MINI-REVIEW

Immunotherapeutic Approach for Better Management of Cancer - Role of IL-18

Manohar Babu Kuppala, Sunayana Begum Syed, Srinivas Bandaru, Sreedevi Varre, Jyothy Akka, Hema Prasad Mundulru*

Abstract

Interleukin-18 (IL-18) is an immune-stimulatory cytokine with antitumor activity in preclinical models. It plays pivotal roles in linking inflammatory immune responses and tumor progression and is a useful candidate in gene therapy of lymphoma or lymphoid leukemia. A phase I study of recombinant human IL-18 (rhIL-18) in patients with advanced cancer concluded that rhIL-18 can be safely given in biologically active doses to patients with advanced cancer. Some viruses can induce the secretion of IL-18 for immune evasion. The individual cytokine activity might be potentiated or inhibited by combinations of cytokines. Here we focus on combinational effects of cytokines with IL-18 in cancer progression. IL-18 is an important non- invasive marker suspected of contributing to metastasis. Serum IL-18 may a useful biological marker as independent prognostic factor of survival. In this review we cover roles of IL-18 in immune evasion, metastasis and angiogenesis, applications for chemotherapy and prognostic or diagnostic significance.

Keywords: Interleukin-18 - cancer - angiogenesis - immunotherapy - predictive marker

Immuno Therapeutics

Immunotherapy is defined as the "treatment of disease by inducing, enhancing, or suppressing an immune response". Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies. Cytokines are small cell-signaling protein molecules that are secreted by the immune system and used extensively in intercellular communication.

IL-18 plays pivotal roles in linking inflammatory immune responses and tumor progression. It is a pro-inflammatory cytokine converted to a biologically active molecule by IL-1beta converting enzyme (caspase-1). IL-18 has various biological activities after its secretion as an 18 kDa mature form. A wide range of normal and cancer cell types can produce and respond to IL-18 through a specific receptor (IL-18R) belonging to the toll-like receptor family. The activity of IL-18 is regulated by IL-18-binding protein (IL-18bp), a secreted protein possessing the ability to neutralize IL-18. It stimulates natural killer (NK) and T cells and enhances Th1 immune response. It is an immune-stimulatory cytokine with antitumor activity in preclinical models. It increases the serum concentrations of IFN-g, granulocyte macrophage colony-stimulating factor and soluble Fas ligand (Robertson et al., 2006). A phase I study of recombinant human IL-18 (rhIL-18) in patients with advanced cancer concluded that rhIL-18 can be safely given in biologically active doses to patients with advanced cancer. The rhIL-18 increases expression of activation antigens on lymphocytes and monocytes

(Michael et al., 2008). IL-18 is a useful candidate gene in gene therapy of lymphoma or lymphoid leukemia. (Zhang et al., 2004). The combination of IL-18 and IL-2 is considered a viable strategy to induce an antitumor response in vivo (Young et al., 2001). Plasma levels and mRNA levels of IL-18 and its converting enzyme, caspase-1, were significantly elevated in Cutaneous T-cell lymphoma (Kei-ichi et al., 2006).

IL-18 viral infections

Epstein-Barr virus (EBV) latently infects and immortalizes B lymphocytes and causes lympho proliferative malignancies. EBV nuclear antigen EBNA2 induces expression of the 2 chains of the interleukin-18 receptor (IL-18R) in Burkitt lymphoma (BL) cell lines and in non-transformed B cells. EBNA2 expression is associated with IL-18R expression in vivo in EBV-positive B-lymphomas from AIDS patients (Franck et al., 2005). IL-18 expression in response to a viral latency protein and suggest that IL-18 may play an important role as an endogenous inducer of IFN-g expression, thereby contributing to tumor regression (Lei et al., 2001). IL-18 binding protein (IL-18BP) is a circulating protein that binds IL-18 and neutralizes its activity. IL-18 production is increases in chronic HCV infection. IFN-a administration increased IL-18BP plasma levels 3.24 fold 24 h resulting in a 67.4% reduction of free IL-18. These anti-inflammatory properties might account together with its antiviral action for its clinical efficacy in chronic hepatitis C (Kaser et al., 2002).

*Institute of Genetics and Hospital for Genetic Diseases, Osmania University , Begumpet, Hyderabad, India *For correspondence: hemaprasadm@yahoo.com*

IL-18 Effects on Different Cancers

IL-18 is a systemic, multifunctional cytokine with both pro-cancerous and anti-cancer activities. There is growing evidence suggesting that IL-18 levels may affect individual to virus-associated neoplasia and that single nucleotide polymorphisms within the gene may influence its production. Variations in the DNA sequence in the IL-18 gene promoter may lead to altered IL-18 production, and so this can modulate an individual's susceptibility. IL-18 gene promoter polymorphism is reported to be a genetic risk factor for several types of cancer (Han et al., 2003).

IL-18 gene promoter polymorphism

Reporter gene assay reveals the significance of SNPs of alleles in IL-18 gene promoter in HepG2 and Hep3B cells are associated with the presence of HCC (Kim et al., 2009). Significant genotype differences in the IL-18 promoter region (-607) between the lung cancer patients and controls in Iranian population (Farjadfar et al., 2009). C allele at position -607 was associated with a higher risk of cirrhosis and HCC (Bouzgarrou et al., 2008).

Significant difference in the frequency of -137 G/C genotype were found in colorectal cancers, nasopharyngeal (Nong et al., 2009), breast cancer (Khalili et al., 2009), cervical cancer (Sobti et al., 2008) and prostate cancers (Liu et al., 2007). Haplotype analysis showed statistical significance in patients with stomach cancer -607 C/-137 C and -607 A/-137 G and in patients with colorectal cancer and esophageal squamous cell carcinoma (Wei et al., 2007; Haghshenas et al., 2009).

Effect of Combinational Cytokines with IL-18 on Outcome of Cell Proliferation

Different cytokines show dissimilar activities on cancer progression. Cytokines are key players exerting tumor and anti-tumor properties in the biological processes of malignant tumors. The individual cytokine activity might potentiate or inhibited by combination of cytokines. The relationship between pro-inflammatory and anti-inflammatory cytokines are responsible for the presence and intensity of cancer progression. These cytokines have

a major anti-tumor activity via stimulation of a T-helper type 1 (Th1) and T-helper type 2 (Th2) immune responses. Intra-tumoral cytokine delivery has therapeutic potential for immunotherapy of cancers.

Cytokine expression profiles may depend on type of cancer. The Th1 cytokines, particularly IL-12, were increased in adjacent mucosa of colorectal adenoma, but all Th1 cytokines significantly decreased in adjacent mucosa of colorectal carcinoma (Cui et al., 2007). IL-6 concentration increased as the tumor stage progressed, and a significant difference appeared between stage of head and neck squamous cell carcinoma patients (Mojtahedi et al., 2011).

IL-18, a cytokine that plays an important role in the T-cell-helper response, acts as an angiogenic factor and a tumor suppressor. There is a significant difference in the levels of IL-18 between breast cancer patients with metastatic and non-metastatic cases. IL-18 is an important non-invasive marker suspecting metastasis (Eissa et al., 2005) Metastatic patients showed significantly higher IL-18 mean values with respect to both healthy controls and non-metastatic patients (Lissoni et al., 2000).

Co-administration of low-dose IL-2 plus IL-18 induced a potent primary response to murine neuroblastoma and activation of natural killer cells in the tumor microenvironment. mIL-12 and mIL-18 synergistic effect inhibit tumor angiogenesis (Coughlin et al., 1998). IL-2 plus IL-18cytokine treatment shows complete and durable antitumor response (Redlinger et al., 2003). Intratumoral treatment with IL-18 and IL-12-encoding plasmid DNA has antitumor effects, which is well tolerated and thus holds promise for the treatment of patients with metastatic melanoma (Muller et al., 2011). Both IL-10 and IL-18 levels in the peritoneal cavity increased with tumor progression. Peritoneal exudates cells capable of producing IFN-gamma in response to IL-18 may be influenced by local IL-10 levels in the peritoneal cavity (Majima et al., 2002). IFN-gamma, IL-15, and IL-18were induced in patients treated with rhIL-12. The down-modulation of IFN-gamma induction during rhIL-12 treatment did not relate to IL-10 production or alterations in rhIL-12 bioavailability but was associated with an acquired defect in lymphocyte IFN-gamma production in response to IL-12, IL-2, or IL-15 (Gollob et al., 2000).

Table 1. IL-18 Promoter Polymorphism and Association with Cancer Progression in Different Cancers

S.No	-607 C/A	-137 G/C	Type of Cancer	Patients Vs Control	Association with cancer progression	Cancer out come	Reference
1	C	C	polycystic ovary syndrome	118 Vs 79	Not Associated	Protective role	Yang et al., 2010
2	A	--	lung cancer	73 Vs 97	Associated	cancer risk	Farjadfar et al., 2009
3	A	G	GI cancers	232 Vs 312	Associated	Protective role	Haghshenas et al., 2009
4	A	C	Nasopharyngeal	250 Vs 270	Associated	cancer risk	Nong et al., 2009
5	A	C	ovarian cancer	85 Vs 158	Not Associated	No role	Samsami et al., 2009
6	A	CC	breast cancer	250 Vs 206	Associated	Protective role	Khalili et al., 2009
7	A	C	head and neck carcinoma	111 Vs 212	Not Associated	No role	Asefi et al., 2009
8	C	C	Cervical cancer	115 Vs 180	Associated	Increased Cancer risk	Sobti et al., 2008
9	A	--	Nasopharyngeal carcinoma	163 Vs 164	Not Associated	Increased cancer risk	Farhat et al., 2008
10	A	--	oral cancer	149 Vs 89	Not associated	No role	Vairaktaris et al., 2007
11	C	--	Esophageal carcinoma	235 Vs 250	Associate	Increased risk	Wei et al., 2007
12	A	C	prostate cancer	265 Vs 280	Associate	Increased risk	Liu et al., 2007

VEGF and IL-18 are markers for transformation of benign cells to metastatic cancer cells. Concentrations of VEGF and IL-18 in the serum are sensitive tumor markers in this patient group before and after treatment. High production of VEGF was associated with low production of IL-18 (Jablonska et al., 2005). PEG interferon alpha-2b treatment was associated with decrease in plasma basic fibroblast growth factor and increase in plasma interleukin-18. Bevacizumab therapy reduces tumor blood flow and resulting anticancer activity. No significant changes in tumor blood flow were observed following PEG interferon (Yao et al., 2008).

Cytokines are responsible for progression of cancers. Serum IL-12 and IL-18 levels were higher in patients with IV stage of esophageal cancer (Diakowska et al., 2006). Intratumoral expressions of IL-12 and IL-18 can play an important role in progression and metastasis of gastric cancer (Ye et al., 2007). Serum IL-12 and IL-18 levels were significantly higher and increased in patients as the pathologic stage progressed in patients with esophageal carcinoma. IL-12 and IL-18 levels correlate with a certain depth of invasion and might be useful tumor markers in patients with esophageal carcinoma (Tsuboi et al., 2004).

Role of IL-18 in Cancer Progression

IL-18 is a pleiotropic, pro-inflammatory cytokine plays a critical role in tumor migration, invasion, and metastasis, with dual effects on tumor development and progression. Immunosuppressive cytokines subvert innate and adaptive immune responses during cancer progression. IL-18 increases the escape immune recognition, increase adherence to the microvascular wall and induce production of angiogenic and tumor growth-stimulating factors via IL-18-dependent mechanism. Thus, the role of IL-18 in

Table 2. Effects of Cytokines

S.No	Combination	Type of Cancer	Reference
Anti Tumor Activity:			
1	IL-12, IL-18	Mammary carcinoma	Coughlin et al., 1998
2	IL-12, TNF-alpha	Breast cancer	Sabel et al., 2010
3	IFN-gamma, IL-12	Gastric carcinoma	Majima et al., 2002
4	IL-10, IL-18	Gastric carcinoma	Majima et al., 2002
5	IL-2, IL-18	Neuroblastoma	Redlinger et al., 2003
6	IL-2, IL-12	Melanoma	Muller et al., 2011
7	VEGF, IL-18	Oral cavity cancer	Jablonska et al., 2005
Tumor Progression:			
1	IL-12, IL-18	Eesophageal carcinoma	Diakowska et al., 2006
2	IL-12, IL-18	Gastric cancer	Sabel et al., 2010
3	IL-12, IL-18	Esophageal carcinoma	Tsuboi et al., 2004
4	IL-10, IL-12	Head and neck squamous cell	Jebreel et al., 2007

*Anti Tumor Activity S. No (1-6)=Nature: Synergism and S. No (7)=Nature: Antagonism. **Tumor Progression S. No (1-3)=Nature: Synergism and S. No (4)=Nature: Antagonism

cancer progression and metastasis remains controversial. The regulation of the IL-18 secretion process is an important step in tumor progression.

Il-18 enhances cancer progression

Chronic inflammation is associated with tumor development and progression. IL-18 plays a central role in inflammation and the immune response, contributing to the pathogenesis and pathophysiology of infectious and inflammatory diseases. High levels of IL-18 production may play a major role in the growth, invasion and metastasis of renal cancer (Saenz et al., 2010). Higher expression of IL-18 is detected in various cancer cells (Park et al., 2007). Patients with high serum IL-18 levels had a poorer survival than those with low serum IL-18 levels. Serum IL-18 level, but not IL-6 and IL-12 levels, was a significant and independent prognostic factor of survival in hepato cellular carcinoma (Tangkiivanich et al., 2007). Signaling through the adaptor protein myeloid differentiation factor 88 (MyD88) promotes carcinogenesis in several cancer models (Salcedo et al., 2010).

Interleukin 18 binding protein (IL-18BP), a potent inhibitor of interleukin 18, significantly up regulated in large volume disease. Elevated IL-18BP secretion from cancer cells suggests an attempt by cancer to escape immune surveillance. IL-18BP merits further study as a marker of aggressive prostate cancer and as a therapeutic target (Fujita et al., 2011). IL-18 inhibits cancer cell immune surveillance by indirect expression of programmed death-1 gene. IL-18 produced by tumor cells promotes the development of NK-controlled metastases in a PD-1-dependent manner. Accordingly, PD-1 is expressed by activated mature NK cells in lymphoid organs of tumor bearers and is up regulated by IL-18, as an immunosuppressive cytokine in cancer (Terme et al., 2011). VEGF-D enhanced cell migration is blocked by inhibiting IL-18. VEGF-D increased IL-18 expression and secretion, suggesting that IL-18 is a critical mediator for VEGF-D-enhanced migration. VEGF-D induced a disintegrin and metalloprotease 33 (ADAM33) expression, which has a metalloproteinase domain (Kim et al., 2009). IL-18 is an important non-invasive marker suspecting metastasis (Eissa et al., 2005).

Mechanism of IL-18 in cancer progression

Hypoxia induces the transcription and secretion of IL-18, which subsequently induces the expression of hypoxia-inducible factor-1alpha (HIF-1alpha). Mechanistically, IL-18 induces HIF-1alpha through the activity of the GTPase Rac1, which inducibly associates with the IL-18receptor beta (IL-18Rbeta) subunit, via a PI3K-AKT-

Table 3. Role of IL-18 in Cancer Progression

S. No	Activity of IL-18	Angiogenic protein	Type of Cancer	Reference
1	Angiogenesis	Down regulation of filamentous-actin polymerization and tensin	Gastric cancer cell lines	Kim et al., 2007
2	Angiogenesis	alpha(v)beta(3) integrin	Micro vascular endothelial cell (HMVEC)	Park et al., 2001
3	Anti- angiogenesis	Activation of T helper type 1 cells	Colon carcinoma	Tasaki et al., 2000
4	Tumor suppressor	Inhibiting fibroblast growth factor-2	Carcinoma	Cao et al., 1999
5	Inhibit immune surveillance	expression of programmed death-1	Lymphoid carcinoma	Terme et al., 2011
6	Inhibiting VEGF	disintegrin and metallo protease 33 (ADAM33)	Gastric cancer	Kim et al., 2009
7	Metastasis	Induction hypoxia-inducible factor-1alpha (HIF-1alpha)	Carcinoma	Kim et al., 2008

NF-kappaB-dependent pathway. HIF-1alpha-mediated tumor progression, in which the induction of IL-18 by hypoxia or inflammatory cells augments the expression of both HIF-1alpha and tumor cell metastasis (Kim et al., 2008).

Role of IL-18 in Immune Evasuion

A strong cell-mediated immune response is critical for controlling viral infections and is regulated by a number of cytokines. Large-scale genome studies have found correlations between single-nucleotide polymorphisms (SNPs) in the IL 18 promoter and spontaneous control of viral infections. IL-18 has been reported to inhibit hepatitis B virus replication in the liver of HBV transgenic mice. Combinations of IL-12, IL-18, and IL-21 have been shown to induce the antigen-independent production of interferon (IFN)-γ by effector and memory CD8 T cells. Orthopox viruses, ectromelia virus, encode immune evasion molecules that specifically target IL-18 and IFN-gamma. Cancer cells metastasize to the other site after escaping from the immune system and vascular endothelial growth factor (VEGF) play important roles in this process.

CD8 T cells produce IFN-γ and upregulate CD25 following exposure to certain combinations of IL-12, IL-18, and IL-21. The unresponsiveness of exhausted CD8 T cells is associated with down regulation of the IL-18-receptor-α (IL-18Rα). Exhausted T cells lose their susceptibility to antigen-independent activation by cytokines, which compromises their ability to detect bacterial co-infections (Ingram et al., 2011). Absence of both IL-12p40 and IL-18 resulted in increased susceptibility to infection and reduction in NK and CTL responses. IL-12p40 and IL-18 act in concert and play an important antiviral role through the up-regulation of IFN-gamma production and cell-mediated immune responses (Wang et al., 2009). Post transplant lympho proliferative disease tissues express significantly lower levels of IL-18 and interferon-gamma permitting the uncontrolled expansion of Epstein-Barr virus (EBV)-infected B lymphocytes, compared to lymphoid tissues diagnosed with acute EBV-induced infectious mononucleosis (Setsuda et al., 1999).

IL-18, can enhance Fas ligand expression and suppress the immune system (Cho et al., 2000). Cancer cells escape immune response by IL-18 and IL-18 receptors expression. IL-18 dose-dependently enhances proliferation accompanied by nuclear factor kappaB activation. IL-18-pretreated gastric cancer cells, decreased susceptibility to perforin or interferon-gamma production (Majima et al., 2006). IL-18 plays a key role in regulating the immune escape by production of Thrombospondin (TSP-1). TSP-1 is known to inhibit angiogenesis in several cancers. IL-18 enhanced the expression of phosphorylated JNK. Overall, these results suggest that IL-18 plays a key role in TSP-1 expression involving JNK (Kim et al., 2006). Endogenous IL-18 facilitate cancer cell immune escape by suppressing CD70 and increasing metastatic ability by upregulating CD44 and VEGF (Kang et al., 2009). IL-18 show dual effects on inhibition HBV replication and promotion of metastasis and migration in human hepatocytes. IL-18/

IL-18R-triggered signaling pathway increased activities of extracellular matrix metalloproteinase (MMP)-9, MMP-3, and MMP-2 by IL-18, which upregulated the mRNA levels of MMP-3 and MMP-9 in a NF-ϰB-dependent manner (Zang et al., 2011). IL-18 grow/invade and evade immune surveillance in the hosts.

Mechanism of immune suppression by IL-18

Said et al. showed that inflammatory cytokines cause an IL-10-dependent inhibition of CD4 T-cell expansion and function by up-regulating PD-1 levels on monocytes which leads to IL-10 production by monocytes after binding of PD-1 by PD-L.

Role of IL-18 in Cancer Metastasis

Cancer cells metastasize to the other site after escaping from the immune system and CD70, CD44 and vascular endothelial growth factor (VEGF) play important roles in this process. Implantation and growth of metastatic cancer cells at distant organs is promoted by inflammation-dependent mechanisms.

IL-18 is a pro inflammatory cytokine, key marker for matastasis. IL-18 levels suppress CD70 expression and increases immune susceptibility of cancer cells. Endogenous IL-18 facilitate cancer cell immune escape by suppressing CD70 and increasing metastatic ability by upregulating CD44 and VEGF (Kang et al., 2009). Expression of IL-18/IL-18R were remarkably up regulates and triggered signaling pathway related to metastasis in hepatocellular carcinoma (Zang et al., 2011). Expression of discoidin domain receptor 2 (DDR2) is essential for metastatic activity as it is regulate expression of IL-18 in hepatic stellate cells (HSC). DDR2 deficiency in HSCs led to decreased gene expression of interleukin IL-18 and insulin-like growth factor-I; and increased gene expression of prometastatic factors IL-10, transforming growth factor (TGF)β and vascular endothelial growth factor (VEGF) (Badiola et al., 2011). Erythroid differentiation regulator (Erdr1) is a stress-related survival factor. The expression of Erdr1 is negatively correlated with IL-18 expression. Erdr1 over expression markedly inhibited the level of cell migration, invasion, and proliferation in B16F10 cells in vitro (Jung et al., 2011). Selenium can prevent metastasis by inhibiting IL-18 gene expression in a dose-dependent manner. Selenium might be a potent inhibitor of the metastatic capacity of melanoma cells, via down-modulation of IL-18 expression (Song et al., 2011).

IL-1 gene is frequently expressed in metastases from patients with several types of human cancers. IL-1Ra
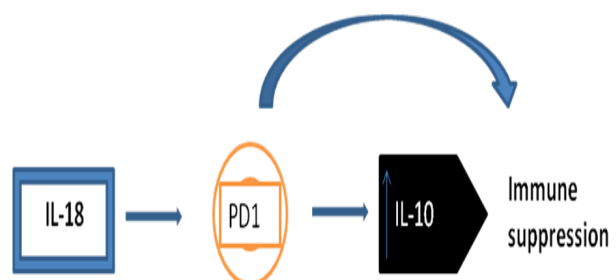

Figure 1. Mechanism of Immune Suppression by IL-18

inhibits xenograft growth in IL-1-producing tumors but has no direct antiproliferative effects in vitro; decreased tumor levels of IL-8 and VEGF may be an early surrogate of IL-1Ra-mediated antitumor activity. IL-1Ra may have a role alone or with other agents in the treatment of human cancers (Elaraj et al., 2006).

Resveratrol is anti inflammatory drug remarkably inhibited hepatic retention and metastatic growth of melanoma cells. The mechanism involved IL-18 blockade by resveratrol prevented IL-18-dependent expression of VCAM-1 by tumor-activated hepatic sinusoidal endothelium, preventing melanoma cell adhesion to the microvasculature and inhibited adhesion- and proliferation-stimulating effects of IL-18 on metastatic melanoma cells (Salado et al., 2011). Furthermore, IL-18-induced C6 migration and microfilament disassembly were antagonized by iNOS inhibitor, guanylate cyclase (GC) inhibitor and protein kinase G (PKG) inhibitor. IL-18 secreted by microglia, enhanced migration of C6 glioma through NO/cGMP pathway (Yen et al., 2011). Serum IL-18 negatively associated with overall survival in small cell lung cancer (NSCLC). Serum IL-18 levels were significantly higher in NSCLC with metastasis than in NSCLC without metastasis (Okamoto et al., 2009).

Role of IL-18 in Angiogenesis

Cell migration and angiogenesis are key steps in tumor metastasis. The relationship between pro-angiogenic and anti-angiogenic factors is responsible for the presence and intensity of neoangiogenesis. IL-18, a cytokine belonging to the IL-1 family, and is potent cytokine that induces the neo vascularization. IL-18 also called interferon-gamma (IFN-gamma)-inducing factor, has been characterized as a potent IFN-gamma-inducing cytokine. IL-18 is a highly regulated inflammatory cytokine that is elevated in synovial tissues and synovial fluids of patients with rheumatoid arthritis (RA). IL-18 induces endothelial cell migration and angiogenesis by binding and activating endothelial cells and indirectly by vascular endothelial growth factor. IL-18 mediates all these inflammatory processes by binding to its receptor, IL-18 receptor, and initiating the activation of different signaling cascades leading to changes in target cells gene expression and behavior. IL-12 and IL-18 play an important role as immunomodulatory factors in cancer pathogenesis (Volin et al., 2011).

Mechanisms of IL-18 in angiogenesis

IL-18 significantly enhanced the production of stromal cell-derived factor 1alpha (SDF-1alpha)/CXCL12, monocyte chemoattractant protein 1 (MCP-1)/CCL2, and vascular endothelial growth factor (VEGF). IL-18-induced SDF-1alpha/CXCL12 up-regulation was dependent on JNK, p38 MAPK, phosphatidylinositol 3-kinase (PI3K), and NFkappaB. IL-18-induced production of SDF-1alpha/CXCL12 was also dependent on protein kinase Cdelta (PKCdelta), production of MCP-1/CCL2 was dependent on PKCalpha, not PKCdelta. IL-18-induced MCP-1/CCL2 production was mediated by JNK, PI3K, and NFkappaB. IL-18 induced phosphorylation of JNK, PKCdelta, p38
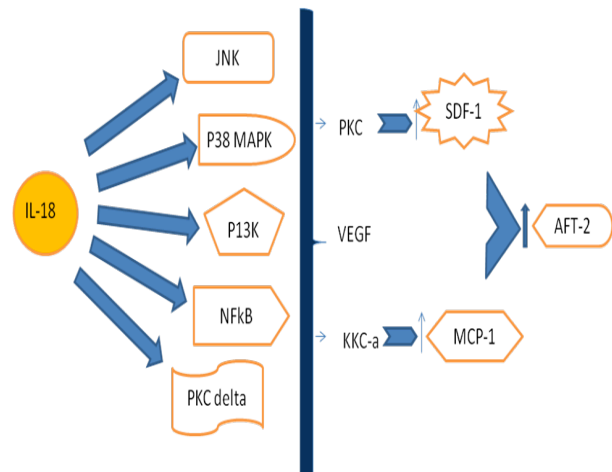
Figure 2. Mechanism of IL-18 in Angiogenesis by Different Pathways. IL-18; Interleukin-18, MCP-1; monocyte chemoattractant protein 1, SDF-1alpha; stromal cell-derived factor 1alpha, PKCdelta; protein kinase Cdelta, PI3K; phosphatidylinositol 3-kinase, ATF-2; activating transcription factor 2

MAPK, and activating transcription factor 2 (ATF-2) in fibroblasts in a time-dependent manner, with JNK-2 being upstream of PKCdelta, ATF-2, and NFkappaB. IL-18 has a unique role in inducing the secretion of angiogenic SDF-1alpha/CXCL12, MCP-1/CCL2, and VEGF in RA ST fibroblasts, via distinct signaling intermediates (Amin et al., 2007).

IL-18 enhances angiogenesis

IL-18 is associated with the induction of angiogenic factors, migration and malignant progression of tumors. Inhibiting IL-18 markedly reduced the level of Vascular endothelial growth factor (VEGF)-enhanced migration, and IL-18 increases cell migration directly through filamentous-actin polymerization and tensin down regulation (Kim et al., 2007). Human IL-18 induces micro vascular endothelial cell (HMVEC) migration. IL-18 appears to act on HMVECs via alpha(v)beta(3) integrin. The angiogenesis is independent of the contribution of local TNF-alpha. Down-regulation of IL-18 activity or AP-1 signal pathway can be potential therapeutic targets for rheumatoid arthritis. VEGF plays an important role in angiogenesis in rheumatoid synoviocytes (Cho et al., 2006). Microvascular abnormalities are one of the most important causes of persistent diabetic complications. Higher serum levels of sE-selectin and IL-18 were demonstrated in diabetic patients compared to controls. Significant differences of sE-selectin and IL-18 serum concentrations were observed between diabetic patients with microangiopathy and controls suggest that abnormalities in nailfold capillaroscopy may reflect the extent of microvascular involvement and are associated with higher sE-selectin and IL-18 serum levels, as well as with microangiopathic complications in diabetic patients (Kuryliszyn et al., 2011). Hyper glycaemia increases inflammatory cytokine concentration in the blood. Elevated levels of IL-18, in patients with Type 2 diabetes mellitus (DM2) and nephropathy. Recombinant human IL-18 injected intra dermally to murine skin

induced significant neovascular reaction. DM2 patients sera contained higher concentration of IL-18 and induced stronger neovascular reaction in mice skin than did the sera of corresponding control people (Skopinski et al., 2005). IL-18 regulates pathogenic retinal neovascularization by promoting its regression rather than inhibiting its development in an oxygen-induced retinopathy and is a useful, new approach to treating retinopathy in humans (Qiao et al., 2007).

IL-18 and Chemotherapy

Resistance to chemotherapy is the major cause of failure in cancer treatment. Time-dependent chemotherapeutic agents can selectively target tumor cells in susceptible phases of the cell cycle however a fraction of tumor cells in non-vulnerable cell cycle phases remain drug-resistant. Immunotherapy represents a promising approach to overcome the limitation of phase-specific drugs and improve their clinical efficacy. The cytokines associated with drug resistance, may represent potential serum biomarkers or novel drug targets. Mechanism of action of some anti cancer drugs by inducing or inhibiting specific cytokines. alpha-Galactosylceramide (alpha-GalCer) shows antitumor effects by activating natural killer (NK) cells indirectly through stimulation of the secretion of cytokines IL-18. The safety profile of IL-18 and its positive interactions with select anticancer chemotherapeutic agents strongly supports the clinical investigation of this combinatorial approach.

Role of IL-18 in chemo sensitive
Tumor immunotherapy with IL-18 can significantly augment the killing fraction of phase-specific chemotherapeutic drugs and provide survival benefit. Drug-resistant cells were more immunogenic with elevated expression of MHC-I and Fas (Alagkiozidis et al., 2011). Serum IL-18 concentration predicted the clinical outcome of patients with aggressive non-Hodgkin's lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). High serum levels increases overall survival rate in DLBCL. The high serum IL-18 patients with poor prognostic group in revised IPI or with non-germinal center B-cell phenotype had a very poor prognosis. Serum IL-18 might be a powerful prognostic factor for DLBCL. (Tsurumi et al., 2011). IL-18 in combination with alpha-GalCer exerts an antitumor effect on NK cell-sensitive tumors primarily by the direct stimulation of NK cells by IL-18 and the indirect stimulation of NK cells by alpha-GalCer through its activation of NKT cells (Nishio et al., 2008). Interleukin (IL)-18 plays important roles in cancer progression and metastasis. IL-18bp-Fc treatment was effective in inhibiting the lung metastasis tumor progression, validated by ex vivo examination of the lung (Cao et al., 2008). Selenium inhibits IL-18 gene expression in a dose-dependent manner. IL-18 protein level was suppressed by treatment with selenium. The wound-healing assay revealed that the anti-metastatic effect of selenium was abrogated by treatment with exogenous IL-18. These results suggest that selenium might be a potent inhibitor

of the metastatic capacity of melanoma cells, via down-modulation of IL-18 expression (Song et al., 2011).

High levels of interleukin (IL)-12 and IL-18 were associated with a sustained virological response. Conversely, high baseline IL-10 levels were significantly associated with a nonresponse to treatment. In multivariate analysis, low IL-10, high IL-12, and high IL-18 levels were independently associated with an SVR. Serum IL-10, IL-12, and IL-18 levels are predictive of the response to HCV treatment with pegylated interferon and ribavirin (Yoneda et al., 2011). Methicillin-resistant Staphylococcus aureus (MRSA) infection is a grave concern in burn-injured patients. IL-18 treatment increased the serum tumor necrosis factor (TNF), IL-17, IL-23, granulocyte colony-stimulating factor (G-CSF), and macrophage inflammatory protein (MIP-2) levels, as well as the neutrophil count, after MRSA infection of burn-injured mice (Kinoshita et al., 2011).

Cytokine quantification may assist in understanding the mechanisms leading to repeated IVF/ICSI failure: either depletion of cytokines necessary for the apposition-adhesion, or an excess of cytokines leading to local cytotoxicity, may impair the implantation of the embryo. Follicular concentration of G-CSF appears as a useful biomarker of oocyte competence before fertilization (Ledee et al., 2011).

Role of IL-18 Cytokines in Cancer Diagnosis

IL-18 is a pro inflammatory and immune-enhancing cytokine, which exerts antitumor effects in vivo, mediated by the induction of interferon (IFN)γ. Chronic inflammation is recognized as a predisposing factor for the development of cancer, but the molecular mechanisms linking inflammation and tumorigenesis have remained elusive. Some cytokines IL-2, IL-11, transforming growth factor (TGF) beta stimulate, while others IL-12, IL-18, Interferons (IFNs) inhibit breast cancer proliferation and/or invasion. Thus suggesting careful preclinical studies are needed to determine the proper application of IL-18 in cancer therapy.

IL-18 is a diagnostic marker
The IL-18 level in gastric cancer patient group was significantly higher than that in gastric ulcer patient group. The IL-6 level in gastric cancer patients with distant metastasis was significantly higher than that in those with no metastasis. The role of IL-10 and IL-12 levels in gastric cancer patients was to provide data with no significant difference. Serum IL-6 and IL-18, but not IL-10 and IL-12 levels may be the useful biological markers of clinical correlation and prognostic factor in patients with gastric cancer. Moreover, IL-18 could serve as a diagnostic marker for gastric cancer with a high positive predictive value (Thong et al., 2006). VEGF levels in induced sputum may have a prognostic role in the survival of small cell lung cancer (SCLC). The ratio VEGF/IL-18 in induced sputum differs between non-small cell lung cancer (NSCLC) and SCLC, indicating differences in angiogenesis mechanisms and immunological response in these two major histological types of lung cancer

(Rovina et al., 2011). The role of alpha foetoprotein (AFP) in the diagnosis of advanced HCC is well recognized. Increased levels of circulating interleukin-18 (IL-18) a suitable marker for the diagnosis of HCV-related HCC complementary to AFP, especially in cases with AFP level less than the diagnostic value (Mohran et al., 2011). IL-18 was an early and the most reliably detected host response to HCV infection measured in blood (Chattergoon et al., 2011). Inflammation regulated by is NOD-like receptor protein Nlrp3 through the assembly of proinflammatory protein complexes termed inflammasomes. IL-18 production downstream of the Nlrp3 inflammasome is critically involved in protection against colorectal tumorigenesis (Zaki et al., 2010). Expression levels of the IL-18 in the primary breast cancer tissue in relation to the unchanged breast tissue in same patients is significantly higher in breast cancer tumour tissue as compared to its expression in surrounding unchanged tissue of the same patients (Srabovic et al., 2011). IL-18 was reported as a potential biomarker of epithelial ovarian carcinoma (EOC) cells. IL-18 in EOC fluids is predominantly tumor-derived and that its lack of biological activity may represent a mechanism of tumor-escape (Orengo et al., 2010). Effects of a new combination, cytosine deaminase (CD) + uracil phosphoribosyl transferase (UPRT)-mediated gene-directed enzyme prodrug therapy (GDEPT) with interleukin (IL)-12 and IL-18, was effective against local and systemic prostate cancer and improved survival. Monitoring serum levels of IL-4 and MCP-1 may accurately reflect tumor burden and, hence, host response to therapy (Khatri et al., 2009).

IL-18 show antitumor activity by promoting expansion of gammadelta T cells. Incubation of gamma delta T cells in the presence with IL-18 produces higher levels GM-CSF, IFN-gamma, and TNF-alpha in human peripheral blood mononuclear cells (PBMCs) (Li et al., 2010).

Acknowledgements

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Manohar Babu Kuppala et al

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