Role of interleukin-32 in cancer progression (Review)

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Received July 13, 2023; Accepted November 8, 2023

DOI: 10.3892/ol.2023.14187

Abstract. Interleukin (IL)-32 is induced by pro-inflammatory cytokines and promotes the release of inflammatory cytokines. Therefore, it can promote inflammatory responses. The present review article summarized the role of the receptors required for IL-32 action, the biological function of IL-32 and its mechanism of action in tumors. Moreover, it assessed the significance of aberrant IL-32 expression in associated diseases and analyzed the effects of IL-32 on four key types of cancer: Colorectal, gastric, breast and lung. However, the mechanism of action of IL-32 needs to be further demonstrated by assessing the role of this cytokine in cancer to elucidate novel and reliable targets for future cancer treatments.

Contents

1. Introduction

In 1992, Dahl *et al* (1) identified and analyzed a transcript selectively expressed in lymphocytes for the first time from a cDNA library of human activated natural killer (NK) cell origin. It was named N-terminal and four kringle domains (NK4) of hepatocyte growth factor protein. Using sequence analysis, the mass of NK4 protein was measured to be 27 kDa. The presence of a signal loss deletion in the transmembrane region suggested that NK4 was a secreted protein (1). In 2005, Kim *et al* (2) demonstrated that IL-18 unresponsive cell was converted to a responsive cell by transfection of the IL-18 receptor beta chain, and IL-18-induced microarray revealed high expression of a cytokine-like gene. The cytokine was the NK4 protein, which was renamed IL-32. The IL-32 gene is ~1.2 kbp in length and the coding gene is located on human chromosome 16p13.3, containing eight exons that combine to form different IL-32 splice isoforms. A total of nine IL-32 isoforms have been identified as follows: IL-32α, IL-32β, IL-32γ, IL-32δ, IL-32η, IL-32θ, IL-32ε, IL-32ζ, and IL-32 small. IL-32α is the most abundantly expressed, IL-32γ has the highest biological activity of all isoforms and IL-32β has the highest genetic homology with humans. Although IL-32 is primarily expressed in immune cells, it has also been found in the spleen, thymus, lung, small intestine, colon, prostate, heart, placenta, liver, muscle, kidney, pancreas and brain (3-6).

Studies have reported that human hepatocyte cell lines and primary human blood mononuclear cells produce endogenous IL-32 and increase its levels in response to IL-1β and TNF-α stimulation (7-9). In addition, IL-32 is secreted and produced by primary human keratinocytes, macrophages, T lymphocytes and NK and mast cells (7,10). Cytokines, such as IL-2, IL-12, IL-18, IL-1β and IFN-γ, induce the expression of IL-3, whilst recombinant IL-32 notably induces the expression of TNF-α in the Raw 264.7 macrophage cell line (11). However, IL-32 can also induce the opposite effects. For example, it induces release of anti-inflammatory cytokines in immune cells, such as IL-10, and immunosuppressive molecules, such as indoleamine 2,3-dioxygenase (12,13).

In addition to inflammatory disease such as ulcerative colitis and chronic obstructive pulmonary disease (COPD), IL-32 is also involved in cancer disease progression. IL-32 is expressed in several types of cancer, such as gastric, hepatocellular, lung and pancreatic (14,15). However, the specific functions of each subtype of IL-32 and their receptors are still unclear. The present review summarizes the IL-32 receptor, the function of the different IL-32 isoforms, mechanism of action of IL-32 and its role in four major cancer types: Colorectal

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Key words: interleukin-32, colorectal cancer, gastric cancer, breast cancer, lung cancer

cancer (CRC) and gastric, breast and lung. Furthermore, the corresponding mechanism of action of IL-32 in these cancers is summarized.

2. Receptors for IL-32 action

Experimental analysis has identified proteinase 3 (PR3) with a molecular weight of 30 kDa, which binds specifically with high affinity to IL-32α (16). PR3 is a serine protease released in membrane-bound and soluble forms. It is present in neutrophils and monocytes and acts independently of enzymatic activity. The primary function of PR3 is to affect cell proliferation, differentiation and apoptosis. It also cleaves cytokines to enhance cytokine activity. Furthermore, the specific binding of IL-32β to PR3 has been elucidated using surface plasmon resonance. Secreted IL-32 is neutralized or attenuated by inhibiting the activity of PR3 or by using inactive PR3. IL-32 is also blocked by inactivating PR3. It may be possible to exploit the specific binding activity of these molecules for the clinical treatment of related diseases (17-19). The aforementioned effects may be due to PR3 exposure resulting in cleavage of p21 between Thr80 and Gly81, loss of nuclear p21 by cytoplasmic sequestration and depletion of p21 from cyclin/cyclin-dependent kinase (CDK) complexes, which attenuates function of intracellular caspases at the site of inflammation (20).

Studies have reported that expression of IL-32 is associated with disease activity and with glomerulonephritis (21-23). This suggests that IL-32 may be associated with cancer prognosis. To the best of our knowledge, however, the receptor for IL-32 has not been elucidated (16). If receptors corresponding to each subtype of IL-32 are found, the functional role of each subtype may be elucidated and the targeting effect exploited more efficiently for clinical applications.

3. Potential mechanism of IL-32 in cancer development

The roles of IL-32 include induction of the secretion of several cytokines and chemokines and T cell apoptosis and the enhancement of host defense (24,25). IL-32 acts primarily by stimulating pro-inflammatory cytokines through the activation of NF-κB and MAPK p38-mediated production of TNF-α, IL-1β, IL-8 and IL-6 (2), increasing tissue inhibitor of metalloprotease (TIMP)-1 promoter activity and inducing TIMP-1 expression via activation of the activator protein 1 signaling pathway (26) and serving a key role in macrophage differentiation via activation of cysteinyl aspartate specific proteinase-3 (caspase-3; Fig. 1) (27); studies have reported that IL-32 induces human monocyte secretion as well as THP-1 cell differentiation into macrophage-like cells with phagocytic activity against bacteria (28,29). Muramyl dipeptide, a ligand for nucleolar oligomerization structural domain 2 receptor, exhibits no effect on differentiation alone, whereas it enhances monocyte-to-macrophage differentiation via IL-32 (30-36). IL-32 also exhibits the opposite effect; in a previous study it was reported that the granulocyte-macrophage colony-stimulating factor IL-4-induced differentiation of dendritic cells into macrophage-like cells is reversed by IL-32 (32,36). Moreover, IL-32-induced differentiation of monocytes into macrophages is mediated by a caspase-3-dependent mechanism (26).

Isoforms of IL-32 do not serve the same roles and IL-32 may serve completely opposite roles in different types of cancer. IL-15 could effectively induce IL-32α expression in dendritic cells (DCs) and additional studies of IL-32α indicate that IL-32α could act on NK cells to inhibit IL-15-mediated phosphorylation of STAT5 (37-39). Moreover, it could inhibit IL-15-induced expression of effector molecules and cytolytic activity. The biological role of IL-32 as a cytokine has been demonstrated by inhibition of IL-15α during co-culture of DCs with NK cells, which is reported to result in the enhancement of NK cell effector molecule expression and augmentation of their cytolytic activity. This suggests the existence of a feedback mechanism of IL-32α in IL-15-mediated NK cell activation (37-40). IL-32α can also act on DCs by downregulating IL-15-induced IL-18 production (37). Park *et al* (40) reported that IL-32θ inhibits phosphorylation of MAPK and NF-κB *in vivo*. In addition, IL-32θ attenuates TNF-α promoter activity and inhibits binding of NF-κB with the TNF-α promoter (40). Previous studies have also reported that IL-32γ notably downregulates the expression levels of important cancer progression proteins, including antiapoptotic, cell proliferation and tumor progression-promoting genes, while it markedly induces upregulation of the expression of apoptotic genes (41-43). Furthermore, IL-32γ decreases levels of cytokines that promote tumor growth, such as TNF-α, IL-1β and IL-6, while increasing levels of IL-10 cytokines. IL-32γ inhibits progression of certain cancer types, such as melanoma, colon cancer, prostate cancer, liver cancer, and lung cancer (41,44). In addition, it induces the activation of cytotoxic T and NK cells to the tumor site to amplify the effect of cancer therapy (30,31). Studies have reported that IL-32β may promote antitumor effects by downregulating key cancer progression proteins, including antiapoptotic, proliferative and cell proliferation regulatory proteins, via the NF-κB and STAT3 proteins (45-47). In addition, IL-32β induces expression of proapoptotic proteins and regulates release of cytokines from colon and prostate cancer cells (45). However, high expression of IL-32α activates the NF-κB and STAT3 pathways and induces IL-6 production, thereby promoting cancer progression in patients with multiple myeloma (48). In summary, each IL-32 isoform serves a complex role. It is possible that interactions are present between the isoforms or that their roles differ due to cancer type and the tumor microenvironment.

4. Role of IL-32 in cancer

Numerous mediators of the inflammatory response, such as cytokines, free radicals, prostaglandins and growth factors, induce genetic and epigenetic changes, including point mutations in tumor suppressor genes, DNA methylation and post-translational modifications lead to alterations in key pathways that maintain normal cellular homeostasis, thereby promoting cancer development and progression (49). In summary, IL-32 is a cytokine that may serve a key role in the progression of cancer. Table I outlines the major roles and mechanisms of IL-32 in the progression of four types of cancers.

5. Role of IL-32 in CRC

Cytokines, such as IL-10, IL-17, IL-22, IL-23 and IL-35, may have clinical significance in the development of CRC (50-52).

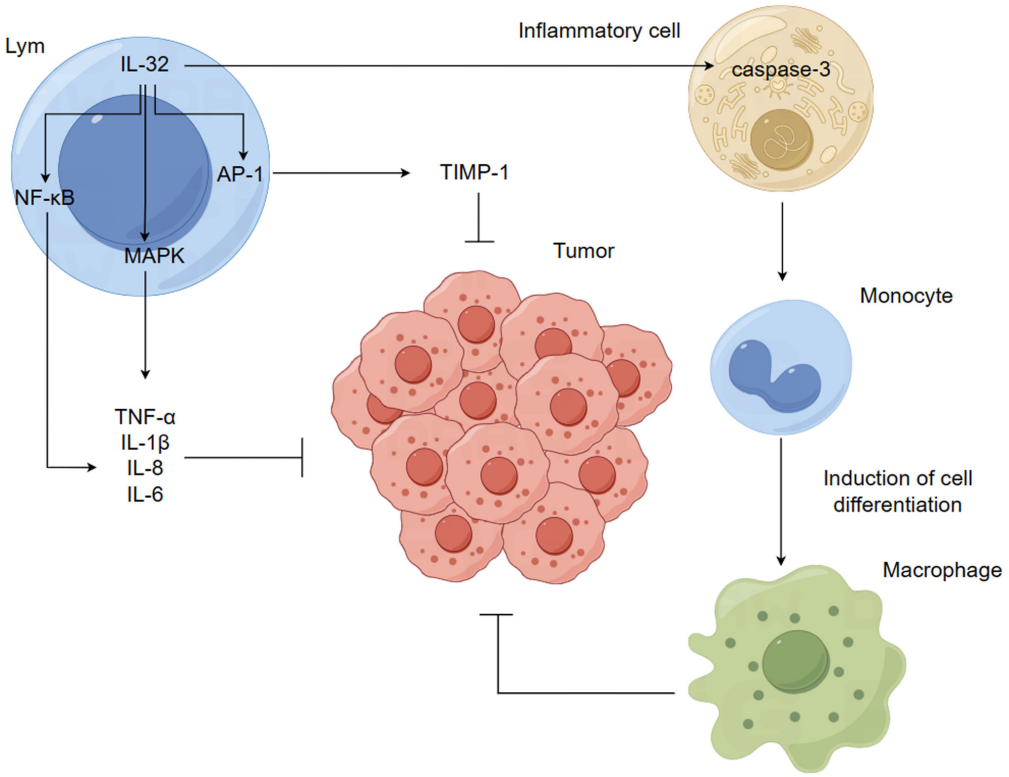

Figure 1. Mechanisms of action of IL-32. IL-32 stimulates pro-inflammatory cytokines via activation of NF-κB and MAPK p38-mediated production of TNF-α, IL-1β, IL-8, and IL-6; ② IL-32 increases tissue inhibitor of metal protease 1 (TIMP-1) promoter activity and induces TIMP-1 expression via activation of the activator protein 1 signaling pathway; ③ IL-32 plays a key role in macrophage differentiation through activation of cysteinyl aspartate specific proteinase-3 (caspase-3). IL, interleukin; Lym, lymphocyte; AP-1, activator protein 1; TIMP-1, tissue inhibitor of metalloproteinases 1; caspase-3, cysteinyl aspartate specific proteinase-3.

IL-32 has been reported to induce the release of numerous cytokines and chemokines (24,26), leading to increased expression of cytokines in the stroma. In a previous study, immunohistochemical (IHC) and statistical analysis of cancer tissue from patients with CRC and normal tissue demonstrated that the lymph node metastatic rate of IL-32(+)-CRC is 60%, which is considerably higher than for the cases without lymph node metastasis (53). This indicated that the levels of IL-32 expression may affect the grade of CRC, in which the overexpression of IL-32 stimulates organic and lymph node metastasis of CRC. IL-32 may be a biological marker of CRC metastasis. However, IL-32α expression can inhibit colon cancer cell proliferation and suppress CRC progression via reactive oxygen species, c-Jun N-terminal kinases and cysteine signaling. Increased IL-32α expression can also increase expression of tumor necrosis factor receptor 1 (TNFR1) and TNFR1-associated death domain protein (54), which promote cell death and reduce inflammatory damage (55). This suggests that elevated IL-32α expression may inhibit CRC progression.

6. Role of IL-32 in gastric cancer

Seo *et al* (56) assessed IL-32 expression in human gastric cancer using ELISA and demonstrated that high levels of IL-32 are present in gastric cancer mucosa compared with those noted in non-tumor mucosa. Tsai *et al* (57) identified the downstream effector molecules of IL-32 by assessing gastric cancer cells in the presence of ectopic expression or silencing of IL-32. This determined the effects of IL-32 on cancer cell motility, invasion and lung metastasis *in vivo*. IL-32 expression is notably upregulated in gastric cancer and positively associated with strong invasiveness and poor prognosis. Ectopic expression of IL-32 induces elongated morphology and increases cell migration and invasion via induction of IL-8, VEGF and matrix metalloproteinase (MMP)-2 and MMP-9 expression, mediated by the phosphorylated (phosphor)-AKT/phospho-glycogen synthase kinase 3β/active β-catenin and the hypoxia-inducible factor 1α signaling pathways (57). A further study evaluated the clinical role of IL-32 in development of gastric cancer, in which IHC assays were performed with tumor and non-tumorous tissue of the stomach from patients with gastric cancer who had undergone radical gastrectomy (58). Depth of tumors and the metastasis of lymph nodes were notably more severe in IL-32(+) patients with gastric cancer than in those who were IL-32(-) and cancer cells of the IL-32(+) group exhibited markedly more severe invasion of lymphatic ducts and veins than the cancer cells lacking IL-32 expression. IL-32, a pro-inflammatory factor, could induce immunosuppression by means of paracrine secretion, suggesting its expression in gastric cancer may serve as a preferential metastatic condition that allows cells to evade host antitumor immunity, thus promoting metastasis of tumor cells.

7. Role of IL-32 in breast cancer

Studies have established breast cancer tumor xenograft models and used specific experimental assays, such as MTT assay and TUNEL staining, to assess the effect of IL-32 on tumor cell proliferation and apoptosis (59-61). IL-32 notably increases

Table I. Roles and mechanisms of IL-32 in progression of colorectal, gastric, breast and lung cancer.

First author, year	Type of cancer	Role and mechanism of IL-32	(Refs.)
Yun *et al*, 2015	Colorectal	Immunohistochemistry suggests that overexpression of IL-32 stimulates organic and lymph node metastasis of CRC	(54)
Ebach *et al*, 2005		IL-32α suppresses CRC progression through reactive oxygen species, c-Jun	(55)
Seo *et al*, 2008		N-terminal kinase and cysteine signaling	(56)
Ishigami *et al*, 2013	Gastric	IL-32 increases cell migration and invasion via induction of IL-8, VEGF, MMP-2 and MMP-9 expression, mediated by the phospho-AKT/phospho-glycogen synthase kinase 3β/active β-catenin and the hypoxia-inducible factor-1α signaling pathways	(58)
Lin *et al*, 2018	Breast	IL-32 increases rate of cancer cell proliferation and decreases apoptosis, as	(60)
Pham *et al*, 2019		well as enhancing growth of tumor xenografts *in vivo*	(63)
Lee *et al*, 2019		IL-32θ inhibits breast cancer progression by targeting C-C motif chemokine ligand 18-dependent signaling	(64)
Sorrentino *et al*, 2009	Lung	IL-32 expression is associated with the pathogenesis of the majority of lung	(67)
Yun *et al*, 2018		cancer histotypes	(68)
Wallimann *et al*, 2023		IL-32γ increases tissue inhibitor of metalloproteinases-3 expression by	(43)
Liu *et al*, 2017		inactivating NF-κB activity via hypomethylation, thereby decreasing lung	(69)
Wang *et al*, 2017		tumor growth	(70)

IL, interleukin; CRC, colorectal cancer.

the rate of cancer cell proliferation and decreases the rate of cancer cell apoptosis. IL-32 markedly enhances growth of tumor xenografts *in vivo*, indicating that it exerts an inductive effect on the progression of breast cancer. However, studies have reported the inhibitory effect of IL-32θ on breast cancer progression (59,62). The mRNA expression levels of IL-32θ and chemokine ligand 18 (CCL18) have been analyzed in breast cancer tissue by reverse transcription (RT)-quantitative (q)PCR. To assess the effect of IL-32θ on cancer metastasis and cancer cell molecular signaling, *in vitro* cellular experiments have been performed using MDA-MB-231 cells expressing IL-32θ. *In vivo* xenograft, IHC and optical imaging models have been generated to further evaluate the *in vitro* and clinical findings. Clinical data demonstrate that IL-32θ overexpression notably attenuates the migration, invasion and release of pro-tumorigenic factors in breast cancer cells. IL-32θ serves as an intracellular regulator that inhibits macrophages by targeting CCL18-dependent signaling to promote breast cancer progression (63). The effects on cancer may be bidirectional due to the different actions of IL-32 isoforms.

8. Role of IL-32 in lung cancer

Due to the association between cancer and inflammation, studies have assessed whether pro-inflammatory cytokine IL-32 may be involved in lung carcinogenesis and therefore may be a novel therapeutic target (64,65). These studies analyzed association between IL-32 expression in patients with lung cancer (precancerous and malignant lesions) and clinicopathological and survival data. Confocal microscopy, microdissection and RT-qPCR have been used to identify the cellular origin and expression levels of IL-32 and the results indicated that IL-32 expression is markedly absent in the majority of squamous cell carcinoma (SCC; 76%) and precursor lesions but was strongly upregulated in adenocarcinoma (73%) and their precursors, 64% of large and 77% of small cell lung cancers. This suggests the possible association of IL-32 expression with pathogenesis of the majority of lung cancer histotypes. By contrast, IL-32 expression is not associated with the pathogenesis of SCC (66,67). Inhibition of TIMP-3 may promote tumor development based on the low expression of TIMP-3 in the inflammatory response. Previous studies have reported that promoter methylation results in a notable increase in TIMP-3 expression in lung cancer cells transfected with IL-32γ cDNA plasmid (67,68). Furthermore, mechanistic studies have indicated that TIMP-3 overexpression decreases NF-κB activity, leading to the inhibition of cell proliferation in IL-32γ-transfected lung cancer cells. The aforementioned study also indicated that IL-32γ inhibits expression of DNA (cytosine-5-)-methyltransferase 1, which demonstrates that IL-32γ could increase TIMP-3 expression by inactivating NF-κB activity via hypomethylation, thereby decreasing lung tumor growth (42,68,69). This suggests that the effect of IL-32 subgroups on lung cancer is also bidirectional.

Increased or decreased IL-32 expression in tumor tissue or serum may reflect the progression of certain diseases and its abnormal expression may have several implications. Firstly, IL-32 may serve as a marker of the presence of certain tumors. IL-32 is upregulated in the majority of lung cancer precursor lesions and tumor tissue compared with that of normal lung tissue (70). The marked elevation of IL-32α levels in peripheral blood samples of patients with hepatocellular carcinoma may aggravate degree of liver cell damage and a similar finding is reported in pancreatic and esophageal cancers (71). Secondly, upregulation of IL-32 may be associated with aggressiveness and distant metastasis of cancer and overexpression of IL-32 in CRC induces metastasis (72,73). Furthermore, RT-qPCR and western blot analyses have

demonstrated increased levels of IL-32 expression in highly invasive pancreatic cancer cells at the RNA and protein levels (74). Thirdly, IL-32 serves as an independent prognostic assessment factor for certain types of cancer. IL-32 expression is markedly upregulated in gastric cancer and positively associated with cancer aggressiveness and poor prognosis. Ectopic expression of IL-32 induces expression of IL-2, VEGF, MMP-2, MMP-9 and MMP-3, as determined using fluorescent-AKT/phospho-glycogen synthase kinase 8β/active β-linked protein, to increase gastric cancer cell migration and invasion (75). Therefore, the association between increased IL-32 expression and poor prognosis of gastric cancer indicates that IL-32 may be an independent prognostic assessment factor for this cancer type (57).

9. Conclusion

In the present study the primary functions of isoforms of IL-32 and their roles were described in different types of cancer, indicating the complex functions of each isoform of IL-32 and the possible presence of different isoforms in different tumors and microenvironments. To the best of our knowledge, the receptors of IL-32 and functions and mechanisms of action of each isoform are not well-studied (24) and further studies are required to determine functional characteristics of IL-32 under different disease conditions to use these functions for the purpose of disease treatment.

Acknowledgements

Not applicable.

Funding

The present study was supported by Natural Science Foundation of Heilongjiang Province (grant no. LH2021H106) and the Basic Research Fund of Universities of Heilongjiang Province (grant no. 2021-KYYWF-0598).

Availability of data and materials

Not applicable.

Authors' contributions

DM performed the literature review and wrote the paper. HD and JW was responsible for reviewing the literature and revising the final paper. CW and RZ were involved in the literature search and the insertion of these and were involved in summarizing and amending the abstract. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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