Chapter

Glance on the Critical Role of IL-23 Receptor Gene Variations in Inflammation-Induced Carcinogenesis

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Abstract

In this chapter, we will discuss the importance of genetic variations in the IL-23 receptor (IL-23R) gene in driving the process of inflammation-induced carcinogenesis. By applying bladder cancer (BLC) as a model, we will focus on two contradictory genetic mutations within the receptor gene. The first one is enhanced by cancer and induces inflammation-induced carcinogenesis via up-regulating IL-23/IL-17 inflammatory axis. However, the other preventive one deregulates this inflammatory pathway by distorting the protein nature of the receptor, leading to block its binding affinity. During the process of carcinogenesis, cancer genetically inclines the balance towards the protumor, via over-expressing the IL-23R on the surfaces of immune-bearing cells, particularly tumor-associated monocytes (TAMs) and thus increasing the levels of pro-angiogenic cytokines IL-23 and IL-17.

Keywords: bladder cancer model, IL-23 receptor, IL-23/IL-17 inflammatory axis, Tumor-associated monocytes, IL-23R gene variants

1. Introduction

Interleukin-(IL) 23 is a heterodimeric cytokine formed by a distinct p19 subunit and a shared p40 subunit with IL-12 (**Figure 1**) [2]. IL-23 engages with the heterodimeric IL-23 receptor, which consists of IL-23R chain and IL-12Rβ1 chains, so as to activate intracellular Janus kinases (JAKs), mainly tyrosine kinase-2 (TYK2) and JAK2, which stimulates signal transducer and activator of transcription (STAT3). Subsequently, the JAKS-STAT-3 pathway plays a critical role in the upstreaming genes of a variety of proinflammatory cytokines, such as IL-6 and IL-17 [3].

Antigen-presenting cells (APCs), such as DCs and macrophages, are thought to be the predominant provider of both IL-23 and IL-12 cytokines [4]. It is now acknowledged that the imbalance between the inflammatory cytokine IL-23 and IL-12 in tumors can re-shape the development of pro-tumor or anti-tumor immunity. Given that the role of IL-12 in boosting anti-tumor immunity is well recognized and recently evaluated [5].

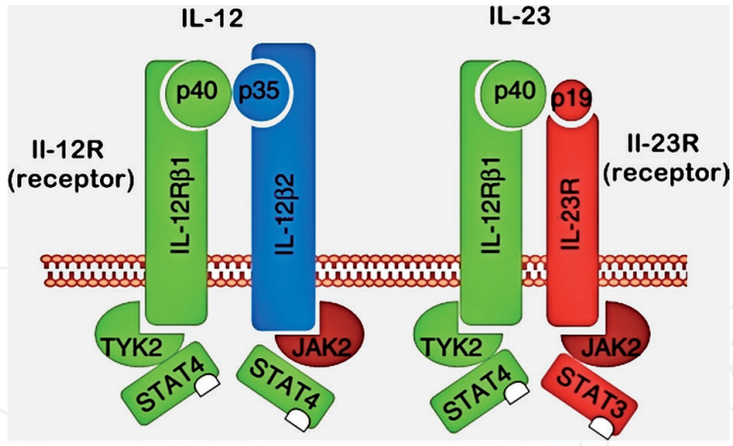

Figure 1.
Schematic representation of the interleukin (IL)-12 and IL-23 cytokine family and their receptors structures, and associated Janus kinases (JAKs) and signal transducers and activators of transcription (STATs) signaling partners [1].

Concerning common in vitro trials, mice that were deficient for IL-23p19 protein injected with chemical carcinogen-induced fibrosarcomas, showed a declined rate and frequency of tumor-growth compared to wild-type (WT) controls [6]. However, rodents lacking IL-12/23p40 or IFN-γ were found to have a significantly higher chance of developing carcinomas [7–9]. Also, using chemical carcinogen-induced skin cancer, IL-23-p19-deficient mice revealed significantly decreased numbers of cutaneous papillomas compared to WT mice, while the opposite was observed in IL-12p35-deficient mice [10].

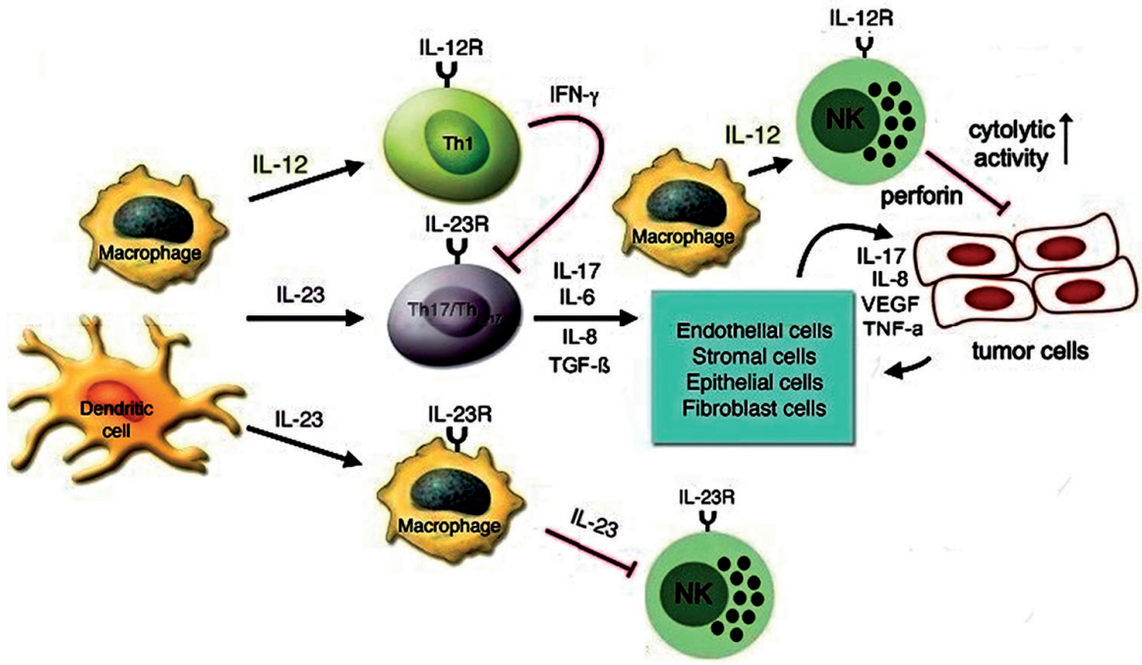

Figure 2.
Role of IL-23/IL-17 inflammatory axis in cancer. IL-23 produced by tumor-associated macrophages via autocrine and paracrine manners enhances the development of IL-17 producing T-cells called Th-17 cells and that stimulates the generation of pro-tumorigenic cytokines, such as IL-6, IL-17, VEGF, and TNF-α, thus, contributing to tumor growth. However, IL-12 produced by anti-tumor macrophages promotes, cytotoxic T-lymphocytes and natural killers to produce INF-γ and thereby killing tumor cells [11].

In vivo, IL-23 plays a vital role in inducing the effector function and proliferation of Th-17 cells (**Figure 2**), which are characterized by the expression of proinflammatory cytokine IL-17, under the influence of the master transcription factor retinoic-acid receptor-related orphan-receptor-γt (RORγt) [12–16].

Prolonged activation of the IL-23/IL-17 pathway is believed to stimulate the incidence and tumor growth [17]. This is owing to its ability to facilitate tumor growth and metastasis by up-regulating the synthesis of pro-angiogenic factors in fibroblasts and endothelial cells [18, 19].

IL-12, on the other side, mediates the anti-tumor immunity by driving the differentiation of Th-1 cells to cytotoxic T-lymphocytes and producing Interferon-gamma-(IFNγ)-II [5, 20]. In similar manner, IL-12, produced by anti-tumor macrophages, acts mainly on lymphoid cells such as NKs (**Figure 2**), to directly augment NKs proliferation and activate its cytotoxic function against tumor cells via IFN-γ secretion [5, 21, 22].

In the tumor micro-environment, it has been shown that IL-23 produced by tumor-associated monocytes (TAMs) by autocrine and paracrine manners may lead to the down-regulation of perforin, IL-12, and IFN-γ, thereby, suppressing T-cytotoxic lymphocytes and NKs effector functions and that indirectly results in enhancing tumor growth and development [6, 23].

2. IL-23 receptor

IL-23 receptor (IL-23R) is a heterodimeric construct formed by IL-23R and IL-12Rb1 subunits. IL-12Rb1 is also a part of the IL-12 receptor, however, IL-23R is restricted to the IL-23 receptor complex [24, 25].

IL-23R is mainly expressed on the surfaces of memory T-cells, NKs, macrophages, and Dendritic cells (DCs), while its expression is induced on $CD4^+$ T-cells during the differentiation towards the Th-17 cells with cellular responsiveness to IL-23 [24, 26–28].

In cancer-related inflammation, IL-23/IL-23R interaction is truly required for Th-17 cell-mediated immune response [29, 30] and represents the potential connection between the failure of the adaptive immune surveillance and tumor-promoting pro-inflammatory processes [10].

The intrinsic signaling pathway begins when IL-23 ligates to its receptor and that induces autophosphorylation and transphosphorylation of receptor-associated proteins namely Janus kinases (JAK2) and tyrosine kinases (TYK2) which are located in the intracellular domain of the receptor subunits (**Figure 3**). These phosphorylated residues serve as docking sites for the phosphorylation homodimerization of the signal transducer and activator of transcription (STAT) molecules. To detail, STAT3 is the main player in the IL-23 signaling pathway, while STAT4 is the central player in the IL-12 pathway [24, 25, 31, 32].

Once activated, the homodimers of STAT3 translocate into the nucleus, wherein they bind to the DNA in the promoter region of the target gene, such as the IL-17 gene [31, 32].

It has recently been reported that STAT3 has key role in the differentiation of T-helper-17 [33], however, STAT5 activation hinders T-helper 17-cell development [34]. For these reasons, the selective activation of certain STAT molecules may be functionally important in disease susceptibility because of the role that these molecules have in the regulation of naive $CD4^+$ T-cell differentiation [35].

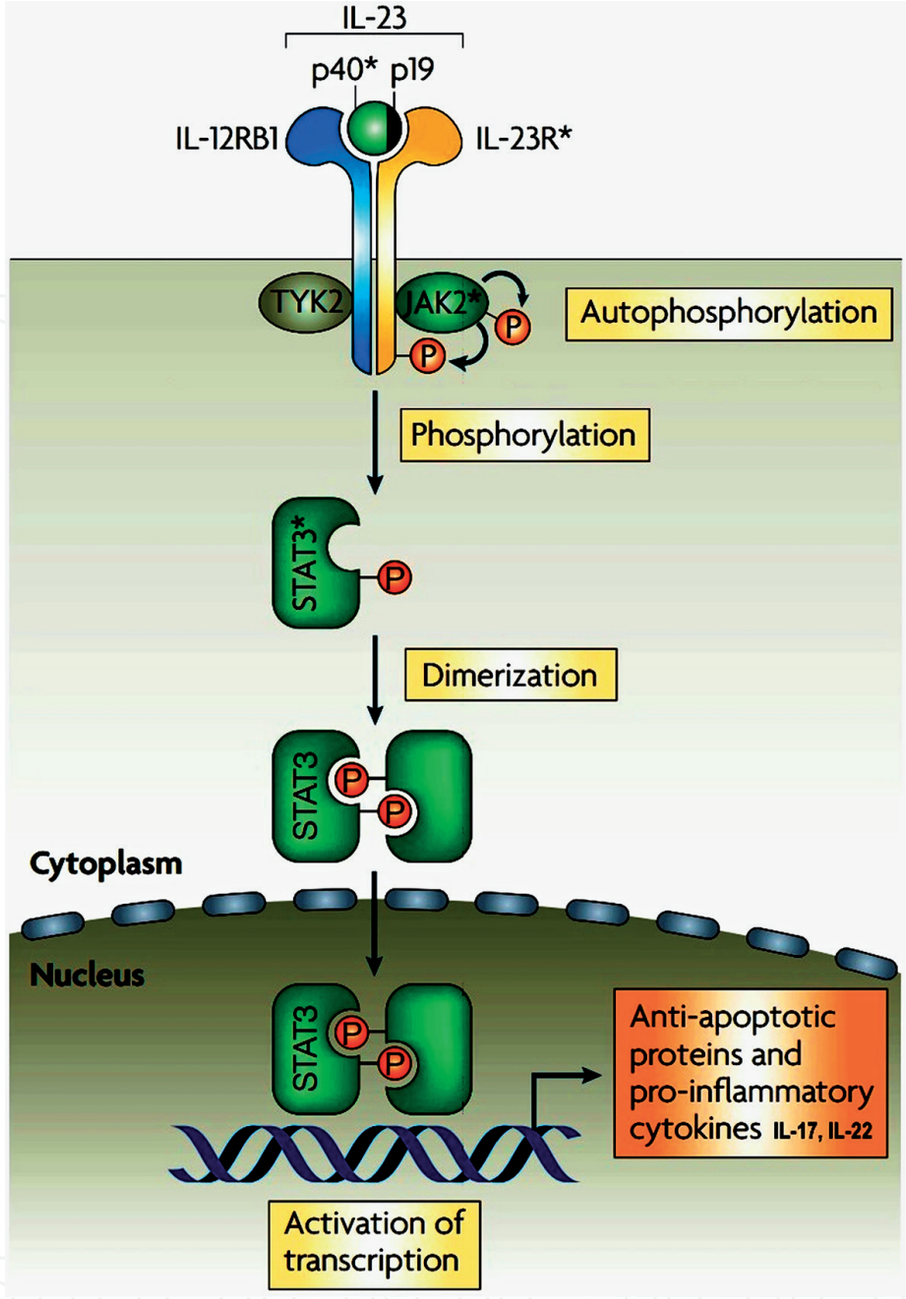

Figure 3.
IL-23 signaling pathway. Functional interleukin-23 receptor (IL-23R) signaling issued from the interaction of a heterodimeric cytokine (formed from p40 and p19 subunits) with a heterodimeric receptor (formed from IL-23R and IL-12RB1 subunits). On engagement of IL-23 with IL-23R, Janus-kinase-2 (JAK2) is activated, resulting in JAK2 autophosphorylation and tyrosine phosphorylation of the receptor. Phospho-STAT3 proteins homodimerize and translocate into the nucleus inducing transcription of anti-apoptotic proteins and cytokines, such as IL-17 and IL-22 [31, 32].

In cancer-related inflammation, malignant cells trigger systemic and local alterations in the tumor microenvironment, enabling them to evade anti-tumor immune response, and contribute to niche creation for tumor progression and metastasis. Of note, the tumor microenvironment is a multicellular system consisted of resident stromal cells (including endothelial cells, fibroblasts, and mesenchymal cells) and tumor-associated myeloid-derived cells aggregated into the extracellular matrix, which closely interact with malignant cells and contribute to tumorigenesis [36].

The tumor-infiltrating myeloid cell is composed of mast cells, TAMs, DCs, T-helper-17 (Th-17), neutrophils, natural killers (NKs), and myeloid-derived suppressors cells. These cells (excluding NKs) are driven to the primary tumor location, to sustain a permanent state of inflammation by producing pro-inflammatory mediators, such as reactive nitrogen radicals, tumor necrosis factor-α, chemokine receptor type-7, vascular endothelial growth factor (VEGF), cyclooxygenase-2 enzyme and hypoxia-inducible factor-1. These agents are shown to generate DNA damage to the tissue cells as well as drive neoplastic transformation [37–42].

IL-23, a proinflammatory cytokine, is a member of the family of heterodimeric cytokines comprising of a unique IL-23p19 subunit covalently bound to a p40 subunit shared with IL-12 [43–45].

IL-23 is synthesized mainly by macrophages and DCs as well as maintains the self-promotion of these phagocytes via IL-23 receptor (IL-23R)-mediated autocrine manner. The core role of IL-23 is to boost the differentiation of naïve $CD4^+$ T-cells and hinder T-helper (Th)-1 and Th-2 differentiation for the generation of T-helper-(Th)-17 cells [10, 46–50]. In an apparent paradox, it has been reported that IL-12 contributes to the anti-tumor immune response by mediating a polarization of the Th-1-cells to secrete interferon-γ and that increases the cytotoxic activity of both NKs and $CD8^+$ T-cells against tumor cells [51, 52].

During carcinogenesis, Th-17 cells, by expressing high amounts of IL-17, are believed to be responsible for increased the production of VEGF from fibroblast and endothelial cells that correlated with stimulating vascular endothelial proliferation, causing the induction of angiogenesis, tumor growth, and metastasis [10, 46, 47, 49].

3. IL-2R gene polymorphisms and cancer

The human IL-23R gene is situated in the short-arm of chromosome-1 [1p31.2 ~32.1] between 67,260,000–67,580,000 base-pairs and separated by 150 kb from the neighboring gene, IL12Rb2 [53]. The native form of the human IL-23R gene has 11 exons. The transcribed mRNA is translated into a protein of 629 amino acids as a constituent part of the receptor transmembrane proteins [43]. Importantly, data shows that single nucleotide polymorphisms (SNPs) in the IL-23R gene (**Figure 4**), especially rs-6682925, rs-1884444, and rs-10889677 have significant impacts on the cancer susceptibility [54].

Based on the NCBI SNP database, it was reported that the rs6682925 T/C variant is correlated with a higher risk of hepatocellular carcinoma [55], esophageal cancer [56] and acute myeloid leukemia [57]. It is attributable to the variant located at the promoter region of IL-23R gene at 907-bp upstream from the transcriptional start position) was linked to increased reporter gene activity [55].

With respect to the rs-1884444 SNP, several case-control studies have examined the association between the variant and the risk of multiple cancers, such as hepatocellular carcinoma [55, 58], esophageal [56, 59, 60], gastric cancer [61] acute myeloid leukemia [57], colorectal cancer [62], colorectal adenoma [62, 63], colon cancer [63], rectal cancer [63], lung cancer [64], nasopharyngeal cancer [64], breast cancer [64, 65], and acute lymphoblastic leukemia [66].

Rs-1884444 "G/T" is a non-synonymous single nucleotide polymorphism (SNP) positioned at the exon-2 in the coding region of the IL-23R gene, that causes the amino acid glutamine (Gln) to be replaced by histidine (His) in the signal-peptide at the extracellular domain of IL-23R, influencing its specificity and affinity to IL-23 [61, 67].

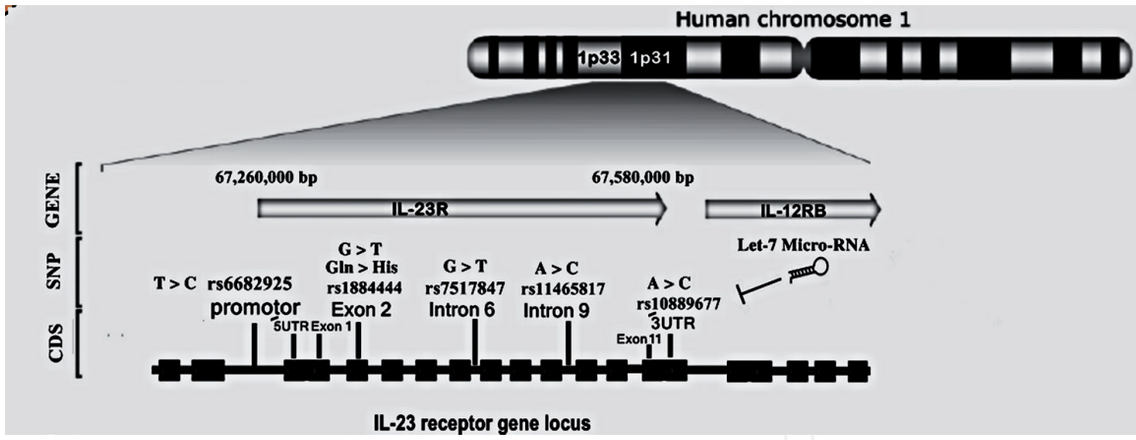

Figure 4.
Schematic diagram of the IL-23 receptor SNPs in cancer. A total of 6 SNPs were genotyped across a 320 kb region and were reported to associate with cancer incidence. Positions and gene boundaries were determined by the NCBI database. Abbreviations; CDS, Coding sequence. SNP, single nucleotide polymorphism.

Previous reports indicated that rs-10889677 "A/C" SNP is correlated with genetic susceptibility to various tumors, such as gastric cancer [68–70], oral cancer [71], colorectal cancer [72], hepatocellular carcinoma [73], bladder cancer [74], breast cancer [65], ovarian cancer [75], lung and nasopharyngeal cancers [64]. That is because the rs-10889677 A/C polymorphism resides in the 3′-untranslated region (3′-UTR) of the IL-23R, results in the substitution of nucleobase adenine (A) by cytosine (C), which could increase the binding affinity of micro-RNA let-7f and, thus, elevated the transcription of the IL-23R gene in vitro and in vivo [64]. Eventually, Zhang and co-workers indicated that higher frequencies of both rs11465817 "A" and rs7517847 "G" alleles were associated with advanced ovarian cancer [75].

4. Impact of IL-23R gene polymorphisms on reshaping tumor micro-environment

By the ligation with the IL-23 receptor (IL-23R), IL-23 exerts its biological activities on the surface of target cells [43–45].

Under cancer-causing inflammation, we embarked to discuss in this chapter the potential relationship between SNPs rs-10889677 "A/C" and rs-1884444 "G/T" in IL-23R and the susceptibility to and progression of cancer.

When proposed bladder cancer (BLC) as a model, Gedamy et al. [76] found that the silent variant rs-10889677 "A/C" has been closely correlated with the development and progression of BLC. This was obvious because people bearing the "C" allele were more susceptible to develop BLC, compared with individuals carrying "A" allele. In addition, they showed a notable increase in the expression levels of IL-23R in the sera of BLC patients as a result of the SNP rs10889677 "A/C" variation.

The possible rationale is that the rs10889677 SNP lies within a predicted binding site for human mi-let-7f [64, 65]. This micro-RNA would therefore lose its binding ability to IL-23R mRNA transcripts bearing the rs10889677C allele, resulting in the up-regulation of IL-23R expression. Amazingly, Gedamy et al. [76] observed a corresponding uptick in serum levels of IL-23 and IL-17 as a logical consequence, highlighting the importance of the rs10889677 "A/C" polymorphism in driving the prolonged activation of IL-23/17 inflammatory axis and thus beefing up the mechanism of inflammation-related carcinogenesis [18, 19, 47, 64, 65].

In the process of carcinogenesis, functional interactions could probably occur between infiltrating TAMs and cancer cells, to create a pathway for augmenting IL-23 and IL-17 production, and ultimately leads to tumor progression and metastases [49, 77, 78]. To generate TAMs during the process of carcinogenesis, IL-23 originated from TAMs requires to act on them via the IL-23R-mediated autocrine way, by which this mechanism of stimulation is largely reliant on the amounts of IL-23R on the surfaces of these cells [24, 26, 43, 79].

In response to the SNP rs-10889677" variation (enhanced by cancer), up-regulation of IL-23 receptor on TAMs surfaces and more cellular auto-activation can be acquired. In this situation, a virtuous loop emerges in which the production of the pro-tumor cytokine IL-23 is increased [24, 26, 43, 79].

Following that, two functional interactions between TAM-expressed IL-23 and other receptor-bearing cells are anticipated to occur (**Figure 5**). First, researchers have

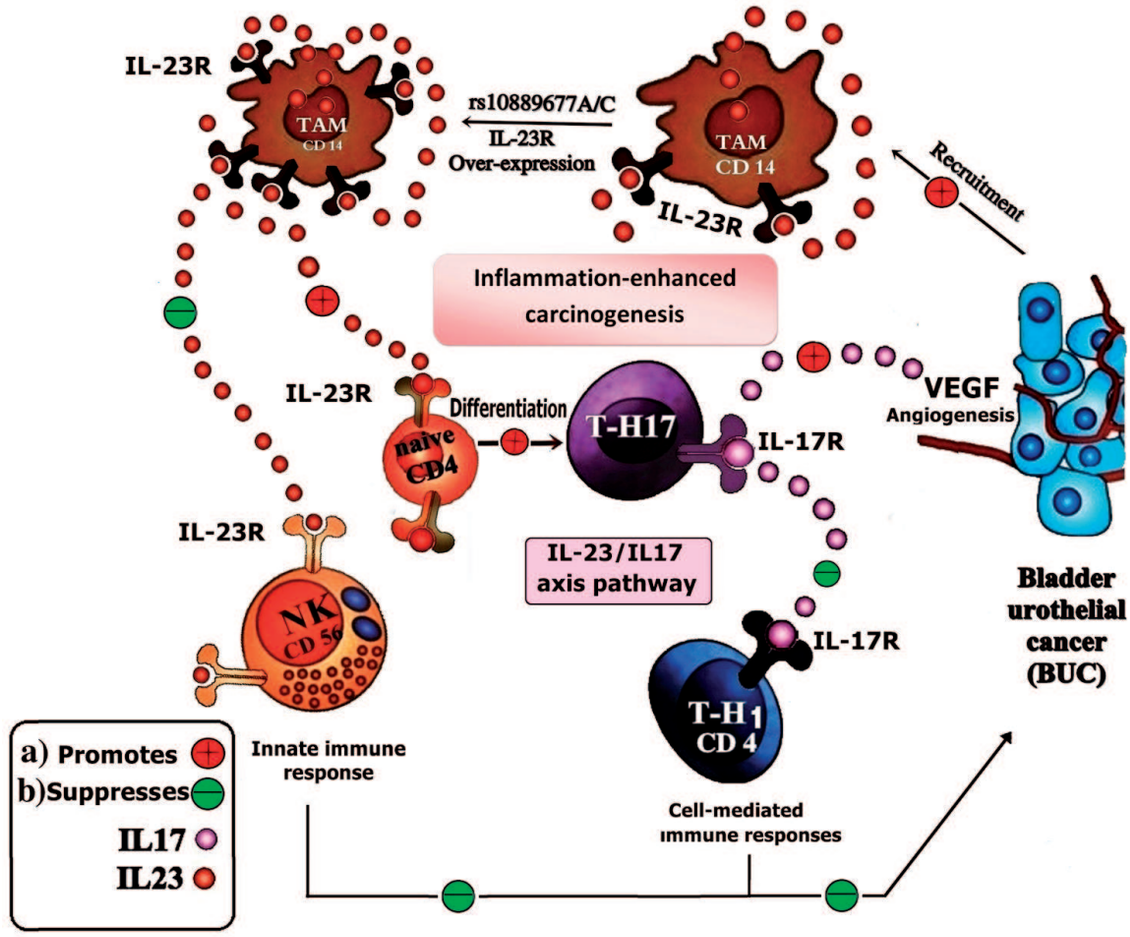

Figure 5.
The schematic diagram depicted the contributor function of IL-23R rs10889677"A/C" in inflammation-induced Bladder urothelial carcinogenesis. First, rs10889677 variant impairs transcription binding sites of microRNA (miR-let-7f) to 3′UTR of the IL-23R-gene, leading to the up-regulation of IL-23R expression on the surfaces of receptor-harboring immune cells including IL-23R-positive NKs, TAMs and $CD4^+$ cells. In the case of IL-23R-positive TAMs, over-expression of IL-23R causes these cells to self-activate (in an autocrine way) and enhance their production of IL-23. Second, binding to the IL-23R complex is required for IL-23 action. After binding to the receptor, IL-23 plays two contradictory roles on the IL-23R-harboring cells and such roles will increase gradually as a result of IL-23R over-expression; A) Promotion role: IL-23 promotes the differentiation and maturation of naïve CD4+ T-cells for the generation of T-helper 17 cells. The following increase in IL-17 thwarts T-helper (Th)-1 and stimulates VEGF synthesis from vascular-endothelial-cells and thus causes the enhancement of angiogenesis and metastasis. B) Suppression role: IL-23 consecutively contributes to inherent innate immuno-suppression by hindering the natural killers (such as CD56+ NK) [76].

observed that the increased amounts of IL-23 in tumor stroma may contribute to the dampening of the NK anti-tumor response by down-regulating IL-12 and IFN-γ, thereby letting tumor cells to escape from immune surveillance [6, 80].

Second, IL-23 is involved in the transformation of naive CD4+ into Th-17 cells, as well as the production of IL-17, a cytokine that mediates promotion of pro-tumor immune response; a body of evidence implies that IL-17 can directly block Th-1 cell differentiation, leading to a reduction in T-cell-mediated responses against cancer cells [81, 82]. In tumor milieu, increased levels of IL-17 also are positively inked to profuse production of a variety of pro-angiogenic factors from the endothelial cells and fibroblasts. Such pro-angiogenic factors, including VEGF, Transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF) mediate the neo-vascularization process requisited by malignant cells for invasion and spread [10, 46, 47, 49, 83, 88].

Briefly, the rs10889677 variant, by up-regulating IL-23 receptors on the surface of TAMs stimulating overproduction of IL-23, governs an indirect pro-tumor role either by maintaining the survival and expansion of Th17-cells for augmenting the expression of IL-17, or suppressing innate (e.g., NKs) and adaptive (e.g., T-helper cells) immune cells [48, 50]. This gradually leads to a pro-tumorigenic induced environment more prone to creating malignancy [10, 29, 30].

As the body's defense against the risk of tumor-associated chronic inflammation, it is biologically reasonable that genetic and epigenetic variations in IL-23R gene that result in altered IL-23R expression, structure, and/or function may play a role against cancer pathogenesis. In support of this perception, two studies observed a close association of a non-synonymous "G/T" SNP in the IL-23R (Gln3His; rs-1884444) with a reduced risk of BLC [89] and hepatocellular carcinoma [55, 58].

Evidences suggest that the protective effect of the rs-1884444 G/T variant might be directly exerted on BLC by dysregulation of the IL-23/IL-17 inflammatory axis, which is evidenced by as a substantial drop in the levels of IL-23 and IL-17 under all tested genetic models. This clearly shows that the non-conservative G/T genetic variation may disrupt the receptor's ligand-binding ability, hence mitigating the proinflammatory effects of the IL-23/IL-17 axis and lessening the process of inflammation-related carcinogenesis [90].

Considering to the rs-1884444 SNP, Gedamy et al [89] unveiled the protective role of "G/T" variant, enhanced by the host's immune surveillance, against the BLC risk. Because the "G/T" variation occurs inside the coding region of the IL-23R gene, potential IL-23 binding sites on the receptor can be altered, causing the receptor to either fail to bind IL-23 or radically diminish binding, and thereby TAMs will be restricted from the production of IL-23 [61, 67]. That would explain the underlying cause for the decline in serum levels of IL-23 and IL-17 accompanied by such non-conservative polymorphism.

As we outlined in **Figure 6**, the interaction between the rs-1884444"G/T" variant and IL-23R is required for exerting a decisive anti-tumor effects on certain cell types bearing IL-23R on their surface, involving either to enhance adaptive (e.g., T-helper cells) and innate immune cells (e.g., NK cells) with anti-tumor influences, or alternatively impede the activation of suppressive immuno-regulatory cells (e.g., TAM). Therefore, It is plausible to believe that this variant exerts its protective activity against cancer risk mainly by disrupting IL-23/IL-23R binding function on the surface of TAMs, resulting in driving abortive activation of these cells.

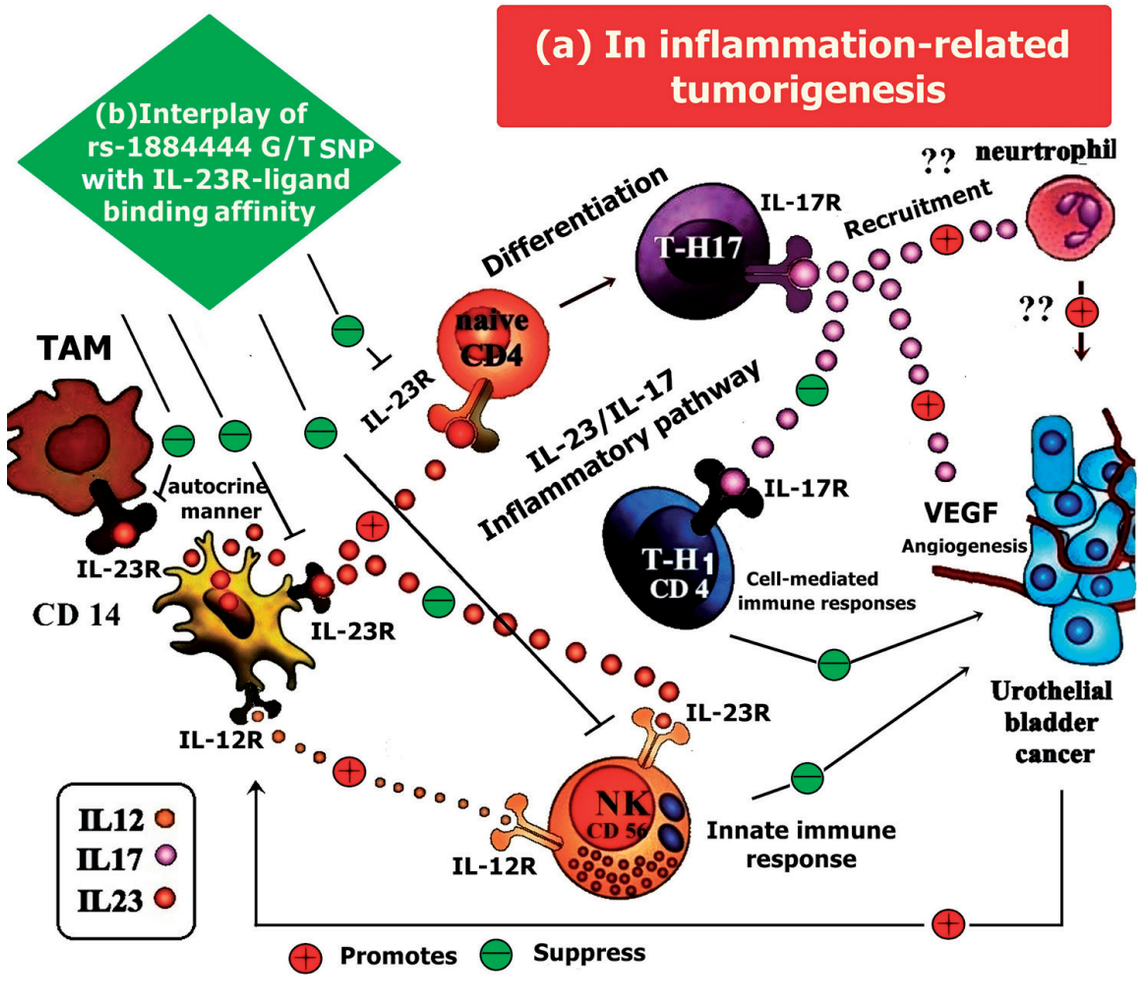

Figure 6.
Schematic diagram depicted the protective function of IL-23R rs-1884444 "G/T" variation against bladder carcinogenesis. (a) In inflammation-related tumorigenesis. Through IL-23R-mediated autocrine manner, an immune response promotes the expression of proinflammatory mediators involving IL-23 from antigen-presenting-cells seduced by cancer, such as tumor-associated monocytes ($CD14^+$ TAMs) and dendritic cells (CD14+). IL-23 function is mediated by binding to the IL-23R complex. After binding to the receptor, IL-23 plays two opposing roles (suppression and promotion) on the IL-23R harboring cells; IL-23 promotes the maturation of naïve CD4+ T-cells for the production of Th-17 cells. The subsequent increase in IL-17 levels impairs T-helper (Th)-1 differentiation (cell-mediated immune response) and induces VEGF synthesis from vascular-endothelial-cells, causing the induction of tumor angiogenesis and metastasis. IL-23 contributes to innate immuno-suppression by limiting the natural killers (such as CD56+ NK) function. (b) Interplay of rs-1884444 "G/T" variant with IL-23R-ligand binding affinity. This non-conservative polymorphism in the IL-23R gene causes glutamine (Gln) to histidine (His) conversion, which modifies the IL-23R-IL-23 binding function on the surface of IL-23R-positive cells. Anti-tumor influence of the G/T variant is attained by attenuating the TAMs-IL-23/TH17-IL17 pro-tumor inflammatory axis and antagonizing the inhibitory role of IL-23 on NKs, thus enhancing the NK anti-tumor activity against tumor cells. Notably, IL-17 induces the flock of neutrophils to the neoplastic tissue, but its role in the process of tumorigenesis is still unclear [89].

The imbalance between the protective mechanism and anti-tumor mechanism plays a critical role in inclining the inflammatory tumor micro-environment towards the protumor profile. Eventually, these insights targeting the IL-23R are fostering new (immune)-therapeutic approaches for cancer treatment.

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References

[1] Yan J, Smyth MJ, Teng MW. Interleukin (IL)-12 and IL-23 and their conflicting roles in cancer. Cold Spring Harbor perspectives in biology. 2018;**10**:a028530

[2] Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;**13**:715-725

[3] Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Communication and Signaling. 2017;**15**:23

[4] Hunter CA. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. Nature Reviews Immunology. 2005;**5**:521-531

[5] Tugues S, Burkhard S, Ohs I, Vrohlings M, Nussbaum K, Vom Berg J, et al. New insights into IL-12-mediated tumor suppression. Cell Death & Differentiation. 2015;**22**:237-246

[6] Teng MWL, Andrews DM, McLaughlin N, von Scheidt B, Ngiow SF, Möller A, et al. IL-23 suppresses innate immune response independently of IL-17A during carcinogenesis and metastasis. Proceedings of the National Academy of Sciences. 2010;**107**:8328-8333

[7] Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, et al. Demonstration of an interferon γ-dependent tumor surveillance system in immunocompetent mice. Proceedings of the National Academy of Sciences. 1998;**95**:7556-7561

[8] Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, et al. Adaptive immunity maintains occult cancer in an equilibrium state. Nature. 2007;**450**:903-907

[9] Smyth MJ, Thia KY, Street SE, Cretney E, Trapani JA, Taniguchi M, et al. Differential tumor surveillance by natural killer (NK) and NKT cells. The Journal of Experimental Medicine. 2000;**191**:661-668

[10] Langowski JL, Zhang X, Wu L, Mattson JD, Chen T, Smith K, et al. IL-23 promotes tumour incidence and growth. Nature. 2006;**442**:461-465

[11] Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. Journal of Clinical Investigation. 2006;**116**:1218-1222

[12] Aggarwal S, Ghilardi N, Xie M-H, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. Journal of Biological Chemistry. 2003;**278**:1910-1914

[13] Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. Journal of Experimental Medicine. 2005;**201**:233-240

[14] Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ. IL-12 and IL-23: Master regulators of innate and adaptive immunity. Immunological Reviews. 2004;**202**:96-105

[15] Monin L, Gaffen SL. Interleukin 17 family cytokines: Signaling mechanisms, biological activities, and therapeutic

implications. Cold Spring Harbor Perspectives in Biology. 2018;**10**:a028522

[16] Patel DD, Kuchroo VK. Th17 cell pathway in human immunity: Lessons from genetics and therapeutic interventions. Immunity. 2015;**43**:1040-1051

[17] Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity. 2004;**21**:467-476

[18] Numasaki M, Fukushi J-i, Ono M, Narula SK, Zavodny PJ, Kudo T, et al. Interleukin-17 promotes angiogenesis and tumor growth. Blood. 2003;**101**:2620-2627

[19] Takahashi H, Numasaki M, Lotze MT, Sasaki H. Interleukin-17 enhances bFGF-, HGF-and VEGF-induced growth of vascular endothelial cells. Immunology Letters. 2005;**98**:189-193

[20] Colombo MP, Trinchieri G. Interleukin-12 in anti-tumor immunity and immunotherapy. Cytokine & Growth Factor Reviews. 2002;**13**:155-168

[21] Cao X, Leonard K, Collins LI, Cai SF, Mayer JC, Payton JE, et al. Interleukin 12 stimulates ifn-γ–mediated inhibition of tumor-induced regulatory T-cell proliferation and enhances tumor clearance. Cancer Research. 2009;**69**:8700-8709

[22] Chan SH, Perussia B, Gupta JW, Kobayashi M, Pospisil M, Young HA, et al. Induction of interferon gamma production by natural killer cell stimulatory factor: Characterization of the responder cells and synergy with other inducers. The Journal of Experimental Medicine. 1991;**173**:869-879

[23] Langowski JL, Kastelein RA, Oft M. Swords into plowshares: IL-23 repurposes tumor immune surveillance. Trends in Immunology. 2007;**28**:207-212

[24] Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. Journal of Immunology. 2002;**168**:5699-5708

[25] Zou J, Presky DH, Wu C-Y, Gubler U. Differential associations between the cytoplasmic regions of the interleukin-12 receptor subunits β1 and β2 and JAK kinases. Journal of Biological Chemistry. 1997;**272**:6073-6077

[26] Belladonna ML, Renauld J-C, Bianchi R, Vacca C, Fallarino F, Orabona C, et al. IL-23 and IL-12 have overlapping, but distinct, effects on murine dendritic cells. The Journal of Immunology. 2002;**168**:5448-5454

[27] Caspi RR, Rachitskaya AV, Horai R, Li Z, Luger D, Villasmil R, et al. NKT cells constitutively express IL-23 receptor and RORγt, and rapidly produce IL-17 upon receptor ligation in an IL-6-independent fashion. FASEB Journal. 2008;**22**:1069.5

[28] Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, et al. IL-12 and IL-23 cytokines: From discovery to targeted therapies for immune-mediated inflammatory diseases. Nature Medicine. 2015;**21**:719-729

[29] Chen Z, Laurence A, O'Shea JJ. Signal transduction pathways and transcriptional regulation in the control of Th17 differentiation. Seminars in Immunology Journal. Academic Press. 2007;**19**:400-408

[30] Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupé P, Barillot E, et al. A critical function for transforming

growth factor-β, interleukin 23 and proinflammatory cytokines in driving and modulating human T H-17 responses. Nature Immunology. 2008;**9**:650

[31] Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. Nature Reviews Immunology. 2008;**8**:458-466

[32] Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 Axis in the Immunopathogenesis of Psoriasis. Journal of Investigative Dermatology. 2009;**129**:1339-1350

[33] Watford WT, Hissong BD, Bream JH, Kanno Y, Muul L, O'Shea JJ. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunological Reviews. 2004;**202**:139-156

[34] Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity. 2007;**26**:371-381

[35] Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, et al. IL-6 programs TH-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nature Immunology. 2007;**8**:967-974

[36] Horimoto Y, Polanska UM, Takahashi Y, Orimo A. Emerging roles of the tumor-associated stroma in promoting tumor metastasis. Cell Adhesion and Migration. 2012;**6**:193-202

[37] Balkwill F, Mantovani A. Inflammation and cancer: Back to Virchow? The Lancet. 2001;**357**(9255): 539-545

[38] Lin C, Lin W, Yeh S, Li L, Chang C. Infiltrating neutrophils increase bladder cancer cell invasion via modulation of androgen receptor (AR)/MMP13 signals. Oncotarget. 2015;**6**:43081-43089

[39] Nesi G, Nobili S, Cai T, Caini S, Santi R. Chronic inflammation in urothelial bladder cancer. Virchows Archiv. 2015;**467**:623-633

[40] Sui X, Lei L, Chen L, Xie T, Li X. Inflammatory microenvironment in the initiation and progression of bladder cancer. Oncotarget Oncotarget. 2017;**8**:93279-93294

[41] Williams CB, Yeh ES, Soloff AC. Tumor-associated macrophages: Unwitting accomplices in breast cancer malignancy. Npj Breast Cancer. 2016;**2**:15025

[42] Zhu Z, Shen Z, Xu C. Inflammatory pathways as promising targets to increase chemotherapy response in bladder cancer. Mediators Inflamm. 2012;**2012**:528690-528690

[43] Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R. The Journal of Immunology. 2002;**168**:5699

[44] Sun L, He C, Nair L, Yeung J, Egwuagu CE. Interleukin 12 (IL-12) family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease. Cytokine. 2015;**75**:249-255

[45] Vignali DA, Kuchroo VK. IL-12 family cytokines: Immunological playmakers. Nature Immunology. 2012;**13**:722-728

[46] Crew J, O'Brien T, Bradburn M, Fuggle S, Bicknell R, Cranston D, et al. Vascular endothelial growth factor is a predictor of relapse and stage progression in superficial bladder. Cancer Research Journal. 1997;**57**:5281-5285

[47] Martin-Orozco N, Dong C. The IL-17/IL-23 axis of inflammation in cancer: Friend or foe? Current Opinion in Investigational Drugs. 2009;**10**:543-549

[48] Moschen AR, Tilg H, Raine T. IL-12, IL-23 and IL-17 in IBD: Immunobiology and therapeutic targeting. Nature Reviews. Gastroenterology & hepatology. 2019;**16**:185-196

[49] Murugaiyan G, Saha B. Protumor vs antitumor functions of IL-17. The Journal of Immunology. 2009;**183**:4169

[50] Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity. 2006;**24**:179-189

[51] Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nature Reviews Immunology. 2003;**3**:133

[52] Watford WT, Moriguchi M, Morinobu A, Oshea JJ. The biology of IL-12: Coordinating innate and adaptive immune responses. CGFR. Cytokine and Growth Factor Reviews. 2003;**14**:361-368

[53] Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science Journal. 2006;**314**(5804):1461-1463

[54] Yao J, Liu L, Yang M. Interleukin-23 receptor genetic variants contribute to susceptibility of multiple cancers. Gene. 2014;**533**:21-25

[55] Xu Y, Liu Y, Pan S, Liu L, Liu J, Zhai X, et al. IL-23R polymorphisms, HBV infection, and risk of hepatocellular carcinoma in a high-risk Chinese population. Journal of Gastroenterology. 2013;**48**:125-131

[56] Chu H, Cao W, Chen W, Pan S, Xiao Y, Liu Y, et al. Potentially functional polymorphisms in IL-23 receptor and risk of esophageal cancer in a Chinese population. International Journal of Cancer. 2012;**130**:1093-1097

[57] Qian X, Cao S, Yang G, Pan Y, Yin C, Chen X, et al. Potentially functional polymorphism in IL-23 receptor and risk of acute myeloid leukemia in a Chinese population. PloS One. 2013;**8**:e55473

[58] Peng Q, Qin Y, Chen Z, Deng Y, Xu J, Li S, et al. Correlation between interleukin23 receptor gene polymorphisms and risk of hepatitis B virus infection in patients. Molecular Medicine Reports. 2013;**8**:613-620

[59] Li M, Yue C, Jin G, Guo H, Ma H, Wang G, et al. Rs1884444 variant in IL23R gene is associated with a decreased risk in esophageal cancer in Chinese population. Molecular Carcinogenesis. 2019;**58**:1822-1831

[60] Ni B, Chen S, Xie H, Ma H. Functional polymorphisms in interleukin-23 receptor and susceptibility to esophageal squamous cell carcinoma in Chinese population. PLoS One. 2014;**9**:e89111-e89111

[61] Chen J, Lu Y, Zhang H, Ding Y, Ren C, Hua Z, et al. A nonsynonymous polymorphism in IL23R gene is associated with risk of gastric cancer in a Chinese population. Molecular Carcinogenesis. 2010;**49**:862-868

[62] Li B, Gan A, Zhang X, Huang W, Yu Z, Chen X. Application of high resolution melting assay to explore the correlation between the single nucleotide polymorphisms of IL-23/IL-17 gene and colorectal cancer.

New England Journal of Medicine. 2016;**47**:661-665

[63] Poole EM, Curtin K, Hsu L, Duggan DJ, Makar KW, Xiao L, et al. Genetic variability in IL23R and risk of colorectal adenoma and colorectal cancer. Cancer Epidemiology. 2012;**36**:e104-e110

[64] Zheng J, Jiang L, Zhang L, Yang L, Deng J, You Y, et al. Functional genetic variations in the IL-23 receptor gene are associated with risk of breast, lung and nasopharyngeal cancer in Chinese populations. Carcinogenesis. 2012;**33**:2409-2416

[65] Wang L, Liu W, Jiang W, Lin J, Jiang Y, Li B, et al. A miRNA binding site single-nucleotide polymorphism in the 3'-UTR region of the IL23R gene is associated with breast cancer. PLoS One. 2012;**7**:e49823

[66] Zareinejad M, Samiei A, Valibeigi B, Gholami T, Zareifar S, Amirghofran Z. Interleukin-23 receptor gene variants in acute lymphoblastic leukemia and their relation to prognostic factors. Iranian Journal of Immunology. 2017;**14**:59-72

[67] Kan SH, Mancini G, Gallagher G. Identification and characterization of multiple splice forms of the human interleukin-23 receptor alpha chain in mitogen-activated leukocytes. Genes and Immunity. 2008;**9**:631-639

[68] Chen B, Zeng Z, Xu L, Wu X, Yu J, Xue L, et al. IL23R +2199A/C polymorphism is associated with decreased risk of certain subtypes of gastric cancer in Chinese: A case-control study. Cancer Epidemiology. 2011;**35**:165-169

[69] Dong K, Xu Y, Yang Q, Shi J, Jiang J, Chen Y, et al. Associations of functional MicroRNA binding site polymorphisms in IL23/Th17 inflammatory pathway genes with gastric cancer risk. Mediators of Inflammation. 2017;**2017**:6974696

[70] Jia Z-F, Cao D-H, Wu Y-H, Jin M-S, Pan Y-C, Cao X-Y, et al. Lethal-7-related polymorphisms are associated with susceptibility to and prognosis of gastric cancer. World Journal of Gastroenterology. 2019;**25**:1012

[71] Chien MH, Hsin CH, Chou LS, Chung TT, Lin CH, Weng MS, et al. Interleukin-23 receptor polymorphism as a risk factor for oral cancer susceptibility. Head Neck. 2012;**34**:551-556

[72] Mosallaei M, Simonian M, Esmaeilzadeh E, Bagheri H, Miraghajani M, Salehi AR, et al. Single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene is a strong colorectal cancer determinant: Report and meta-analysis. Cancer Genetics. 2019;**239**:46-53

[73] Peng Q, Qin Y, Chen Z, Deng Y, Xu J, Li S, et al. Correlation between interleukin-23 receptor gene polymorphisms and risk of hepatitis B virus infection in patients. Molecular Medicine Reports. 2013;**8**:613-620

[74] Tang T, Xue H, Cui S, Gong Z, Fei Z, Cheng S, et al. Association of interleukin-23 receptor gene polymorphisms with risk of bladder cancer in Chinese. Fam Cancer. 2014;**13**:619-623

[75] Zhang Z, Zhou B, Zhang J, Chen Y, Lai T, Yan L, et al. Association of interleukin-23 receptor gene polymorphisms with risk of ovarian cancer. Cancer Genetics and Cytogenetics. 2010;**196**:146-152

[76] El-Gedamy M, El-khayat Z, Abol-Enein H, El-said A, El-Nahrery E. Rs-10889677 variant in interleukin-23 receptor may contribute to creating an inflammatory milieu more susceptible to bladder tumourigenesis: Report and meta-analysis. Immunogenetics Journal. 2021;**73**:207-226

[77] Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, et al. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell Journal. 2009;**15**(2):114-123

[78] Schön MP, Erpenbeck L. The interleukin-23/interleukin-17 axis links adaptive and innate immunity in psoriasis. Frontiers in Immunology Journal. 2018;**9**:1323

[79] Grohmann U, Bianchi R, Belladonna ML, Vacca C, Silla S, Ayroldi E, et al. IL-12 acts selectively on CD8α– dendritic cells to enhance presentation of a tumor peptide in vivo. The Journal of Immunology. 1999;**163**(6):3100-3105

[80] Konjević GM, Vuletić AM, Martinović KMM, Larsen AK, Jurišić VB. The role of cytokines in the regulation of NK cells in the tumor environment. Cytokine Journal. 2019;**117**:30-40

[81] Nakae S, Iwakura Y, Suto H, Galli SJ. Phenotypic differences between Th1 and Th17 cells and negative regulation of Th1 cell differentiation by IL-17. Journal of Leukocyte Biology. 2007;**81**(5):1258-1268

[82] O'Connor W Jr, Kamanaka M, Booth CJ, Town T, Nakae S, Iwakura Y, et al. A protective function for interleukin 17A in T cell–mediated intestinal inflammation. Nature Immunology Journal. 2009;**10**(6):603-609

[83] Kryczek I, Wei S, Zou L, Altuwaijri S, Szeliga W, Kolls J, et al. Cutting edge: Th17 and regulatory T cell dynamics and the regulation by IL-2 in the tumor microenvironment. The Journal of Immunology. 2007;**178**(11):6730-6733

[84] Chen X, Wan J, Liu J, Xie W, Diao X, Xu J, et al. Increased IL-17-producing cells correlate with poor survival and lymphangiogenesis in NSCLC patients. Lung Cancer Journal. 2010;**69**(3):348-354

[85] Chi LJ, Lu HT, Li GL, Wang XM, Su Y, Xu WH, et al. Involvement of T helper type 17 and regulatory T cell activity in tumour immunology of bladder carcinoma. Clinical & Experimental Immunology Journal. 2010;**161**(3):480-489

[86] Iida T, Iwahashi M, Katsuda M, Ishida K, Nakamori M, Nakamura M, et al. Tumor-infiltrating CD4+ Th17 cells produce IL-17 in tumor microenvironment and promote tumor progression in human gastric cancer. Oncology Reports Journal. 2011;**25**(5):1271-1277

[87] Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. Mediators of Inflammation Journal. 2014:623759

[88] Miyashita M, Sasano H, Tamaki K, Hirakawa H, Takahashi Y, Nakagawa, et al. Prognostic significance of tumor-infiltrating CD8+ and FOXP3+ lymphocytes in residual tumors and alterations in these parameters after neoadjuvant chemotherapy in triple-negative breast cancer: A retrospective multicenter study. Breast Cancer Research journal. 2015;**17**(1):1-13

[89] El-Gedamy M, El-Khayat Z, Abol-Enein H, El-Said A, El-Nahrery E. Rs-1884444 G/T variant in IL-23 receptor is likely to modify risk of bladder urothelial carcinoma by regulating IL-23/IL-17 inflammatory pathway. Cytokine. 2021;**138**:155355

[90] Akbay EA, Koyama S, Liu Y, Dries R, Bufe LE, Silkes M, et al. Interleukin-17A promotes lung tumor progression through neutrophil attraction to tumor sites and mediating resistance to PD-1 blockade. Journal of Thoracic Oncology. 2017;**12**:1268-1279