamily and exert immunological and anti-tumor functions. The latter can be mediated by activation of immune responses or by the direct activity on cancer cells. Recently, the role of IL-12, IL-23 and IL-27 in the control of pediatric B-ALL has been unveiled. Here, we discuss in a translational perspective the role of IL-12 family cytokines in pediatric B-ALL, highlighting similarities and differences in their mechanisms of action.

Keywords: Cytokines; Cytokine receptors; B-ALL

Abbreviations: IL, interleukin; ALL, acute lymphoblastic leukemia; R, receptor; EBI3, EBV-induced 3; TCCR, T cell cytokine receptor; IFN, interferon; JAK-STAT, Janus activated kinase-signal transducer and activator of transcription; Th, T helper; CTL, cytotoxic T lymphocyte; NK, natural killer; Ig, immunoglobulin; CXCL, chemokine (C–X–C motif) ligand; B-CLL, B cell chronic lymphocytic leukemia; AML, acute myeloid leukemia; MM, multiple myeloma; G-CSF, granulocyte-colony stimulating factor; miRNA, microRNA; BCL-2, B-cell lymphoma 2; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; TIMP, tissue inhibitor of metalloproteinases; TIC, tumor initiating cells; NOD/SCID, non-obese diabetic/severe combined immune deficiency; NOD/SCID/*Il2rg*$^{-/-}$, NOD/SCID/interleukin 2 receptor gamma chain deficient.

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1. The IL-12 cytokine superfamily

Interleukin (IL)-12 is the prototype of a cytokine family that includes structurally and functionally related IL-23, IL-27 and IL-35 [1] (Table 1). With the exception of IL-35 whose receptor has not yet been characterized, IL-12 superfamily and their receptors (R) are heterodimeric proteins made up of both shared and exclusive components [1]. IL-12 is formed by p35 and p40 subunits [2] and its receptor is composed of the IL-12Rβ1 and IL-12Rβ2 chains [3]. P40 associates also with p19 to form IL-23 [4], that binds to a receptor composed of the shared IL-12Rβ1 and the

Table 1
Structural and functional features of IL-12, IL-23 and IL-27.

Cytokine	IL-12	IL-23	IL-27
Cytokine subunits	p35/p40	p19/p40	EBI3/p28
Receptor subunits	IL-12Rβ1/IL-12Rβ2	IL-12Rβ1/IL-23R	gp130/WSX-1
Signal transduction	STAT4 NFkB	STAT3	STAT1, STAT3, STAT5
Producing cells	Dendritic cells Macrophages	Dendritic cells Macrophages	Dendritic cells Macrophages
Immunological functions	Th1 differentiation Generation of CTL Induction of IFN-γ from NK and CTL cells Induction of IFN-γ and IgM from B cells	Proliferation of memory Th1 cells Proliferation of Th17 cells Regulation of IgG and IgM production from human plasma cells	Th1 polarization Suppression of Th2 and Th17 functions Production of anti-inflammatory cytokines (IL-10) from T cells Regulation of IgG and IgM production and induction of chemotaxis in plasma cells

individual IL-23R chain [5]. IL-27 is formed by p28 and EBV-induced 3 (EBI3) [6] which is strictly homologous to the p40 subunit, and IL-27R is composed of the gp130 subunit, shared with the IL-6R, and of the individual component WSX-1, also known as IL-27Ra/TCCR [7]. Both chains of each receptor are essential for the corresponding cytokine signal transduction.

IL-12, IL-23 and IL-27 are mainly produced by antigen presenting cells in response to microbial and host immune stimuli such as Toll-like receptors ligands and interferons (IFN) [1]. Besides the structural similarities, these cytokines activate similar Janus activated kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways, a feature that may explain part of the overlapping effects exerted on T lymphocytes [1]. Thus, all three cytokines are involved in the development of T helper (Th) 1 lymphocytes, although they play distinct functional roles: IL-27 induces polarization of naïve $CD4^+$ T cells to Th1 cells by inducing T-bet expression and up-regulating the IL-12Rβ2 chain, two functions shared with IFN-γ and IL-12 itself [8]; IL-12 consequently acts on committed Th1 cells by inducing their differentiation and production of IFN-γ [9]; finally, IL-23 stimulates the proliferation of memory Th1 cells [4].

In addition to such similar features, IL-12, IL-23 and IL-27 show divergent immunological functions [1]. IL-12 induces cytotoxic T lymphocytes (CTL) generation and stimulates natural killer (NK) and $CD8^+$ T cells to produce IFN-γ [9]. IL-23 stimulates the proliferation of a particular $CD4^+$ T cell subset characterized by the production of IL-17, namely Th17 cells, that play a key role in inflammatory diseases and autoimmunity [10]. IL-27 exerts immune-suppressive functions by inhibiting the differentiation of Th2 [11] and Th17 cells [12], and shows anti-inflammatory properties mainly mediated by the production of IL-10 from T lymphocytes [13].

It is of note that although *in vitro* differentiation of naïve Th cells into Th1 or Th17 cells is mutually exclusive using the polarizing signals identified so far, a different and more dynamic situation has been observed *in vivo*. In this regard, it has been recently reported that Th17 cells can be induced to develop into Th1/Th17 cells by combined action of IFN-γ and IL-12 [14]. However, *ex vivo* isolated Th17 cells lacked IL-12Rβ2 expression and are not responsive to IL-12 alone but, upon stimulation with IFN-γ, the IL-12Rβ2 expression was restored thus rendering these cells responsive to IL-12 [14]. Finally, concomitant stimulation of Th17 cells with IFN-γ and IL-12 results in a rapid transition to Th1 phenotype mediated by stable induction of T-bet, functional imprinting of IFN-γ gene for re-expression and STAT-4 activation [14]. Furthermore, *in vivo* studies demonstrated that the propagation of committed Th17 precursors in the presence of IL-23 resulted in progressive extinction of IL-17F and, to a lesser extent, IL-17A and promoted the emergence of IFN-γ producing cells that lacked IL-17 production [15].

IL-12, IL-23 and IL-27 can also regulate B cell functions. For example, IL-12 promotes the production of immunoglobulin (Ig) M and IFN-γ by tonsillar B cells [16], whereas IL-27 stimulates plasma cell differentiation of naïve B cells and induces a modest IgG1 production [17]. In this context, it has been also demonstrated that both IL-23 and IL-27 stimulate the production of IgM, while dampening that of IgG in human plasma cells [18]. Moreover, IL-27 is chemotactic for the latter cells [18].

Another common feature showed by these cytokines is represented by their anti-tumor properties. At variance with IL-12 and IL-27, the role of IL-23 in cancer appears controversial [19,20]. It has been proposed that exogenous *vs* endogenous over-expression of IL-23 in the tumor microenvironment may account for the discrepancies among published results [21]. In several murine models of cancer [20,22,23] it was shown that exogenous over-expression of IL-23 induced a potent anti-tumor response that is mainly mediated by CTL activation. By contrast, high levels of endogenous IL-23, that are commonly associated to human tumors, appears to promote inflammation, to increase angiogenesis and to suppress CTL tumor infiltration [19,21,24].

The anti-tumor functions of IL-12 and IL-27 have been clearly established and shown to be largely dependent on activation of NK and CTL responses against tumor cells [25–27],