Immune Network
http://dx.doi.org/10.4110/in.2012.12.1.1
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Molecular Mechanisms Governing *IL-24* Gene Expression

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Interleukin-24 (IL-24) belongs to the IL-10 family of cytokines and is well known for its tumor suppressor activity. This cytokine is released by both immune and nonimmune cells and acts on non-hematopoietic tissues such as skin, lung and reproductive tissues. Apart from its ubiquitous tumor suppressor function, IL-24 is also known to be involved in the immunopathology of autoimmune diseases like psoriasis and rheumatoid arthritis. Although the cellular sources and functions of IL-24 are being increasingly investigated, the molecular mechanisms of *IL-24* gene expression at the levels of signal transduction, epigenetics and transcription factor binding are still unclear. Understanding the specific molecular events that regulate the production of IL-24 will help to answer the remaining questions that are important for the design of new strategies of immune intervention involving IL-24. Herein, we briefly review the signaling pathways and transcription factors that facilitate, induce, or repress production of this cytokine along with the cellular sources and functions of IL-24.
[Immune Network 2012;12(1):1-7]

INTRODUCTION

Interleukins are an integral part of our immune system and are often involved in stimulating or suppressing the immune system and inflammation. They are mainly produced by T lymphocytes, monocytes, macrophages, and endothelial cells. The induction and expression of interleukins require the coordinated action of lineage-restricted complex transcriptional networks. For example, IFN-γ, IL-4 and IL-10 have been extensively studied for their cellular sources, functions and the factors involved in regulation of their expression in response to diverse stimuli (1-9).

IL-24 was identified by subtraction hybridization of cDNA libraries from human melanoma cells and was initially named as melanoma differentiation associated gene 7 (MDA-7) (10). IL-24 is located in chromosome 1 along with IL-10, IL-19 and IL-20 and shares both structural and sequence homology (11). The cellular sources and functions of IL-24 have been a subject of active research and have been well documented in published reviews (12-14). However a few recent studies from our group and others have reported molecular mechanisms directly related to *IL-24* gene regulation in various cells. Here we concisely discuss the recent information regarding the signaling pathways and transcription factors along with chromatin remodeling and epigenetic events involved in the transcriptional regulation of *IL-24* gene in the reported cell types.

CELLULAR SOURCES OF INTERLEUKIN-24

IL-24 is produced by various immune cells such as peripheral blood mononuclear cells (PBMC), preferably monocytes, and T and B cells. Antigenic stimulations by concavalin A, lipopolysaccharide, or cytokines induce IL-24 expression in monocytes (15,16). TCR stimulation aided by anti-CD3 and CD28 or PMA and Ionomycin also induce physiological levels of IL-24 in T helper 2 (Th2) lymphocytes (17,18). Similar to Th2 cells, B cell receptor signaling (anti-IgM plus CD40-L) also triggers IL-24 expression in B lymphocytes (19). Apart from these cells of the immune system, physiological levels of IL-24 is also produced by cells of non-lymphoid origin like

Received on December 20, 2011. Revised on January 5, 2012. Accepted on January 10, 2012.

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Keywords: IL-24, Chromatin remodeling, Epigenetics, Transcription factor, Gene regulation

cultured melanocytes, dermal keratinocytes, and IL-1 stimulated human colonic subepithelial myofibroblasts (SEMFs) (10,20,21). Although IL-24 expression is abundant in melanocytes, it is gradually lost during melanoma progression and is usually absent in various malignant melanoma and other cells. However IL-24 expression is revived in these cells upon treatment of IFN-β and mezerin which induce differentiation in melanoma cells (10,22). IL-1β stimulation also induces IL-24 expression in both keratinocytes and SEMFs (20).

FUNCTIONS OF INTERLEUKIN-24

The secreted IL-24 protein interacts in a paracrine manner with IL-20R1/IL-20R2 and IL-22R1/IL-20R2 receptor complexes (23-25). Both these receptors are abundant in several tissues such as those from the reproductive and respiratory systems and various glands making them the main targets of IL-24. Keratinocytes express both the IL-24 receptor complexes and stimulation of normal human epidermal keratinocytes (NHEK) with IL-24 *in vitro* induces STAT3 activation which alters their differentiation, proliferation and induces the expression of a number of psoriasis-related genes. Taken together these findings suggest a role for IL-24 in the pathogenesis of psoriasis and other inflammatory conditions in the skin (21,26). Increase in IL-24 expression has been seen at the edge of excisional skin wounds, in the joints of rheumatoid arthritis patients and in active lesions from patients who have ulcerative colitis and Crohn's disease (20,27,28). However the exact cell subsets producing IL-24 in the above places are not clear.

Most immune cells lack the IL-20R1 or IL-22R1 receptors but the IL-20R2 is expressed in these cells. Adenovirus mediated ectopic expression of IL-24 can activate the IFN-γ and NF$\kappa\beta$ pathways and also induce the secretion of pro-Th1 cytokines like IFN-γ, IL-6, TNF-α, IL1β, IL-12 and GM-CSF in human PBMCs favoring a Th1 type immune response (15). The upregulated IFN-γ in turn can further up-regulate IL-22R1 expression in keratinocytes and a formation of IL-22R1/IL-20R2 complex promotes the innate immunity of tissues (29). IL-24 also inhibits differentiation of germinal center B cells into mature plasma cells by coordinating multiple molecular events like downregulation of transcription factors like IRF4, Blimp1 and Bcl6 which play a crucial role in plasma cell differentiation (19). Although down-regulation of IRF4 and Blimp1 could be directly involved in inhibition of plasma cell differentiation, the role of Bcl6 in this matter is still unclear. Since Bcl6 facilitates expansion of the germinal centre B cells (30) and IL-24 blocks entry of the plasma cell precursors into the cell cycle, down regulated Bcl6 by IL-24 could indirectly lead to plasma cell differentiation inhibition. However the exact effect of downregulated Bcl6 upon addition of IL-24 in the context of plasma cell differentiation inhibition needs further scrutiny. Analysis of IL-24 transgenic mice reveal a largely redundant role of IL-24 with IL-20 and IL-22 in epidermal functions (31). Unfortunately no published reports showing the phenotype of mice deficient of IL-24 are available, however mice deficient of the IL-20R2 shows that IL-24 along with IL-19 and IL-20 are part of a signaling network that down-modulate T cell responses in mice (32).

Although IL-24 is a cytokine produced by various immune cells, rather than its physiological role in the immune system, its tumor suppressor role has been well documented. Mechanisms leading to cell death in human melanoma and various kinds of other cancer cell lines by adenovirus mediated overexpression of IL-24 have been extensively studied and reviewed (13,14,33,34). Upregulation of endoplasmic reticulum (ER) stress, activation of the p38 MAPK pathway and the GADD family genes leads to apoptosis in cancer cells upon adenoviral expression of IL-24 (35-37). IL-24 induces cancer cell specific oxidative stress by generation of reactive oxygen species (ROS) followed by mitochondrial dysfunction uniquely in cancer cells and also inhibits angiogenesis, invasion and migration of cancer cells (38-42). Ectopic expression of IL-24 also induces IFN-γ and IL-6 secretion from melanoma cells having potent anti-tumor functions (12, 15). Administration of IL-24 via adenoviral vector (Ad.MDA-7) generates a significant increase in the CD3+CD8+ population thus promoting immune activation, leading to anticancer immunity. Phase-I clinical trial in melanoma showed transient increases in circulating cytokines such as IL-6, IL-10 and TNF-α in response to IL-24 and a significant increase in CD3+CD8+ T cells suggesting that Ad.MDA-7 may be associated with a Th1-like response (13,43,44).

TRANSCRIPTIONAL REGULATION OF INTERLEUKIN-24

Mutually exclusive patterns of cytokine production in fully committed CD4+ or CD8+ T lymphocytes are precisely regulated by diverse signaling pathways and transcription factors upon exposure to antigen and polarizing cytokines ex vivo. During this process, the differentiating cells undergo extensive changes in transcriptional activity, signature gene ex-

pression and cell specific functions. The important role of chromatin remodeling and epigenetic regulation mechanisms for transcription of cytokine genes in mammalian cells have been also reported (45-51). Unlike its Th2 cell counterparts, the molecular mechanisms governing IL-24 production are less well defined. As mentioned in the previous section, physiological levels of IL-24 are produced by cells of both lymphoid and non-lymphoid lineages. However the factors and mechanisms driving the differential expression of IL-24 are not completely understood and have not been fully identified in any cell type.

Non-immune cells

Initial studies in the beginning of the last decade characterized the functional promoter of the *IL-24* gene for the first time in human melanoma (HO-1) cells. A study by Madireddi et al showed that reexpression of IL-24 in human melanoma cells upon treatment of differentiation inducers such as IFN-β and mezerin is dependent on the AP-1 family member c-Jun and the C/EBP family member C/EBP-β. Both these factors directly bind to the human IL-24 promoter and elevate IL-24 expression by activating its promoter (52). According to another report the increased IL-24 expression during terminal differentiation in human melanoma cells is also regulated at posttranscriptional level. The study showed that although the IL-24 promoter is active and IL-24 mRNA is actively transcribed in melanoma cells, the 3' UTR of IL-24 containing AU-rich elements (ARE) makes the IL-24 mRNA unstable in these cells leading to gradual decrease in IL-24 production upon melanoma progression. This message is stabilized upon treatment of differentiation inducers IFN-β and mezerin leading to reexpression of IL-24 in these cells (53). Although the above study suggested that mRNA stabilization is of major importance to IL-24 expression, the pathways responsible for the regulation of IL-24 mRNA stability were not identified. A recent report showed that IL-1β stimulation induced IL-24 expression in cultured normal human keratinocytes is strongly dependent on p38 MAPK activation. Inhibition of this pathway accelerates IL-24 mRNA destabilization mediated by the 3' UTR of IL-24 mRNA suggesting that p38 MAPK regulates IL-24 expression at the post transcriptional level (54). Apart from melanocytes and keratinocytes, IL-24 expression in the inflamed mucosa of patients with inflammatory bowel disease (IBD), was also reported and the molecular mechanisms responsible for its expression in human colonic SEMFs were identified. Similar to differentiated melanoma (HO-1) cells, AP-1 and C/EBP binding to the IL-24 promoter was reported in these cells upon IL-1β stimulation leading to enhanced IL-24 mRNA and protein expression. IL-1β also led to increased IL-24 mRNA stabilization in SEMFs (20).

Immune cells

As mentioned previously, cells of the immune system are also major producers of IL-24. However similar to its nonimmune counterparts, reports about the signaling pathways and transcription factors inducing IL-24 expression in immune cells are few. Schaefer et al. for the first time identified IL-24 in mouse CD4+ T lymphocytes and designated it as FISP (IL-4-induced secreted protein), which is selectively expressed and secreted by Th2 cells. Detectable levels of IL-24 (FISP) are observed only 3 days after initiation of Th2 differentiation and its expression requires at least two signals: TCR signaling involving protein kinase C (PKC) activation and Stat6-dependent IL-4R signaling (18). Recently our group further delineated the exact molecular mechanism responsible for this Th2 cell specific expression of IL-24. We identified the proximal promoter region that confers Th2 cell specificity to the *IL-24* gene. Our data also showed that the IL-24 promoter locus has an active chromatin configuration in Th2 cells upon TCR stimulation (17). Similar to human melanoma cells and SEMFs, the role of AP-1 family member c-Jun is predominant in regulating IL-24 expression in Th2 cells suggesting that regulation of the *IL-24* gene is conserved in mice and human and also across cell types. TCR signaling as well as mezerin which is a nonphorbol ester both activate PKC which further activates the AP-1 family of transcription factors. Stat6, a member of the STAT family of proteins which acts downstream of the IL-4 signaling pathway also binds to the IL-24 promoter locus along with c-Jun and transactivate it. This increased binding is facilitated by the accessible chromatin structure and active histone marks evident by increased recruitment of acetyl histone H3 lysine9/14 (H3AcK9/14) and histone H3 lysine 4 methylation (H3K4Me2) at the IL-24 promoter in Th2 cells (17). The above active histone modifications and open and accessible chromatin are usually associated with the promoters of actively transcribed genes (55-57). A report by Wei et al. also showed direct binding of Stat6 along with active chromatin configuration (H3k4me3 and H3k36me3) at the IL-24 promoter. These modifications were shown to be Stat6 dependent, since Stat6 deficient mice showed decreased or less recruitment of the above proteins at the IL-24 promoter (58). The same locus however is occu-

pied by histone deacetylase (HDAC) 1 in Th1 cells. Our current investigations reveal that this increased HDAC1 recruitment to the IL-24 promoter is mediated by other repressive factor(s) like Ets-1 pre-bound to the IL-24 genomic locus specifically in the Th1 cells (unpublished data). Thus, chromatin remodeling may contribute to the cell-specific expression of IL-24, controlling the access of appropriate key transcription factors and the transcriptional machinery to the promoter. Our unpublished studies also indicate the involvement of specific transcription factors and chromatin remodeling events in IL-24 expression in effector $CD8^+$ T cells. IL-24 is also optimally induced by B cell receptor triggering and CD40 engagement in germinal centre B cells (19). However the transcription factors downstream of these pathways which aid in IL-24 production in B lymphocytes still remain to be identified.

EPIGENETIC REGULATION OF INTERLEUKIN-24 IN CANCER

Chromatin remodeling and epigenetic events not only play an important role in regulating the lineage specific expression of IL-24 in Th2 cells but also it plays important role in cancer cells. A recent report showed that the expression of IL-24 was upregulated by the HDAC inhibitors trichostatin A (TSA) and sodium butyrate, whereas it was downregulated by HDAC4 in human melanoma (A375) cells. The histone acetylation level and the binding of the transcriptional factor Sp1 to the human IL-24 promoter in these cells were reduced upon HDAC4 overexpression (59). This gradual suppression and absence of IL-24 expression could also be attributed to other forms of epigenetic silencing, since no inactive mutation or structural rearrangements were identified in IL-24 in any type of cancer cell (60,61). Various studies have suggested that there is direct correlation between epigenetic modifications, such as histone methylation, histone acetylation, DNA methylation, and gene expression in disease-relevant cells, including cancer cells. Epigenetic inactivation of tumor suppressor genes or tumor related genes by hyper methylation in promoter region is a common event in human tumor cell lines and human cancer (62,63). The importance of epigenetic events in development and proper function of various normal cellular processes is also increasing attention. Our unpublished findings show increased DNA methylation at the IL-24 promoter in Th1 cells compared to Th2 cells. Inhibition of DNA methyltransferases by treatment of 5'Azacytidine increases IL-24 production not only in Th1 cells but also in a few types of cancer cells. Hence apart from identifying factors important to upregulate IL-24 expression, understanding the molecular mechanisms underlying *IL-24* gene silencing could be of great significance.

SUMMARY AND FUTURE PERSPECTIVES

Altogether the above findings suggest that *IL-24* gene transcription requires the combined action of transcription factors, as well as active chromatin remodeling and epigenetic modifications in the IL-24 promoter locus in both normal cells and cancer cells. The effect of transcription factors and epigenetic modifications on the regulation of gene expression and the concomitant relationship to human diseases has become a key area of biological research in the recent years. Exploration of the basic events involved in altered gene transcription patterns and/or silencing of IL-24 in normal cells or cancer cells will also help in developing ways to pharmacologically alter the epigenetic abnormalities and lL-24 expression.

ACKNOWLEDGEMENTS

This study was carried out with the support of "Research Program for Agricultural Science & Technology Development (Project No.: PJ907153)", National Academy of Agricultural Science, Rural Development Administration, Republic of Korea.

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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