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Review Article

IL-32θ: a recently identified anti-inflammatory variant of IL-32 and its preventive role in various disorders and tumor suppressor activity

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Abstract: Interleukin-32 theta (IL-32θ) is newly identified isoform of IL-32 which plays a vital role in inflammatory responses. Like IL-32α and IL-32β, IL-32θ isoform acts as an intracellular inflammatory modulator. It results in reduction of IL-1β production by attenuating the expression of PU.1 and inhibition of monocytes differentiation into macrophages. IL-32θ hinders TNF-α expression by inhibiting p38 MAPK and inhibitor of κB (IκB) as well. It also reserved STAT3-ZEB1 pathway leading to the inhibition of epithelial-mesenchymal transition (EMT) and stemness. Hence, it can be concluded that IL-32θ is an anti-inflammatory cytokine that can act as a tumor suppressor and can play vital role in colon cancer therapies. IL-32θ also plays a crucial role in immune system responses and cellular differentiation during disease pathogenesis. To our best knowledge this is the first ever review to condense the importance, precise mode of action in disease progression and latent remedial implications of IL-32θ in several inflammatory disorders.

Keywords: Cancer, cellular differentiation, IL-32θ, inflammation, remedial, tumor suppression

Introduction

A number of biological processes like development, differentiation and activity of immune cells are regulated by the specific soluble proteins known as cytokines [1]. Cytokines are produced and responded by almost all cells [2]. Any alteration in production and activity of these cytokines leads to the onset of various autoimmune disorders (inflammatory bowel disease, gastric cancer etc) and autoimmunity [1]. Several studies proved that cytokines exercise a pivotal job in the development and progression of multiple ailments like crohn's disease, inflammation and rheumatoid arthritis besides considered as important component that may prove to be effective therapeutic targets [3, 4]. Numerous growth factors and cytokines are involved in injury induced neural damage and repair as well as orchestrate cellular behavior in cornea healing [5, 6]. Cytokines have been reported to be useful in HIV treatment therapies as well as in therapies that enable immune system to identify and destroy cancerous cells [7-9]. Therefore, cytokines are helpful in immunogenic tumors and hematologic malignancies treatment.

Broadly cytokines can be classified into various protein families on the basis of structural homology i.e. hemopoietic cytokines, TNF family and IL-1 and related proteins. The hemopoietic cytokine family is a large cytokine group containing helical bundles and collectively play vital and varied role in regulation of immune system [10].

Interleukins (ILs) are cytokines that act as messenger molecules transmitting signals between cells of immune system. They are secreted by lymphocytes and macrophages and their production is initiated in response to infection and injury. Interleukins activity has been reported to influence cells of the immune system along with the tissues and organs i.e. liver and brain [11]. They are of various types ranging from IL-1 to IL-37 [12].

Interleukin-32 (IL-32) is a recently reported interleukin, encoded by a gene present on

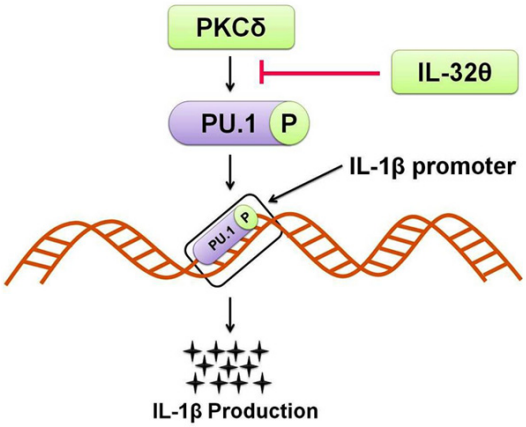

Figure 1. How IL-32θ inhibits IL-1β production: IL-32θ attenuates IL-1β production by inhibiting the PKCδ interaction to PU.1. As IL-32θ inhibits PKCδ mediated PU.1 phosphorylation it ultimately prevents IL-1β transcription and production.

human chromosome 16 p13.3, consisting of eight coding regions (exons). Pathogenesis of various disorders is mediated by IL-32 that involves interplay among body cells and immune system [13]. IL-32 induces the expression of various inflammatory cytokines and macrophage inflammatory protein-2 (MIP-2) which are known to be involved in progression of various inflammatory diseases and pathogenesis including cancer, inflammatory bowel disease (IBD), rheumatoid arthritis, gastric inflammation and chronic obstructive pulmonary disease (COPD) [14].

Review

IL-32 exhibits six isomeric forms (α, β, γ, δ, ε, and ζ) that arise from alternative splicing of mRNA [15-17]. Among the variants, IL-32α is the most abundant protein secreted by natural killer (NK) cells, T cells, monocytes, epithelia and endothelial cells. It acts as an important effector and mediator of abnormal immune responses that lead to the auto immune responses and multiple inflammatory disorders including COPD, IBD, rheumatoid arthritis etc. [13]. IL-32β was reported to influence the secretion and expression of an anti-inflammatory cytokine i.e. IL-10 [18-22]. Besides, previously reported six isoforms of IL-32, three more isoforms (η, θ, s) are newly reported. It has been reported that IL-32θ interacts with IL-32β and ceases IL-10 production [19].

IL-32θ in myeloid cell differentiation

Myeloid cell differentiation is a strictly controlled process regulated by a number of cytokines and some transcription factors because any interruption in myeloid lineage differentiation results in blood cancer and immune problems [23]. Lineage commitment is under tight regulation of GM-CSF and some other key interleukins [24-26]. Previously, most of the studies involving IL-32 were carried out to understand its proinflammatory activities in innate immune response. However, some studies have been carried out recently focusing the involvement of IL-32 in apoptosis and metastasis. Furthermore, its level has been reported as a potent diagnostic marker of gastric cancer [27-30]. Since the time of its discovery, progress in the study of the relationship of IL-32 with cell differentiation is quite slow. IL-32 by thymic stromal lymphopoietin provokes monocytic differentiation in macrophages [31]. Moreover, it synergistically causes differentiation of osteoclasts along with IL-17 which is a key regulator of osteoclastogenesis *in vitro* [32, 33]. IL-32γ has also been reported to be involved in dendritic cell maturation by inducing IL-12 and IL-6 expression [34]. IL-32αbyrestrainingPU.1expressioninaSTAT3-dependent manner was shown to be involved in differentiation of THP-1 cells [35]. Cell differentiation by all other isoforms of IL-32 is still unclear, and it seems that myeloid differentiation depends on each isoforms of IL-32. It has been previously reported that IL-32θ expression leads to a reduction of IL-1β production by attenuating phosphorylation of PU.1 [36] (**Figure 1**). PU.1 is an important element of Ets family of transcription factors that not only regulates the expression of various macrophage-specific genes *viz,* glycoprotein pDP4 [37], CD11b [38], CD18 [39] but is also required for monocytic differentiation [40-42]. Therefore it could be expected that IL-32θ may suppress PU.1 expression by binding to a distal enhancer on the PU.1 promoter region, as PU.1 executes auto-regulatory functions [43]. Similarly, CCAAT-enhancer-binding protein α (C/EBPα) is also an important transcription factor like PU.1 that is significantly involved in differentiation of monocytes into macrophage [44]. C/EBPα induces PU.1 expression via binding to distal enhancer of PU.1 [45]. Kim MS *et al.,* (2015) reported the involvement of IL-32θ in the inhibition of phorbol 12-myristate 13-acetate (PMA)-induced

monocytic differentiation in both THP-1 and HL-60 cell lines. Even macrophage cell surface markers, CD11b, CD18, and CD36 expression has been repressed by IL-32θ. Expression of cell cycle related factors was neither affected by IL-32β nor by IL-32θ, thus, it has no contributions towards PMA-induced cell cycle arrest. IL-32θ attenuates PU.1 expression, thus in THP-1/IL-32θ cells transitory expression of both C/EBPα and PU.1 results in rescuing the differentiation defect acting synergistically [46]. Thus, IL-32θ inhibits monocytic differentiation by suppressing PU.1 expression. Various attempts i.e. 'differentiation therapy' have been made in the past to treat myeloid leukemia [47, 48]. IL-32θ is a significant contributor and may prove to be a useful therapeutic tool in treating myeloid differentiation-mediated diseases.

IL-32θ in acute myeloid leukemia (AML)

AML, a malignancy of hematopoietic stem cells, is characterized by a reduced production of normal blood cells as well as a buildup of dysfunctional myeloid cells [49]. A number of factors of varying nature including carcinogens [50], mutations [51, 52] and radiation [53] are responsible for AML. AML is regulated by a network of cytokines regarding propagation, apoptosis, and differentiation of leukemic cells [54]. Level of various cytokines in patients of AML is reported to be higher than that of healthy individuals. Cytokines produced in leukemogenesis are TNF-α, IL-6, and IL-1β which induce AML blast growth via colony stimulating factor (CSF)-induced clonogenicity *in vitro* [55]. In contrast to it, cytokines involved in development and differentiation of AML cells are downregulated by IL-10 [56]. In a study, NF-κB has been reported as an active constituent whose level is fairly maintained in AML patients in RelA/p50 and p50/p50 complexes [57]. A consistent higher level of TNF-α results in persisting proliferation and is maintained by NF-κB activation in AML blasts [58]. Certain hematologic diseases like AML oftenly develop because of an altered profile of cytokines [59, 60]. TNF-α expression in leukemia blasts has been reported to be much higher in patients with AML than in cells of healthy persons [61]. In hematopoiesis, TNF-α is pleiotropic in action as it increases the expression of IL-1β and GM-CSF [62], induces apoptosis in leukemic cells [63] and results in senescence as well as chromosomal instability [64]. Leukemic blasts of AML normally show a highly activated and over-expressed PKCs level [65]. In various cell types, TNF-α gene transcription is regulated by PKC via PKC signaling pathways [66]. Rottlerin (a PKCδ-specific inhibitor) not only influences the synthesis of a number of cytokines but restrains TNF-α production as well [67]. It has been attempted to prevent AML tumorigenesis in some recent trials by targeting PKC-mediated signal transduction pathways [68]. PKCs mostly trigger p38 MAPK and NF-κB signaling either directly or indirectly [69-71]. Activation of p38, in Mo7e human megakaryoblastic leukemia cell line, partially supports NF-κB (p65) transcriptional activation function [72]. Furthermore, upon regulation by p38, NF-κB transcriptional activation via p65 phosphorylation leads to TNF-α production [73]. Various molecules, regardless of p38 association with NF-κB, involved in PKC signaling may be positive regulators of TNF-α gene expression [74]. In a study, NF-κB via autocrine TNF-α secretion constitutively activated AML [58]. On the basis of above mentioned observations, it may be proposed that TNF-α production is provoked by complex signaling pathways that require the activation of PKC, p38 MAPK and NF-κB either individually or together. Various isoforms of IL-32 have been named for their involvement in a number of inflammatory disorders that are characterized by upregulation of proinflammatory cytokines [75]. In contrast to it, some recent studies have reported IL-32 as an intracellular intermediary molecule as it interacts with many other molecules [35, 76, 77]. Regulation of a spectrum of pro- and anti-inflammatory cytokines including IL-1β, IL-6, and IL-10 in the cells associated with PKC isoforms by IL-32 has been reported previously [18, 36, 78]. As IL-32θ inhibit the IL-1β and CCL-5 expression which via PKCδ association and regulation of its downstream signals is involved in the pathogenesis of inflammatory diseases, considered as an anti-inflammatory component. Furthermore, IL-32θ by attenuating PU.1 expression suppresses monocytic differentiation into macrophage [46]. Kim MS *et al.,* (2015) reported the expression of endogenous IL-32θ in 38% of the patients suffering from AML compared to healthy individuals. TNF-α level was not found to be increased with IL-32θ expression. PMA-induced TNF-α production was reported to be attenuated by IL-32θ. IL-32θ

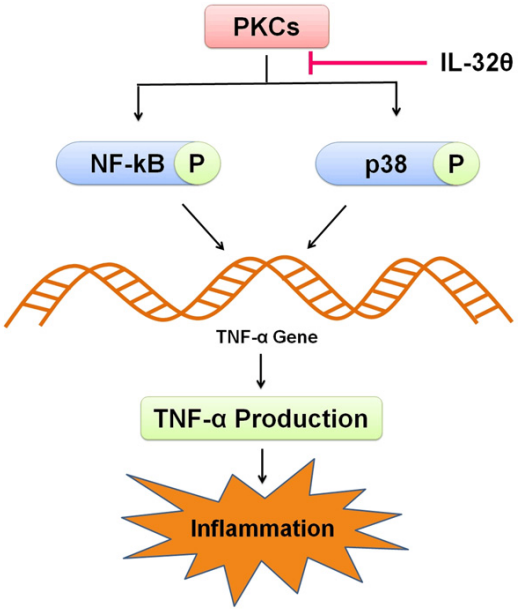

Figure 2. Attenuation of TNF-α production by IL-32θ. PKCs promote TNF-α production through p38 MAPK and NF-κB signaling. As IL-32θ prevents nuclear translocation of NF-κB by inhibiting p38 MAPK, it ultimately prevents inflammation by inhibiting TNF-α production.

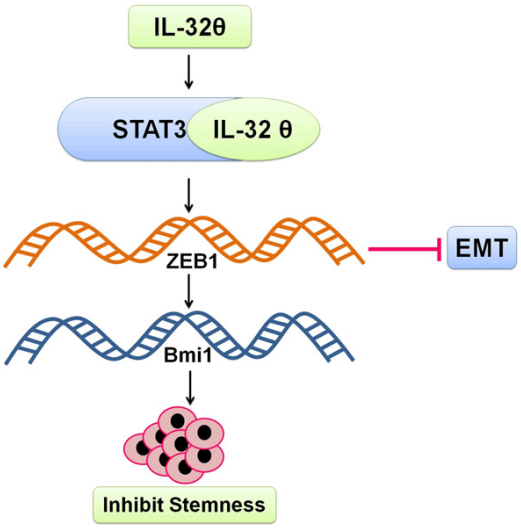

Figure 3. Inhibition of stemness and EMT by IL-32θ. IL-32θ interacts with STAT3 pathway to suppress ZEB1 and Bmi1 transcription and ultimately prevents stemness and EMT in colon cancer cells.

inhibited activity of nuclear translocation of NF-κB (a key positive regulator of TNF-α expression) by inhibiting phosphorylation of p38 MAPK. Hence, it may prove as an inhibitor of TNF-α in AML patients [79] (**Figure 2**).

IL-32θ in colon cancer

Colon cancer is the 2nd largest cause of cancer-related mortality. Some cancer cells are resistant to current therapies i.e. cancer stem cells (CSCs) [80]. Entire tumor population has been reported to be recapitulated by CSCs *in vitro* and *in vivo* [81]. There has been growing evidence of the presence of CSCs in breast [82], colon [80] ovarian [83] and brain cancer [84]. They have been associated with recurrence, progression and drug resistance of cancer [85]. Like undifferentiated hematopoietic stem cells, CSCs also express markers of stem cells [84] and show self-renewal ability [86]. Such an ability is responsible for promoting tumorigenesis [87]. Constant activation of STAT3 has been reported to be responsible for perpatuation of colon cancer [88, 89] and colon cancer-initiating cells [90]. STAT3 is one of the significant signaling pathways among various oncogenic pathways in cancer. Several researchers have previously tried to elaborate abnormalities in this pathway during colon cancer [91, 92]. However, the exact mechanism involved in STAT3 inhibition during colon cancer is still unclear. The fate of CSCs is determined by both intrinsic and extrinsic pathways *viz,* cytokine networks [85, 93]. In breast cancer, IL-6 and IL-8 enhance CSC self-renewal [94, 95] while in colon cancer, stemness and invasiveness of CSCs is stimulated by IL-1β [96]. Similarly, IL-32 has also been reported to regulate various types of cancer. IL-32α has been reported to be involved in the development of hepatocellular carcinoma [29] but in contrast, it has also been reported to repress colorectal cancer [97]. Furthermore, IL-32β has been reported to inactivate NF-κB and STAT3 pathways as well as found to promote cytotoxic lymphocyte activation and stimulate breast cancer cells migration as well [98, 99]. Role of IL-32θ in colon cancer is still to be elucidated. IL-32θ has sequence homologies with IL-32β but lacks exon 6 [100]. Bak Y *et al.,* (2016) reported suppression of IL-32θ mRNAs expression in colon cancer patients in tumor regions. IL-32θ leads to repression of invasive and migratory potential of HT29 colon cancer cells by inhibiting epithelial-mesenchymal transition (EMT). IL-32θ amends genes of CSCs responsible for sphere formation and expression of stemness. IL-32θ tends to inhibit transcription of Bmi1 and ZEB1 (downstream factors) by directly binding to

STAT3 and inhibiting nuclear translocation. IL-32θ stops key factors of EMT and inhibits stemness by inhibiting STAT3-ZEB1 pathway (**Figure 3**). They concluded that IL-32θ may be a tumor suppressor and may probably be used in near future as therapy for colon cancer [101].

IL-32θ in IL-1β production

Immune system responses to various types of stimuli have been reported to be mediated by human myelomonocytes THP-1 cells. The isomers of IL-32 were typically characterized as being pro-inflammatory cytokines in the immune system [102, 103]. The isomers of IL-32β induce anti-inflammatory cytokine IL-10 [18]. It can therefore be suggested that IL-32 performs both anti- and pro-inflammatory effects on cells of immune system. Moreover, its isomers interact with other molecules via their binding motifs and display intercellular activity [18]. IL-32 isomers interact particularly with heterogeneous PKC isomers that lead to the pro- and anti-inflammatory cytokines production [78, 104].

Various immune system responses were mediated by novel PKC family via pro-inflammatory cytokines production [105-107]. PKC-α and PKC-δ induced toll like receptor (TLR)-2/4 expression that leads to the high glucose induced-immuneresponses [108]. PKC-δ also involved in increasing IL-2 production by expressing themselves in lymphoid cells. It has also been reported to be involved in cytokine production and peri-bronchiolar cell proliferation in lungs of PKC-δ knockout mice [109, 110].

PKC-δ binds to the PU.1 and activates it resulting in the phosphorylation of its trans-activator domain [111]. PU.1 may bind with multiple target promoters and is involved in various immune responses [112, 113]. IL-1β also acts as transcription key regulator because PU.1 has an ability to bind to the consensus sequence of IL-1β promoter region [113, 114]. PU.1 along with other transcription factors including interferon regulatory factor (IRF)-4/8 and C/EBPβ regulates IL-1β transcription in human monocytes [113-115].

IL-32θ also acts as a strong intracellular modulator as it reduces the production of IL-1β in THP-1 human myelomonocytes by binding to the PKCδ that ultimately suppresses interaction between the PU.1 and PKCδ. Consequently, it leads to the inhibition of PKCδ-mediated PU.1 phosphorylation and hence inhibits IL-1β production (**Figure 1**). These findings suggest that IL-32θ plays a key role as intracellular modulator in the production of cytokines [36].

IL-32θ down regulates CCL5 expression

Activated CCL5 genes encode a normal T cell-expressed and secreted (RANTES) protein that expresses during late activation of T-cell [116]. CCL5 belongs to CC chemokine family which has two pairs of adjoining cysteine residues locating nearby their amino terminus. Members of this family of chemokines show achemotactic effect on T cells, monocytes, basophils and eosinophils [117-121]. CCL5 expression has been found in different types of cells such as epithelial cells, vascular smooth muscle cells (VSMCs), monocytes, macrophages and fibroblasts [116, 122-124]. CCL5 was reported to be involved in onset of a number of inflammatory disorders [125, 126].

Signal transducers and activators of transcription (STAT) are triggered by several cytokines, kinases and growth factors. Seven STAT family members including (STAT 1, 2, 3, 4, 5A, 5B and 6) have been identified [127-130]. Constitutive activation of STAT leads to the onset of cancer and suppresses immune system [130, 131]. Receptor associated tyrosine kinase family including JAK activates STATs by phosphorylating the target portion on carboxylterminus that causes dimerization and translocation of STAT3 and binding to target genes DNA as well [132, 133]. In comparison to other transcription factors STAT proteins contain Src homology (SH2) domain that acts as receptor-binding domain and facilitates dimerization of STAT proteins [134]. STAT3 can be phosphorylated on both Ser727 and Tyr705 residues and it was found that Tyr705 is highly important for the activation of STAT3 whereas Ser727's role in activation of STAT3 is not clear [135-138].

IL-32θ blocks the CCL5 signaling by altering phosphorylation of STAT3 on Ser727. Upon stimulation of PMA, IL-32θ interacts with PKCδ and form a trimeric complex with it and STAT3. This trimeric complex facilitates the induction of IL-32θ and phosphorylation of STAT3 on Ser727 controlled by PKCδ. IL-32θ activity was

mediated by PKCδ that leads to the inactivation of STAT3. Physical interaction of IL-32θ with PKCδ and STAT3 is phosphorylated at Ser727 which inhibit its trans-activating activity leading to the blockade of STAT3-mediated expression of CCL5. These findings confirmed that IL-32θ interacts with PMA-activated PKCδ that results in phosphorylation of STAT3 at Ser727. IL-32θ-mediated phosphorylation of STAT3 on Ser727, delays its ability to bind to DNA and hinders transcription of CCL5 gene [100]. Even under PMA stimulation, IL-32θ has an ability to inhibit translocation of STAT3 because the transcriptional activation of the CCL5 promoter takes place by binding of STAT3 to CCL5 promoter regulatory element [122]. Furthermore, it was reported that unphosphorylated STAT3 compete with IκB and forms a transcriptional complex with unphosphorylated NF-κB to initiate expression of CCL5 [116].

Therefore, it is concluded that in signaling pathway of IL-32θ, PKCδ acts as a serine kinase of STAT3 that leads to the activation of phosphorylation of STAT3, ultimately leading to inhibition of CCL5 expression.

Conclusion

In the light of the foregoing literature cited on IL-32θ, it can be concluded that IL-32θ plays a crucial role in immune system responses and cellular differentiation during disease pathogenesis as well as tumor suppression. Therefore, in future, it can be used in cancer therapies. However, more critical and extensive clinical investigations are highly recommended for a better and deeper understanding of possible therapeutic applications. To our best knowledge this is the first ever review to condense the role, exact mechanism of pathogenesis and latent therapeutic uses of IL-32θ in several inflammatory disorders.

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Disclosure of conflict of interest

None.

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