REVIEW

Interleukin-18: a regulator of cancer and autoimmune diseases

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Accepted for publication October 23, 2017

To cite this article: Esmailbeig M, Ghaderi A. Interleukin-18: a regulator of cancer and autoimmune diseases. *Eur. Cytokine Netw.* 2017; 28(4): 127-40 doi:10.1684/ecn.2018.0401

ABSTRACT. Interleukin (IL)-18, structurally similar to IL-1β, is a member of IL-1 superfamily of cytokines. This cytokine, which is expressed by many human lymphoid and nonlymphoid cells, has an important role in inflammatory processes. The main function of IL-18 is mediated through induction of interferon-γ (IFN-γ) secretion from T helper (Th1) cells. This cytokine synergistically with IL-12 contributes to Th1 differentiation and, therefore, is important in host defense mechanisms against intracellular bacteria, viruses, and fungi. Recent evidences showing the involvement of IL-18 in Th2 differentiation and ultimately IgE production from B cells have shed a new insight on the dual effects of IL-18 on Th1 and Th2 inflammatory responses. IL-18 in combination with IL-12 can activate cytotoxic T cells (CTLs), as well as natural killer (NK) cells, to produce IFN-γ and, therefore, may contribute to tumor immunity. The biological activity of IL-18 is not limited to these cells, but it also plays a role in development of Th17 cell responses. IL-18 synergistically with IL-23 can induce IL-17 secretion from Th17 cells. The diverse biological activity of IL-18 on T-cell subsets and other immune cells has made this cytokine a good target for investigating its role in various inflammatory-based diseases. Lately, the discovery of IL-18 binding protein (IL-18BP), a physiological inhibitor of IL-18 and a hallmark of IL-18 biology, made this cytokine an attractive target for studying its pros and cons in the treatment of various diseases. In recent years, the biology, genetics, and pathological role of IL-18 have been studied in a number of diseases. In this article, we aimed to present an updated review on these aspects regarding the contribution of IL-18 to important diseases such as cancer, autoimmunity, and inflammatory-mediated conditions including allergic diseases, metabolic syndrome, and atherosclerosis. Emerging data indicating prognostic, diagnostic, and therapeutic features of IL-18 and its related molecules will also be discussed.

Key words: IL-18, cancer, autoimmunity

Interleukin (IL)-18, previously known as "Interferon gamma (IFN-γ) inducing factor," was in 1989 initially purified from serum and liver of mice following sequential administration of *Propionibacterium acnes* [1]. At first, it was thought that this purified cytokine was IL-12; however, by molecular cloning, it was found to be a different cytokine and called as IL-18 [1]. This cytokine was resembled to IL-1β, and thus became a member of IL-1 superfamily of cytokines. Both IL-1β and IL-18 are synthesized as inactive 24-kDa precursors without any secretory sequences and are activated after cleavage by IL-β-converting enzyme (ICE, caspase 1) [2]. Regardless of structural similarities of IL-18 and IL-1β, there are several specific differences between these cytokines. For example, unlike IL-1β, IL-18 is expressed in healthy human blood monocytes, as well as in epithelial cells [3].

IL-18 is a single peptide chain, and almost all healthy human cells including blood macrophages, keratinocytes, osteoblasts, and endothelial cells express this cytokine as an inactive precursor. IL-18 mRNA is expressed in all epithelial cells of the human body; however, dendritic cells and macrophages are the primary sources of active IL-18 [3]. IL-18 receptor (IL-18R) is expressed on a wide range of cells such as T cells, natural killer (NK) cells, peripheral B cells, macrophages, and even nonimmune cells such as endothelial cells, epithelial cells, and fibroblasts [3, 4]. This receptor is composed of a binding subunit (IL-18Rα), which is an orphan receptor, and a signaling subunit, with both belonging to the IL-1R family. Once IL-18 is released, signaling is primarily started by binding to IL-18Rα, which is expressed in all cells; however, it results in a low-affinity binding. The coreceptor IL-18Rβ, existing only in T cells and dendritic cells, causes a high-affinity complex, which is required for initiation of signaling [4]. These receptors have a Toll-IL-1R (TIR) domain in their intracellular portion. Because of formation of the signaling complex, the TIR domain approximates and interacts with MyD88, resulting in phosphorylation of the IL-R-associated kinase (IRAK). Thereafter, IRAK is detached from the complex, and its interaction with tumor necrosis factor (TNF)-associated factor (TRAF)-6 leads to degradation of inhibitory κB kinase (IkB) and release of transcription factor nuclear factor, (NF)κB; therefore,

doi: 10.1684/ecn.2018.0401

proinflammatory signal is created [5]. In the absence of IL-18Rβ, there would be no inflammatory signal, unless with the presence of IL-12, which can induce IL-18Rβ expression [4]. IL-18 and IL-12 together synergize the secretion of IFN-γ from Th1 cells. IL-18 upregulates the expression of IL-12Rβ, and IL-12 enhances the role of IL-18Rβ on Th1 cells. The role of IL-18Rα should not be ignored because Th1 cells from IL-18Rα-/- mice cannot bind IL-18 and fail to activate NFκB [6, 7].

THE BIOLOGIC FUNCTION OF IL-18

The significant biologic role of IL-18 in inflammatory processes is due to its capability of inducing IFN-γ production from T, B, and NK cells. IL-12 and IL-18 transduction synergistically leads to the production of IFN-γ. The presence of IL-12 or IL-15 is necessary, beside IL-18, for Th1 differentiation and IFN-γ production [8]. Th1 cells are pivotal in the defense and protection against intracellular microbial infections. Thus, IL-18 synergistically with IL-12 contributes to the defense against microbes by activation of macrophages and by the release of antimicrobial agents such as nitric oxide (NO). The role of IL-18 is not limited to IFN-γ production and Th1-mediated responses. IL-18 without the presence of IL-12 induces the production of Th2-related cytokines [9]. Naïve $CD4^+$ T cells express a low level of IL-18Rα and, in the presence of IL-18 and IL-2 even without antigen stimulation, show modest secretion levels of IL-4 [10]. In the presence of antigen, the IL-4 levels of production are strongly increased. In addition, it has been shown that mast cells and basophils from the bone marrow express IL-18Rα. In addition, in response to IL-18 and IL-13, they release high levels of IL-4 and IL-13, which in turn can elevate IgE production [11]. Due to the importance of mast cells and basophils and related cytokines that are key elements of type I hypersensitivity, IL-18 might be important in triggering allergic inflammation.

Several studies on IL-12p40 and IL-18 knockout mice have shown that IL-18 has a role in the development of Th17 cell responses. IL-18 in combination with IL-23 has the capacity to activate and increase IL-17 secretion from Th17 cells independent of T-cell receptor (TCR) [12]. These data demonstrated that IL-18 has an important role in host defense against infections and enhances innate immunity, as well as both Th1- and Th2-induced responses. The diverse biological functions of IL-18 on T-cell subsets and other immune cells imply that IL-18 immune stimulatory function markedly depends on the milieu in which IL-18 is present [8].

IL-18 in synergy with IL-12 can also act on cytotoxic T cells (CTLs), as well as NK cells, and activate these cells to produce IFN-γ [13]. The evidence for NK cells came from studies in which IL-18- or IL-18Rα-deficient mice have shown low levels of NK activity. CTLs and NK cells have a critical role in elimination of viruses, which suggests the important role of IL-18 in protection against viral infections [8]. The immunostimulatory characteristics of IL-18 on Th1, CTLs, and NK cells may also suggest this cytokine as a tumor-suppressing cytokine. However, the role of IL-18 in cancer immunity is controversial and will be discussed in the forthcoming paragraphs.

IL-18 exhibits some features of other proinflammatory cytokines, for instance increasing cell adhesion molecules, chemokine production, and NO synthesis. It can induce synovial fibroblasts to produce various cytokines such as TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as CXC chemokines and NO. IL-18 can also induce angiogenesis and augment neutrophil chemotaxis and recruitment of white blood cells by enhancing vascular cell adhesion molecule (VCAM)-1 expression on endothelial cells [14].

IL-18 BINDING PROTEIN

The free levels of IL-18 are regulated by the balance of IL-18 and IL-18 binding protein (IL-18BP). IL-18BP, which is widely used in studies and trials, is an inhibitor of IL-18 and blocks binding of IL-18 to IL-18R. This protein is a member of the immunoglobulin superfamily (IgSF) and is constitutively expressed in various human tissues, especially spleen and gastrointestinal tract [15]. During inflammatory processes, IFN-γ produced by the stimulation of IL-18 induces IL-18BP production; therefore, IL-18-mediated production of IFN-γ is decreased through a negative feedback mechanism [16]. This mechanism would help to decrease development of autoimmunity during infections. In some diseases, imbalance between IL-18 and IL-18BP can lead to an increase in IL-18 levels in blood, which in turn may result in more activation of T cells and consequently make diseases more severe or cause tissue damages. Because IL-18 influences other T-cell subsets such as Th2 cells, IL-18BP may also be involved in controlling the Th2 responses [4].

IL-18 AND CANCER

The role of IL-18 in the immune system and host defense brought up the possibility of this protein's role in tumoral processes. Many studies and clinical trials were designed to investigate not only the antitumoral activity of IL-18 but also the possibility and efficacy of using it for therapeutic purposes. In addition, evaluating the association of different polymorphisms of IL-18 gene with different neoplastic conditions has become a point of interest.

Studies have revealed a dual effect of IL-18 on tumoral cells, and it has been explained as a double-edge sword [17]. The role of IL-18 in developing immune responses, which are mostly mediated by IFN-γ production, suggests that IL-18 has antitumoral effects. Tumor regression following administration of IL-18 in animal models of cancer suggests antitumoral properties of this cytokine. On the other hand, high serum levels of IL-18 in some cancers and cancer-associated polymorphisms seem to be a clue to its protumoral effects. This cytokine promotes cancer cells to escape from the immune system by suppressing CD70. In addition, metastasis can be facilitated by IL-18 through upregulation of VEGF and CD44 [18]. The ability of IL-18 to enhance angiogenesis can be involved in tumor progression and metastasis as well. Complexity of the human immune system and the role of IL-18 in immune modulation have led to duality in the role of IL-18 in cancer studies. We are aiming to review some of these studies in the forthcoming paragraphs.

IL-18 IN GASTRIC CANCER

Helicobacter pylori (H. pylori) infection is known as a risk factor for developing chronic gastritis, peptic ulcer diseases, and gastric cancer. In 2017, Tran and colleagues reviewed recent findings on the role of IL-1β and IL-18 in H. pylori-induced inflammation, which can lead to cancer. These two important cytokines have counterbalancing effect on H. pylori-mediated diseases. While IL-1β accelerates inflammation toward chronic gastritis and epithelial hyperplasia, IL-18 limits the process of gastritis [19]. Confirming this issue, it was shown that IL-18-/- mice had a reduced colonization of H. pylori but enhanced production of IL-17, which led to rapid gastric immunopathologies and finally cancer [20]. On the other hand, IL-1R-/- mice showed a reduction in IFN-γ and Th17-mediated responses, which protect the mice against gastritis and the cancer that follows [21]. These studies assent to the protective role of IL-18 in early stages of H. pylori-induced gastric cancer.

In contrast, there are several studies suggesting protumoral effects of IL-18 in progression of gastric cancer in advanced stages. Higher serum levels of IL-18 have been detected in patients with gastric cancer and can be used as a diagnostic marker. However, no correlation was found between serum levels of IL-18 and cancer survival or prognosis [22-24]. In a study conducted in 2006 by Kim *et al.*, administration of IL-18 increased thrombospondin (TSP)-1 mRNA expression and TSP-1 production. TSP-1 stimulates angiogenesis in patients with gastric cancer, which can be a mechanism of tumor progression [25].

Studying the possible mechanisms responsible for protumoral effects of IL-18, Kang and coworkers showed that gastric cancer cells may escape immune system via reducing the surface expression of CD70 induced by endogenous IL-18. CD70 is a costimulatory molecule of TNF family. Its ligand CD27 exists on T and natural killer (NK) cells. Neutralization of endogenous IL-18 by IL-18BP increased CD70 on tumor cell surfaces, which resulted in immune susceptibility of gastric cancer cells to NK and T cells. In addition, upregulation of CD44 and vascular endothelial growth factor (VEGF) triggered by IL-18 increased the possibility of distant metastasis. CD44 has a key role in local invasion and metastasis of tumor cells and is increased in serum of patients suffering malignancies. Reduced expression of CD44 and production of VEGF by gastric cell lines after neutralization of endogenous IL-18 by IL-18BP are suggestive of the possible effects of IL-18 in gastric cancer progression [26].

IL-18 AND COLORECTAL CANCER

Existing evidence suggest a protective role for IL-18 against colorectal adenocarcinomas. Pages and colleagues showed that IL-18 is produced by normal colon epithelia; however, after neoplastic transformation of mucosal cells, colon cancer cells were not able to produce IL-18. It was shown that these cells could not process pro-IL-18; this led to decreased levels of activated IL-18 and consequently diminished IFN-γ and Fas-L transcription in a number of cases. It was concluded that absence of IL-18 in colon cancer may impair IFN-γ and Fas-L-mediated immune responses, which proceeds tumor growth and escape from immune system [27]. Decreased expression of IL-18 in colon cancer in other studies and increased colitis, polyp formation, and colorectal cancer in IL-18-/- mice suggest antitumoral activity of IL-18 in colorectal malignancies [28, 29].

Confirming antitumoral effects of IL-18, Zaki *et al.* showed that Nlrp3 inflammasome-dependent production of IL-18 possibly has a protective role against colorectal adenocarcinomas through IFN-γ production and STAT1 (signal transducer and activator of transcription 1) signaling [30].

Vanachola and colleagues investigated hepatic metastasis of colorectal adenocarcinomas and showed that these cancer cells can induce nonimmune host cell production of IL-18, which can be an indicator of tumor progression and metastasis. They revealed that IL-18 gene expression level was significantly increased in unaffected hepatic tissue surrounding colon adenocarcinoma metastasis compared to normal liver tissue and tumor samples obtained from metastasis [14].

IL-18 AND MELANOMA

Antitumoral activity of IL-18 in melanoma was described in some studies by tumor suppression after administration of IL-18. In a study, oncolytic adenovirus was armed by IL-18 (ZD55-IL-18), and it was added to dacarbazine to treat melanoma cells or nude mouse tumor xenografts. It was demonstrated that ZD55-IL-18 boosted the cytotoxic activity of dacarbazine and induced apoptosis in cancer cells. IL-18 also reduced vascular endothelial growth factor (VEGF) production in melanoma tumor cells and diminished lung metastasis in xenografts of nude mice [31].

Inhibition of angiogenesis is an important antitumoral mechanism illustrated for IL-18 in different studies [32]. Development of antitumor response mostly mediated by antiangiogenic activity after transformation of IL-18 gene to B16F10 melanoma cells is an example of this antitumoral mechanism [33]. Moreover, nonvirulent Salmonella typhimurium engineered to synthesize IL-18 diminished development of primary melanoma and pulmonary metastases in mice [34].

Administration of IL-18 in combination with α-galactosylceramide in mice with melanoma and pulmonary metastasis of melanoma suppressed the number of metastatic foci in lung. Antitumoral response in this experiment was suggested to be due to direct stimulation of NK cells by IL-18, which synergized indirect stimulation of these cells by α-galactosylceramide [35].

Miller *et al.* in 2012 showed that injection of IL-12, IL-15, and IL-18 preactivated NK cells to mice combined with radiation can reduce growth of established tumors in mice [36].

In the study of ChoiIk *et al.*, an oncolytic adenovirus coexpressing IL-18 and IL-12 was administered in intratumoral murine melanoma. Antitumoral effects and cytotoxicity of immune cells were enhanced as a result of synergistic effect of IL-12 on lFN-γ and Th1-mediated responses induced by IL-18 [37].

Another study on B16F10 melanoma cells in 2011 showed that administration of IL-18 in different schedules can cause different biologic effects. As demonstrated in this study, B16F10 metastases were increased by administration of IL-18 twice a week, but daily administration of

IL-18 revealed antitumoral activity. This study showed that endogenous IL-18 accelerated metastatic dissemination by increasing adhesion of melanoma cells to sinusoidal epithelium. In addition, the protumoral mechanism described in this study was through IL-18-mediated upregulation of programmed cell death (PD)-1 expression by activated, mature NK cells in lymphoid organs and consequently reduced NK cell antimetastatic activity in a PD-1-dependent mode [38].

In the study by Carascal *et al.*, administration of IL-18BP in mice with B16 melanoma decreased the number of hepatic metastatic foci by 75% and metastatic volume by 80%. High levels of IL-18 in metastatic melanoma promote tumor progression and metastasis by different mechanisms, which are inhibited by exogenous IL-18BP. According to these results and other similar reports, IL-18BP was suggested as a suitable target for immunotherapy of melanoma [39].

IL-18 AND HEPATOCELLULAR CARCINOMA (HCC)

Asakawa in 2006 investigated the role of IL-18 and IL-18R in hepatitis C virus (HCV)-associated HCC. It was shown that patients with IL-18R expression had worse outcome in comparison to patients negative for IL-18R. Accordingly, expression of IL-18R on tumor cells was suggested as an important factor for poor prognostic outcome, which may be related to IL-18-induced antiapoptotic mechanisms involving NF-κB activation in HCC cells [40].

Furthermore, IL-18 has been introduced as a marker of HCV-induced hepatocellular carcinoma complementary to α-fetoprotein (AFP), because both are significantly increased in patients with HCC compared to the control group [41].

IL-18 IN OVARIAN CANCER

Different regulatory mechanisms are suggested to be responsible for the effects of IL-18 in the cell microenvironment of normal and cancerous ovarian cells. In study of Wang and colleagues in 2002 on ovarian cancer, losing the ability of activating pro-IL-18 during neoplastic transformation was proposed as a mechanism of tumor cells escaping from Th1/IFN-γ mediated responses [42]. In another study performed in 2014 by Medina and colleagues on ovarian cancer, precancerous effects of IL-18 were observed [43]. They revealed that IL-18 and IL-18BP were both expressed in normal and cancerous ovarian epithelial cells. However, IL-18 was elevated in the sera of patients with cancer, whereas IL-18BP production was significantly higher in normal ovarian tissues. In addition, IL18/IL-18 BP ratio as an indicator of actual IL-18 activity was higher in cancerous tissues, showing that in carcinomatous epithelial ovarian cells, the higher level of IL-18 is not counteracted by a similarly higher level of IL-18BP compared to normal epithelial ovarian cells. This study highlighted the significance of IL-18BP regulation mechanism in ovarian carcinoma progression and suggested that the intracellular and local concentrations of IL-18 and IL-18BP determine the biological effects of IL-18 in physiological and pathophysiological contexts [43].

As outlined previously, the precise antitumoral versus protumoral impacts of IL-18 on development of cancer are unclear and varied among different tumors. Therefore, the importance of this single molecule in cancer complexity is on debate. Some studies suggest inhibitory effects of IL-18 on neoplastic conditions following administration of IL-18. Moreover, advanced antitumoral effects of chemotherapeutic agents after adding IL-18 suggest antitumoral effects of this cytokine. Cancer progression following administration of IL-18BP through biological vectors or impaired IL-18-induced production of IFN-γ highlights the antineoplastic role of IL-18. In contrast, it has been shown that IL-18 released from tumoral or host cells can promote metastasis via microvascular endothelial adhesion of cancer cells and tumor growth stimulating factor production. Several protumoral mechanisms such as Fas ligand expression, reducing expression of E-cadherin, promoting adherence of tumor cells to vessels by enhancing vascular cell adhesion molecule (VCAM)-1 and very late antigen (VLA)-4 integrins expressions, and stimulating release of VEGF and various tumor or stromal growth factors have been explained for IL-18. In addition, cancer inhibitory responses after blocking IL-18 by administration of IL-18BP confirm the role of IL-18 in cancer progression in some studies. IL-18BP and IL-18 both can be a target for immunotherapy in further clinical trials. Considering the complexity of cancer in the first place and variant, even dual, effects of IL-18 confronting tumors with different origins, further studies and clinical trials are required to clarify other aspects of cancer pathophysiology and IL-18-mediated mechanisms.

IL-18 POLYMORPHISMS IN CANCER

The effects of IL-18 on cancer have also been evaluated from the perspective of gene polymorphisms (*table 1*). The human IL-18 gene has been mapped to chromosome 11q22.2-q22.3 and comprises six exons and five introns with an overall length of approximately 19.5 kb [44]. Production and activation of IL-18 is regulated by this gene promoter. Important functional polymorphisms of IL-18 gene have been determined including three SNPs in promotor region (-137 G/C [rs187238], -607 C/A [rs1946518], and -656 G/T [rs1946519]) and two SPNs in 5' nontranslated region (+113 T/G [rs360718] and +127 C/T [rs360717] [45]. More information about -607C/A and -137 G/C polymorphisms are available in literature, and many studies have investigated these two SNPs and their genotype frequencies in different medical conditions. When C allele is substituted by A at position -607, cAMP-responsive element protein-binding site will be disrupted, and consequently, transcription factor binding and gene expression will be altered [46]. Changing G to C allele at position -137 changes the H4TF-1 nuclear factor-binding site to a site for an unknown factor, which is found in the GM-CSF promoter. The C allele at position -607 and the G allele at position -137 are associated with increased IL-18 transcription and protein production [45]. Evaluating functional SNPs in cancer gives us a better understanding of the role of IL-18 in tumoral processes and may help us to predict and screen neoplastic conditions in people carrying specific genotype or haplotypes.

Table 1
Association of IL-18 single nucleotide polymorphisms with cancer according to meta-analyses.

Name	Year	No. of studies	Sample size (Case–control)	SNP	Type of cancer	OR and 95% CI
Li *et al.* [47]	2015	29	6,026-6,476	-607 C/A	Overall cancer	AA vs. CC = 1.17 (1.01-1.37) CA vs. CC = 1.15 (1.05-1.25) AA/CA vs. CC = 1.17 (1.06-1.31)
					NPC	AA vs. CC = 1.34 (1.02-1.75) CA vs. CC = 1.36 (1.08-1.7) AA/CA vs. CC = 1.35 (1.09-1.68)
					Esophageal cancer	CA vs. CC = 1.37 (1.04-1.80) CA/AA vs. CC = 1.29 (1.00-1.66)
					Breast cancer	AA vs. CC = 1.80 (1.02-3.21) CA vs. CC = 1.33 (1.00-1.78)
Liang *et al.* [45]	2013	21	3,498-5,222	-137 G/C	Overall cancer	Lack of association
					NPC	GC/CC vs. GG = 1.57 (1.258-1.965) GC vs. GG = 1.48 (1.179-1.864) CC vs. GG = 2.098 (1.336-3.294)
Yao *et al.* [50]	2015	5	1,618-1,115	-607 C/A	GI cancer	CC vs. AA = 0.93 (0.72-1.2) CC vs. CA = 0.76 (0.62-0.92)
					Esophageal cancer	CC vs. AA = 0.9 (0.65-1.25) CC vs. CA = 0.73(0.65-0.96)
Liang *et al.* [51]	2016	8	1,318-2,254	-137 G/C	HCC	Lack of association
Liang *et al.* [51]	2016	7	1,262-1,696	-607 C/A	HCC	Lack of association
GUO *et al.* [55]	2013	5	942-944	-607 C/A	NPC	CA/AA vs. CC = 1.351 (1.089-1.676) AA vs. CC = 1.338 (1.023-1.751) CA vs. CC = 1.357 (1.08-1.704)

OR = Odds Ratio, CI = confidence interval, NPC = nasopharyngeal carcinoma, HCC = hepatocellular carcinoma.

The latest huge meta-analysis on functional SNPs of IL-18 was performed in 2015 by Li and colleagues to summarize the role of -607 C/A polymorphism of IL-18 gene promotor in cancer. In this meta-analysis, 29 case–control studies including 6,026 patients and 6,476 controls were involved. As a result, it was suggested that -607 C/A polymorphism is significantly associated with overall increased risk of cancer, and AA/CA genotypes were more frequent in patients with cancer. Subgroup analysis based on ethnicity revealed increased association of this SNP with cancer among Asian populations and not Caucasians or Africans (AA/CA vs. CC genotypes). In addition, in stratified analysis on cancer types, an increased association with nasopharyngeal cancer (NPC), esophageal cancer, and breast cancer was detected [47].

A previous huge meta-analysis, which was performed in 2013 including 22 case–control studies and 4100 patients with cancer by Wang and colleagues, confirms data achieved by Li *et al.* According to this meta-analysis evaluating -607 C/A polymorphism, the risk of cancer was significantly increased in heterozygous model (CA vs. CC) and the dominant model (AA/CA vs. CC). Stratified analysis showed significant association of mentioned SNP with cancer among Asian population. Among cancer types, nasopharyngeal carcinoma and esophageal carcinoma, not breast cancer, were highly associated with this SNP in this meta-analysis [48].

Another meta-analysis in 2013 investigated 26 studies with 4096 patients and 5022 healthy controls for -607 C/A and -137 G/C polymorphisms [49]. Based on this study, in contrary to -137 G/C polymorphism, -607 C/A polymorphism increased overall risk of cancer, mainly nasopharyngeal carcinoma and gastrointestinal cancer. -137 G/C polymorphism increased cancer risk only among Asian populations and not Caucasians or Africans. The risk of nasopharyngeal carcinoma has been significantly increased by both of these SNPs. The −607A/−137C and −607C/−137C haplotypes were significantly associated with increased risk of nasopharyngeal carcinoma in comparison with the −607C/−137G haplotype [49].

A meta-analysis conducted in 2013 by Liang *et al.* evaluated the -137 G/C polymorphism in a population of 3498 patients and 5022 healthy controls in case of 21 studies [45]. No association between this polymorphism and overall cancer risk was achieved; however, in subgroup analysis, GC and GC/CC genotypes were significantly associated with increased cancer risk among Asian populations as compared to Caucasians. It was concluded that this polymorphism was associated with nasopharyngeal carcinoma, while no significant correlation with other types of cancer was detected. Three genotype models including homozygote model (CC vs. GG), heterozygote model (GC vs. GG), and dominant model (CC+GC vs. GG), as well as -137 C allelic model, were associated with increased nasopharyngeal carcinoma [45].

The oldest pooled analysis for investigating – 607 C/A and -137 G/C polymorphisms was performed in 2011 by Mi *et al.*. A total of 15 case–control studies (2,137 cases and 3,117 controls) for -607 C/A and 15 studies (2,373 cases and 3,476 controls) for -137G/C were included. Both

SNPs were associated with NPC and increased cancer risk among Asians. In addition, -607 A allele was significantly correlated with developing cancer [46].

Other cancer-specific studies are available in literature. Most of the studies have focused on gastrointestinal tract and nasopharyngeal cancer.

The association of -607 C/A polymorphism with gastrointestinal cancer was analyzed by Yao *et al.* in 2015. Five studies and 1618 cases were included in this meta-analysis, and a significant association of dominant model (CA/AA in comparison to CC) with gastrointestinal cancer was noted. This polymorphism was highly associated with cancer susceptibility in esophageal cancer and not in gastric or colorectal cancer. In stratified analysis, no ethnic association of this polymorphism was detected [50].

A study by Haghshenas *et al.* in 2009, evaluating IL-18 gene promotor SNPs in gastric and colorectal cancer in a population of 232 Iranian patients and 312 healthy controls, showed significant difference in -137 G/C genotypes in patients with cancer and healthy controls, implicating the role of this SNP in predisposing patients to gastrointestinal cancer [24]. It was shown that -607AA/-137GC genotype was more frequent among patients with unwell-differentiated colorectal cancers. Haplotype analysis showed that -607C/-137C and -607A/-137G were decreased in gastric cancer, while -607C/-137C showed decrease among patients with colorectal cancer [24].

The association of hepatocellular carcinoma with two important SNPs of IL-18 gene promotor, -607 A/C and -137 G/C polymorphisms, has been evaluated in a meta-analysis in 2016. In this analysis, 8 case–control studies on -137 polymorphism with 1318 patients and 7 case–control studies on -607 polymorphism with 1262 patients were investigated. This meta-analysis revealed no association of the -137 and -607 polymorphisms with HCC [especially hepatitis B virus (HBV) and HCV-induced HCC] risk, but suggested that -137 polymorphism may be useful in predicting metastasis [51].

A case–control study performed by Lau *et al.* in 2016 investigated the association of -607 A/C and -137G/C polymorphisms with HCC [52]. In this study, these two polymorphisms were investigated in a population of 342 cancerous patients and 559 healthy controls. The −137G/C polymorphism of IL-18, but not the - 607A/C polymorphism, had significant association with the risk of HCC. HCC risk had a 1.987-fold increase in participants with heterozygous G/C and homozygous CC genotypes of -137 G/C position in comparison to homozygous wild-type G/G. In addition, serum AFP was higher in patients with GC/CC genotypes [52].

Another study performed by Dai *et al.* in China in 2017 evaluated -137 polymorphism (rs 187238) in 4 groups of participants including healthy people and patients with chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma. The results of this study showed that -137 GG genotype increased the risk of HCC in a healthy population and the risk of liver cirrhosis in chronic hepatitis B carriers; however, GC genotype decreased the risk of liver cirrhosis in a healthy population [53].

The results of studies on HCC seems to be controversial. Meanwhile, the study by Dai *et al.* revealed -137GG correlation with developing HCC. Lau *et al.* concluded that -137 GC and CC genotypes increased the risk of HCC. In addition, a retrospective study by Bao and colleagues published in 2015 showed that GC genotype and C allele were significantly associated with decreased HCC risk [54].

The controversy detected in the study of IL-18 promotor polymorphisms on the hepatocellular carcinoma may be due to genetic background of patients or other IL-18 gene polymorphisms influencing IL-18 expression and activity in HCC, which needs further evaluation.

A meta-analysis in 2013 investigated -607 C/A polymorphism and its association with nasopharyngeal carcinoma. In this meta-analysis, data of 5 studies and 1886 participants (942 patients and 944 controls) were included, and a significant relationship between -607 C/A polymorphism and nasopharyngeal carcinoma was detected in dominant, homozygote, and heterozygote genetic models. This study concluded that patients with C allele had a higher risk of developing nasopharyngeal cancer [55].

Evaluation of these two polymorphisms in 250 Chinese patients with nasopharyngeal carcinoma and 280 controls supported the association of IL-18-137G/C polymorphism with nasopharyngeal carcinoma. Importantly, the GC and CC genotypes were significantly correlated with increased risk of cancer compared to the GG genotypes. In addition, -137C/-607 A haplotype was highly associated with NPC. This haplotype has a lower promoter activity and IFN-γ mRNA level than the other haplotypes [56].

Another study by Pratesi *et al.* in 2006 investigating two IL-18 polymorphisms with undifferentiated nasopharyngeal carcinoma (UCNT) in 89 Italian patients and 130 healthy controls demonstrated that patients with AA genotype at -607 position showed a nearly statistically significant risk of UCNT and C/C or C/G combined genotypes at -137 site, were related to advanced stages of disease. This association could be a consequence of a lower IL-18 gene transcription and protein production as a result of the C allele in -137 position [57].

Another study in India investigated a total number of 272 patients with oral squamous cell carcinoma (OSCC) and 185 healthy controls for the IL-18 -607 C/A and -137 G/C polymorphisms. This study showed that -137 G/C polymorphism was significantly associated with OSCC. In contrast, no significant association of any genotypes or alleles of the -607 C/A polymorphism with OSCC was detected [58].

Controversial results have been achieved in studies with smaller population of patients for IL-18 polymorphisms in head and neck cancers. A study performed in 2009 by Asefi *et al.* on 111 Iranian patients with head and neck carcinoma (including SCC of oral cavity, larynx, and pharynx) and 212 controls showed no association of -607 and -137 polymorphisms with risk of cancer. Farhat *et al.* in a study conducted in 2008 on 163 Tunisian patients with nasopharyngeal carcinoma showed that functional SNPs of IL-18 (at -607 and -137 positions) did not contribute to increased risk of cancer but may contribute to disease onset and severity [59].

Studying these SNPs on breast cancer showed that in a population of 154 Brazilian patients with breast cancer, both -607 and -137 polymorphisms were related to increased cancer risk. Codominant genetic model of -607 polymorphism and recessive genetic model in -137 position were the most significant models in breast cancer [60].

In two studies performed in two different cities of Iran, Shiraz and Zahedan, investigating 250 and 72 patients with breast cancer, respectively, there was no association between -607 C/A polymorphism and breast cancer. In the study of Shiraz, the other functional SNP (-137 G/C) was investigated too. It was shown that CC genotype in this position had a significant decrease in the patient group. However, this genotype was significantly associated with metastasis in the patient group [61, 62].

In a study of Slovakian population, 425 patients with prostate cancer were involved. A statistically significant association of the -607 AC and CC genotypes, as well as C allele, with a higher risk of prostate cancer development was observed. Subset analysis revealed a significant association of the -607 AC genotype with development of higher-grade carcinomas (Gleason score $\geq$7) [63].

In the study by Liu and coworkers in 2013, no overall association was seen between these SNPs and prostate cancer incidence, but the -137 GG genotype was correlated with a 2.165-times higher chance of cancer progression compared to GC genotype [64].

In another study on prostate cancer in Chinese population in 2007, the -137 GC and CC genotypes were increased in patients with prostate cancer compared to the -137 GG genotype. In addition, -137C/-607A haplotype was significantly higher in prostate cancer as compared with the -137G/-607C haplotype [65].

Fewer studies are available on IL-18 functional SNPs in ovarian cancer in literature. Both Bushely (2004) and Samsami (2009) concluded that there was no association between risk of ovarian cancer and IL-18 polymorphisms [66, 67].

In a study performed on thyroid cancer, 5 SNPs in IL-18 gene were analyzed, including 3 SNPs on promotor region (-656 G/T, -607 C/A, and -137 G/C) and +113 T/G and +127 C/T in the 5' untranslated region. In this analysis, it was shown that TT genotype at -656 position was associated with higher risk of thyroid cancer, and +127CC genotype was significantly decreased in thyroid cancers derived from follicular epithelia [68].

A population of 73 Iranian patients with lung cancer was investigated for SNPs at positions -656 (G/T),-607 (C/A), and -137 (G/C). In this study, patients with the -607 CA and AA genotypes had a significant increased risk of lung cancer. Thus, A allele, which is associated with lower IL-18 production, was more frequent in patients with lung cancer [69].

IL-18 IN AUTOIMMUNE DISEASES

Autoimmunity is caused by overactivation of immune system against self-antigens. Various mechanisms are responsible for development of autoimmunity. Cytokine balance plays a key role in maintaining and regulating immune responses, though altered function of cytokines can trigger inappropriate immune responses leading to consequent autoimmunity and host tissue damage. IL-18 may have important impacts on autoimmunity processes particularly through IFN-γ production. On the basis of several studies, elevated IL-18 levels have been associated with incidence and severity of autoimmune diseases. Similar to cancer blocking, IL-18 has been suggested as a therapeutic strategy for treating autoimmune diseases. Functional SNPs are important targets for investigating the role of IL-18 in autoimmune diseases (*table 2*). However, fewer data are available on IL-18 polymorphisms in different autoimmune diseases in comparison to cancer. Limited number of case–control studies and studies with small number of patients have led to controversial results, which requires further studies in this field. Important autoimmune diseases related to IL-18 are discussed in the forthcoming paragraphs.

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1D) is an autoimmune disease caused by immune-related destruction of pancreatic beta cells. It is considered that IL-18 can play an important role in disease progression and severity, mostly by Th1-related mechanisms. Serum levels of IL-18 have been reported to be significantly higher in patients with T1D [70]. High serum levels of IL-18 in patients newly diagnosed with T1D and more significantly in their first-degree relatives with positive autoantibodies for diabetes emphasize the role of this cytokine in disease progression [71]. Elevated serum IL-18 level has been correlated with insulin resistance, and it was associated with higher risk of cardiovascular complications [72]. Moreover, IL-18 serum levels association with glycated hemoglobin (HbA1c) level in diabetic patients and disease complications such as diabetic microangiopathies and diabetic ketoacidosis explain the role of IL-18 not only in disease progression but also in severity [73-75].

Oikawa *et al.* showed that IL-18 expression by plasmid delivery promoted diabetes in mice; however, administration of exogenous IL-18 was protective against insulitis in beta cells. This controversy may be explained by the effects of IL-18 on both Th1- and Th2-mediated mechanisms based on cytokine milieu [76].

Like in other autoimmune diseases, IL-18 effect in T1D is mediated by IFN-γ production, which is enhanced by IL-12 as mentioned earlier. However, due to complex role of this cytokine in the human body, other mechanisms might be involved. IL-18 can increase IL-17 production from Th17 cells and promote inflammation and tissue destruction. During inflammation, beta cells start expressing IL-18 mRNA, which can develop ongoing destruction of beta cells [77]. It was seen that in IL-18-/- mice, the number of reactivated T cells has reduced in comparison to IL-18 positive ones. Therefore, IL-18 is required for self-reactive T-cell expansion in mice. In addition, IL-18 can shift T-cell cytokine production from IL-17 to IFN-γ, which plays an important role in type 1 DM pathogenesis [78]. The role of IL-18 in T1D is also supported by the finding that blocking IL-18 by IL-18BP-Fc fusion molecule reduced disease incident significantly [79].

Association of several SNPs of IL-18 gene promotor with type 1 DM (T1D) has been evaluated in different studies. Current studies do not strongly support IL-18 SNP correlation with T1D. However, in some studies, IL-18 polymorphisms were related to age of diabetes onset and severity. In addition, haplotype and genotype frequencies of these SNPs seem to follow different patterns in different studied groups.

A meta-analysis was performed in 2015, including over 6000 diabetic patients, to evaluate correlation of -607 C/A and -137 G/C polymorphisms with type 1 DM. None of

Table 2
Association of IL-18 single nucleotide polymorphisms in autoimmune and inflammatory-mediated diseases according to meta-analyses.

Disease	Name of author	Year	No. of studies	Sample size (case–control)	SNP		OR & 95% CI
Allergy [111]	Cheng *et al.*	2014	21	5,331-9,658	-607 C/A	Overall	Lack of association
						Allergic Asthma	AC vs. CC = 0.82 (0.69–0.98)
					-137 G/C	Overall	Lack of association
						Allergic dermatitis	CC vs. GG = 0.26 (0.12–0.53) CC vs. CG + GG = 0.30 (0.15–0.60)
T1 DM [80]	Lee *et al.*	2015	10	6,975-5,744	-137 G/C		Lack of association
					-607 C/A	Overall	Lack of association
						Europeans	Lack of association
						Asians	C vs. A = 1.506 (1.172–1.936) CC/CA vs. AA = 2.626 (1.502–4.589) CC vs. CA/AA = 1.571 (1.025–2.410) CC vs. AA = 2.626 (1.502–4.589)
RA [93]	Li *et al.*	2016	14	3,728-3,217	-607 C/A		AA vs. CC = 0.598 (0.395-0.907) AC vs. CC = 0.699 (0.540-0.906) AA/AC vs. CC = 0.677 (0.518-0.884)
			11	1,982-1,947	-137 G/C		Lack of Association
SLE [98]	Song *et al.*	2013	9	2,928-5,225	-607 C/A	Overall	Lack of association
						Europeans	C vs. A = 0.864 (0.757–0.986) CC/CA vs. AA = 0.755 (0.587–0.972) CC vs. AA = 0.714 (0.539–0.947)
						Asians	Lack of association
					-137 G/C	Overall	Lack of association
						Europeans	Lack of association
						Asians	G vs. C = 0.792 (0.629–0.997)
Crohn [102]	Gao *et al.*	2015	7	1,930-1,930	-607 C/A		C vs. A = 2.03 (1.20-3.43) CC vs. AC/AA = 2.39 (1.2-4.43) CC vs. AC = 2.31(1.22-4.38)
					-137 G/C		G vs. C = 1.69 (1.39-2.06) GG/GC vs. CC = 2.04 (1.48-2.81) GG vs. CC = 2.53 (1.82-3.52)

OR = Odds Ratio, CI = confidence interval, T1DM = type 1 diabetes mellitus, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

these two SNPs were significantly associated with the risk of developing T1D. No correlation was found between -137 G/C polymorphism with diabetes in different ethnic groups, but C allele in -607 position was related to type 1 diabetes in Asian patients [80].

Studying 187 Croatian diabetic patients and 236 healthy controls showed that patients with minor alleles at -607 and -137 positions (A and C allele, respectively) developed diabetes in younger ages [81]. A correlation of -137 CC genotype with lower age of disease onset was also found in a study of 91 Turkish diabetic patients. This study showed an association between-607 CC genotype and higher levels of HbA1c [82].

In Chinese Han children with T1D, a lower distribution of AA genotype in -607 position and a higher frequency of -607CC/-137 GG genotype combination was detected in diabetic patients compared with the control group [83].

In contrast to these studies, Mojtahedi *et al.* studying 115 Iranian diabetic patients showed that C allele frequency in -137 position was significantly higher in patients with later onset of disease (15 years or older) compared to the control group. This study showed that −607AA/−137CC genotype combination was associated with increased susceptibility of type 1 DM in Iranians with onset of disease at an older age [84].

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease in which axons of central nervous system are demyelinated by immune-mediated mechanisms. Higher levels of IL-18 and caspase 1 mRNA in blood of patients with MS have been correlated with disease severity [85, 86]. It was shown that IL-18-/-, caspase 1 -/-, and especially IL-18Rα-/- mice were protected against experimental autoimmune encephalitis (EAE, which is similar to MS in human). Administration of caspase 1 inhibitors and antibodies blocking IL-18Rα increased resistant against EAE in separate studies [86]. Moreover, a decrease in disease incidence and severity was detected in IFN-γ-/-, IL-18-/-, and mice treated with adenoviral vector-expressing IL-18BP. Following administration of IL-18BP, IL-18 will be neutralized, and IL-18Rα will be available for anti-inflammatory ligands [76].

Few studies on the correlation of IL-18 functional SNPs with MS are available. A study on 101 Turkish patients with MS in 2014 showed that IL-18 gene SNP at position -137 may be correlated with disease incidence. The frequency of CC genotype at position -137 was significantly higher in patients with MS compared to GG genotype. However, -607 C/A SNP showed no remarkable association with MS in this study [87].

In another study of 113 Turkish patients with MS, -607 SNP was introduced as a major genetic risk factor of MS, because -607AA genotype was correlated with 6 times higher risk of developing MS. However, no significant association was detected between -137 SNP and MS [88].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a Th1-mediated autoimmune disease in which synovial tissue and cartilage are destroyed. IL-18 has an important role in pathology of RA, and IL-18 mRNA and protein are expressed in synovial tissues of patients with RA. In addition, serum levels of IL-18 are increased in patients with RA [89]. Reduced disease severities in IL18-/- mice, or following neutralization of IL-18 by IL-18BP administration or anti-IL-18 antibodies, have been reported [90, 91].

Beside Th1 mechanisms involved in synovial joint destruction, fibroblasts of synovial tissue stimulated by IL-18 may contribute to inflammation, cytokine release, and leukocyte recruitment to the joint. IL-18 available in synovial fluid can also act as an angiogenic factor, which helps maintaining pannus formation in RA [92]. Due to significant role of IL-18 in RA progression, it has been considered as a potential target for immunotherapy in RA.

The latest meta-analysis on IL-18 gene polymorphisms in RA was performed in 2016 [93]. This study included 14 articles and evaluated -607C/A, -920 C/T, -137 G/C, and -105 A/C polymorphisms in RA. A population of 3,728 RA cases and 3,213 controls for -607 C/A SNP and 1982 cases and 1947 controls for -137 G/C SNP were examined. This study revealed that homozygote, heterozygote, and dominant genetic models of -607 C/A were significantly associated with RA. In addition, -920 C/T and -105 A/C polymorphisms were significantly correlated with increased risk of RA while -137 C/G polymorphism was not associated with RA [93].

In a meta-analysis performed in 2014, 10 studies including 2662 patients with RA were investigated for -607 and -137 polymorphisms in IL-18 gene. IL-18-607 C/A polymorphism was significantly associated with RA in allelic and dominant models. This polymorphism was significantly related to RA in the Asian population. However, no significant association was detected between -137 G/C polymorphism and risk of RA [94].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease involving many organs in the human body. Serum levels of IL-18 are correlated with disease severity. It has been suggested that IL-18 may be a prognostic marker of renal involvement in patients with SLE [95, 96]. Moreover, the serum levels of IL-18 have been correlated with severity indices of disease such as dsDNA, 24-hour urine protein, and platelet counts [97].

A meta-analysis carried out in 2013 on 2,928 patients evaluated 3 important SNPs, -607 C/A, -137 G/C, and -1297 C/T, in SLE. On the basis of ethnic stratification in this meta-analysis, -1297 C allele was significantly associated with SLE in all study participants while -607 C allele and -137 G allele were associated with SLE in Europeans and Asians, respectively [98].

A study evaluating the role of IL-18 gene polymorphisms in 50 patients with SLE showed a significant higher frequency of -607 CC genotype and a lower frequency of -607 CA genotype in patients with SLE as compared to the control group. Patients with -607 CC genotype had the highest levels of IL-18. In addition, a statistically significant association was found between -607 CC genotype and lupus nephritis, arthritis, and immunological disorders [99].

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a group of inflammatory diseases of small intestine and colon, which are associated with Th1-mediated responses. It has been shown that IL-18 plasma levels are higher in patients with Crohn's disease and ulcerative colitis. In addition, insufficient amounts of IL-18BP counteracting endogenous IL-18 were suggested as a mechanism involved in pathogenesis of Crohn's disease [100]. IL-18 may contribute to local immunoinflammatory responses and is upregulated in Crohn's disease [101].

A meta-analysis was conducted using 7 case–control studies including 1930 patients with Crohn's disease. It was shown that -607 C/A , -137 G/C, and +113 A/C polymorphisms were correlated with increased risk of Crohn's disease, but -656 G/T polymorphism was not associated with the disease susceptibility. In addition, studies on ethnicity showed that IL-18 SNPs were correlated with

disease incidence among Asians and Africans but not Caucasians [102].

In another study on Tunisian patients with IBD, it was shown that -607 C/A and -137 G/C polymorphisms were correlated to ulcerative colitis while no association was detected between these two SNPs and Crohn's disease [103].

ALLERGIC DISEASES

Allergy is a group of IgE-mediated diseases caused by hypersensitivity of immune system against environmental antigens. Allergic diseases vary from chronic inflammatory diseases such as allergic asthma, allergic rhinitis, atopic dermatitis, and food allergies to severe life-threatening acute conditions such as anaphylaxis. Th2-mediated mechanisms induce IgE production from B cells through cytokines (IL-4 and IL-13) production. In addition, IL-5 released from Th2 cells promotes development and activation of eosinophils [104]. Due to the role of IL-18 on Th2-mediated pathways, this cytokine has been noticed in allergic diseases especially asthma, where IL-18 indirectly increases IgE production [11]. It is interesting that IL-18 especially in the presence of IL-12 may inhibit IgE synthesis through Th1-mediated responses. Therefore, the balance of IL-18 in Th1 and Th2 pathways determines its role in allergic conditions. Administration of IL-18 has led to development of asthma in mice [105]. In addition, increased serum levels of IL-18 in allergic conditions such as allergic asthma and atopic dermatitis and increased IL-18 levels in sputum of asthmatic patients support the role of this cytokine in allergy [106].

Several studies with small sample size have evaluated the association of IL-18 promotor polymorphisms with asthma in different ethnic groups. A study on Indian asthmatic patients concluded that -137 G/C SNP has a protective role in asthma and CC genotype frequencies were lower in the cases than controls [107]. A study on Egyptian asthmatic patients showed no association of -607 C/A polymorphism with development or severity of asthma [108]. In contrary, a study on Tunisians showed that A allele in -607 position was significantly correlated with atopic asthma [109]. A meta-analysis in 2012 evaluated the results of 5 studies with a total population of 1411 patients and 1525 controls and showed that -607 AC/CC genotype was correlated with increased risk of asthma in recessive model. On the other hand, -137 G/C polymorphism showed no significant association with asthma [110].

To sum up the different results on the role of IL-18 SNPs in development of allergic diseases, a meta-analysis was performed by Cheng *et al.* in 2014, which involved twenty-one studies including 5,331 cases and 9,658 controls [111]. The patient group mostly comprised patients with allergic asthma, allergic rhinitis, and dermatitis. Two SNPs of IL-18 promoter -607 C/A and -137 G/C were investigated in these studies. The meta-analyses showed no association of any of these two polymorphisms with overall risk of allergic diseases. In addition, these polymorphisms were not significantly correlated with disease in any ethnic group. In subgroup analyses by allergic type of disease, -607 C/A and -137 G/C polymorphisms had negative associations with risk of allergic asthma and allergic dermatitis, respectively. It was concluded that these two SNPs could play a protective role against the mentioned allergic diseases [111].

IL-18 IN METABOLIC SYNDROME

Metabolic syndrome is defined by presence of three out of five criteria including central obesity, increased blood pressure, impaired fasting glucose, high levels of triglyceride, and low levels of high-density lipoprotein [112]. Patients with metabolic syndrome have higher risk of insulin resistance and cardiovascular diseases. Investigation of pathophysiological mechanisms responsible for metabolic syndrome has shown that metabolic syndrome is associated with a chronic and low-grade inflammation similar to atherosclerosis [112, 113].

Increased plasma levels of IL-18 have been associated with obesity, insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome in different studies [114, 115]. In contrast to the aforementioned findings that support inflammatory role of IL-18 in metabolic syndrome, in a study performed by Netea *et al.*, IL-18-deficient mice presented several characteristics of metabolic syndrome including obesity, insulin resistance and hyperglycemia, lipid abnormalities, and atherosclerosis [116].

Proving the findings of the later study, it was shown that mice without NLRP1 inflammasome developed spontaneous obesity due to intrinsic lipid accumulation similar to IL-18-/- mice. Moreover, mice with an activating mutation in NLRP1, and, therefore, increased IL-18, showed decreased adiposity and resistance to diet-induced metabolic dysfunction. Thus, it was concluded that NLRP1, an innate immune sensor, which functions in the context of metabolic stress to produce IL-18, prevents obesity and metabolic syndrome [117].

To explain the controversy in previous findings, it has been suggested that local IL-18 production, and not circulating IL-18, is important for protecting against obesity and metabolic syndrome. Subsequently, it was explained how high circulating levels of this antiobesity signal do not maintain desirable effects in obese patients. This also suggests that locally acting IL-18 therapies may be useful as a weight-losing strategy in obese patients [117].

A study investigated two SNPs of IL-18 gene including -137 G/C polymorphism on promoter and the þ183A/G polymorphism in 3' untranslated region (rs5744292), where -137C allele and +þ183 G allele are associated with lower transcriptional activity and, therefore, lower IL-18 production. In this study, 636 Caucasians with metabolic syndrome were involved in the assessment of cardiometabolic risk factors [118]. On assessing þ+183A/G polymorphism, the G allele showed a reduced risk of metabolic syndrome. In addition, IL-18 levels were significantly lower in participants carrying the G allele in comparison to A/A carriers. Insulin sensitivity was significantly higher in participants carrying the G allele as compared with A/A carriers. Altogether, these data suggest that the þ183A/G polymorphism can be associated with increased levels of serum IL-18, impaired insulin sensitivity, and increased risk of metabolic syndrome, while no significant association between the -137 G/C polymorphism and metabolic syndrome was detected [118].

IL-18 IN ATHEROSCLEROSIS

Chronic inflammatory processes are involved in atherosclerotic plaque formation. Increased level of IL-18 was seen in patients with myocardial infraction. In addition, increased localization of IL-18 and its receptor's expression was detected in macrophages and endothelial cells of atherosclerotic plaques. Moreover, unstable plaques had significantly higher levels of IL-18 mRNA compared to stable, asymptomatic ones [119].

Due to the role of IL-18 in atherosclerosis, the polymorphisms of IL-18 were checked in coronary artery diseases (CAD). A study performed in 2017 in Saudi Arabia showed that -137 C/G, -607 A/C, and -656 T/G SNPs had no association with CAD [120]. However, Hernesniemi and colleagues showed that -137G/C polymorphism is associated with sudden cardiac death in patients with and without underlying coronary heart diseases [121]. A study in China investigated -607A/C and -372C/G promoter polymorphisms of IL-18 gene and risk of CAD development in 326 patients and showed that frequency of -670 CC genotype was significantly higher in patients with in comparison to other genotypes. No valuable association between -372 C/G polymorphism and increased risk of CAD was detected [122].

IL-18 +183 A/G polymorphism was seen to be associated with stable disease in 1001 patients angiographically diagnosed as having CAD. The +183 AA genotype was significantly higher in patients with CAD [123]. The significance of +183A/G polymorphism in CAD compared to other SNPs has also been reported in other previous studies [124].

CONCLUSION

Current studies agree to the various effects of IL-18 in cancer and autoimmune diseases; however, the precise role of this cytokine in regression and treatment of inflammation-related diseases requires further investigations. Not surprisingly, IL-18 and IL-18-related pathways are attractive targets for clinical studies and trials. On the other hand, recognizing polymorphisms of IL-18 and their correlation with diseases can help us for screening and early diagnosis, especially in cancer. Among the known polymorphisms of IL-18, -607 C/A and -137 G/C are highlighted in literature. These two SNPs have been points of interest in many studies possibly due to their importance in regulating IL-18 expression and production and also more significant associations with different diseases especially cancer. Comparing to other cancers, more studies support significant association of esophageal and nasopharyngeal carcinomas with IL-18 polymorphisms. Usage of related polymorphisms as diagnostic and prognostic markers in these cancers can be considered for further evaluations. With respect to the role of IL-18 in autoimmune diseases, many studies have focused on rheumatologic diseases such as rheumatoid arthritis and SLE, T1D, and IBD. Recent studies on metabolic syndrome, atherosclerosis, and consequent cardiovascular complications, which are directly and indirectly responsible for a significant contribution in patients' morbidity and mortality, open new horizons ahead of possible impacts of IL-18 on mentioned pathologies, which may need further evaluations to clarify the importance of IL-18 SNPs and possibility of clinical usage in these diseases.

Disclosure. *Financial support: This work was financially supported by Shiraz University of Medical Sciences (grant number: 1182) and by grant from Shiraz Institute for Cancer Research (grant number: ICR-100-502). Conflict of interest: none.*

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