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Role of Interleukin-1 Super Family in Progression of Osteoarthritis

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Abstract

Osteoarthritis (OA) is considered as multifactorial disorder characterized by erosion of articular cartilage, tightening of joint space, subchondral bone remodelling and internal synovial inflammation. OA reduces joint function progressively as a person gets older. The most important group of the cytokines or chemokines are pre-dominantly involving in the early progression of the disease includes IL-1, IL-6, IL-18 and TNF-α, etc. IL-1 family of cytokinesare known to be strongest stimulus for progressive synthesis of Matrix Metallo Proteinases (MMPs). Large number of immune cells, chondrocytes and endothelial cells potentially secrete IL-1 with diverse effect on number of diseases. This review highlights the association of IL-1 family cytokine in OA.

Keywords: Cytokine, IL-1 family, Mode of Action, Osteoarthritis

1. Introduction

Osteoarthritis (OA) is a chronic disorder affecting knee, hip and other body joints, that frequently causes the reduction of joint functions and disability (Helmick *et al.,* 2008) (Fu *et al.,* 2015). OA is associated with reduced quality of life and economic burden on society today for middle age and older age people (Arliani *et al.,* 2014), an average 27 million people affected with arthritis in United State population (Lawrence *et al.,*2008). OA is potentially irreversible disease (Wojdasiewicz *et al.,* 2014) that reduces range of motion of joints and characterized by increased catabolic rate of articular cartilage, sub chondral bone remodelling (Swellam *et al.,* 2010) and joint inflammation. The constantly increasing number of risk factors of OA includes obesity, aging, genetic predisposition, drug abuse, trauma and other systemic diseases (Richette *et al.,* 2003) which are responsible for up-regulationof different catabolic mediators like IL-1, IL-6, IL-15, IL-17 and IL-18 etc.

Over catabolism of cartilage destabilizes the joints and limits their functional ability (Choi *et al.,* 2013). Under normal state, joints maintain their homeostasis for synthesis and degradation of articular cartilage, whereas in osteoarthritic condition there is excessive degradation of cartilage occur. In OA, Chondrocytes are the only cells residing in cartilage which are targeted to number of pro-inflammatory mediators. IL-1β in particular consider as a key mediator of cartilage damage and Extra Cellular Matrix (ECM) protein degradation through inducing the ECM degradative enzymes and other catabolic mediators, including IL-6, IL-8 etc (Guerne *et al.*, 1990) (Lotz *et al.,* 1992). Production of proteolytic enzymes in the extracellular space include collagenases such as matrix matelloproteinase-1, 13 (MMP-1, 13), aggrecanases (ADAMTS-4 &5, MMP-3) (Malfait *et al.,* 2002) and hyaluronidase etc. These destructive enzymes are causing breakdown of ECM component (Bau *et al.,* 2002; Lark *et al.,* 1997) (Nagase H and Kashiwagi M., 2003). Two chief glycoproteins are collagen type-II and aggrecans present

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in ECM which established the strength of articular cartilage (Lee *et al.*, 2013). Final output of the cumulative effect of catabolic cytokines on ECM are result in synovitis, pain, joint remodelling, joint destruction, narrowing of joint space, inflammation at the site of destruction and finally loss of joint function that eventually leads to OA. IL-1 has been implicated in pathophysiology, immunological response at sub cellular level and also in pain induction (Barretoa, A. and Braunb, T. R., 2016). The complex mechanism of pathophysiology of the joint cartilage destruction has not been fully elucidated during osteoarthritic condition. The purpose of this review is to highlighting possible association of IL-1 with OA.

2. Interleukin (IL-1) Classification

Cytokines are nearly synthesized by all nucleated cells. These are small, soluble and membrane associated or chemically modified protein (glycoprotein) signal molecules having molecular weight of 8 to 40,000 Da (Banerjee, M. And Saxena, M., 2012). Cytokines are chemically diverse group and categorised into different forms such as interleukin, growth factor, interferon, chemokine and Colony Stimulating Factor (CSF) etc. On the basis of their effect outcomes, cytokines have been broadly divided into two sub classes that are pro inflammatory mediators include IL-1, IL-6, IL-17, PGE-2, TNF-α, TGF-β and anti-inflammatory mediators such as IL-1RN, IL-4, IL-10, IL-13 etc. It has observed that the biosynthesis and secretion of these cytokines varies from disease to disease.

OA is destructive joint disease with elevated level of circulating inflammatory cytokines that have role in progression of disease and its etiological processes. Chondrodestructive inflammatory mediator is IL-1, primarily synthesized by chondrocyte cells (Loughlin *et al.,* 2002). It has reported in human and mice that IL-1 cytokine family consist of 11 different proteins naming from IL-1F1 to IL-1F11 that are encoded from 11 individual genes (Weber *et al.,* 2010). IL-1 super family consist of three main classes of related cytokines such as IL-1α, IL-1β and Interleukin-1 receptor antagonist (IL-1RN) whereas subtypes of IL-1Receptor, Interleukin-1 Receptor-Accessory Protein (IL-1R-AcP) and IL-18 also belongs to IL-1 super family (Banerjee, M. and Saxena, M., 2012) (Fig. 1). IL-RN was identified for counteracting the inflammatory effect of IL-1 without inducing downstream signal transduction (Grover *et al.,* 2006). Genes of

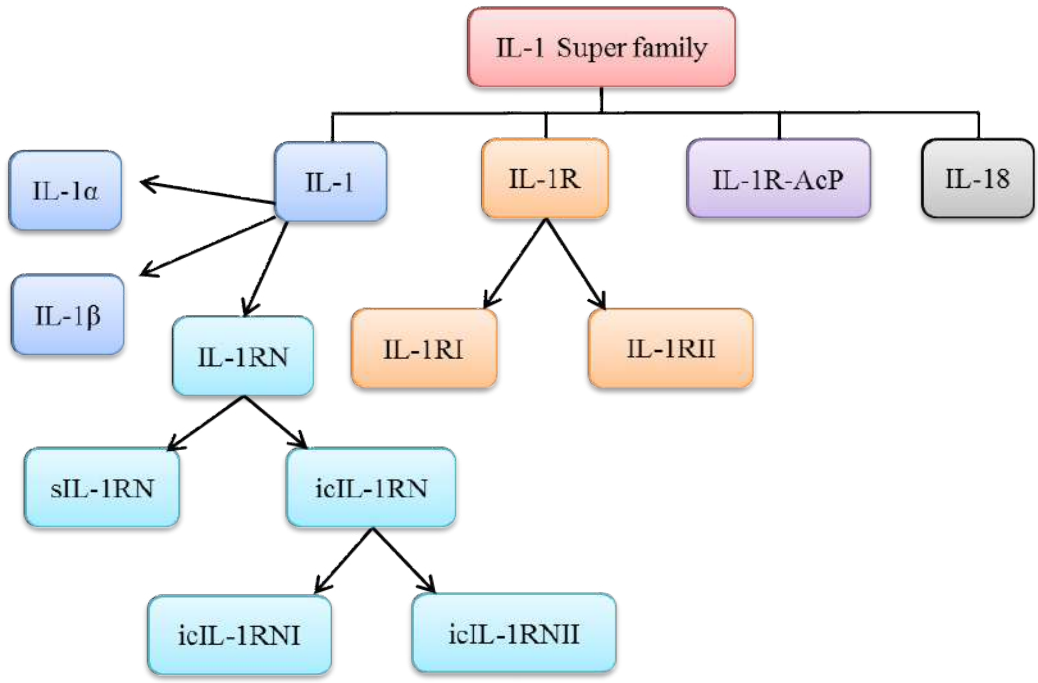

Fig. 1 Flow diagram of classification of IL-1 cytokine. Inteleukin-1alpha (IL-1α); Inteleukin-1alpha (IL-1β); Inteleukin-1receptor antagonist (IL-1RN or IL-1Ra); soluble IL-1RN (sRN-1RN); intra cellular IL-1RN type I and Type-II (icIL-1RNI, II); Inteleukin-1receptor (IL-1R); Inteleukin-1receptor Type-I(IL-1RI); Inteleukin-1receptor Type-II(IL-1RII); Interleukin-1 receptor accessory protein (IL-1RAcP); Interleukin-18 (IL-18).

these three secreted cytokines are situated on long arm of chromosome 2 which occupying <430Kb DNA elements (Loughlin *et al.*, 2002). Both the isoform IL-1α and IL-1β are structurally similar whereas they exhibit different level of gene expression. IL-1α and IL-1β both have pro-inflammatory properties and interact with same receptor. IL-1RN is considered as a natural antagonist that counteracts the proinflammatory properties of IL-1. IL-1RN exists both in secreted form (sIL-1RN) and intra cellular form (icIL-1RNI and icIL-1RNII).

3. IL-1α:

IL-1α considered as key member of cytokine family that is released into the extra cellular space of chondrocyte under certain circumstances. Mature form of IL-1α is derived from a precursor protein proIL-1α (31KDa) which has N-terminal Nuclear Localising Sequence (NLS) signal (Stevenson *et al.*, 1997). The maturation of IL-1α (18KDa) occurs by removal of certain amino-terminal amino acid residues from a precursor protein. The maturation of IL-1α is mediated by membrane bound cysteine protease called Calpain. Both the forms (proIL-1α & IL-1α) are biologically active to perform pro-inflammatory response (Banerjee, M. and Saxena, M., 2012). A detail account of cellular level of signal transduction triggered by IL-1α is often under investigation. Somehow, it seems to have an impact on catabolism of joint cartilage.

4. IL-1β:

It is well recognised cytokine involved in progression of OA. The biosynthesis of active IL-1β (17.5KDa) takes place by proteolytic digestion of immature proIL-1β (31KDa). Proteolytic enzyme, *Caspase-1* has an important role in maturation of proIL-1β (Dinarello, C.A., 2011). The

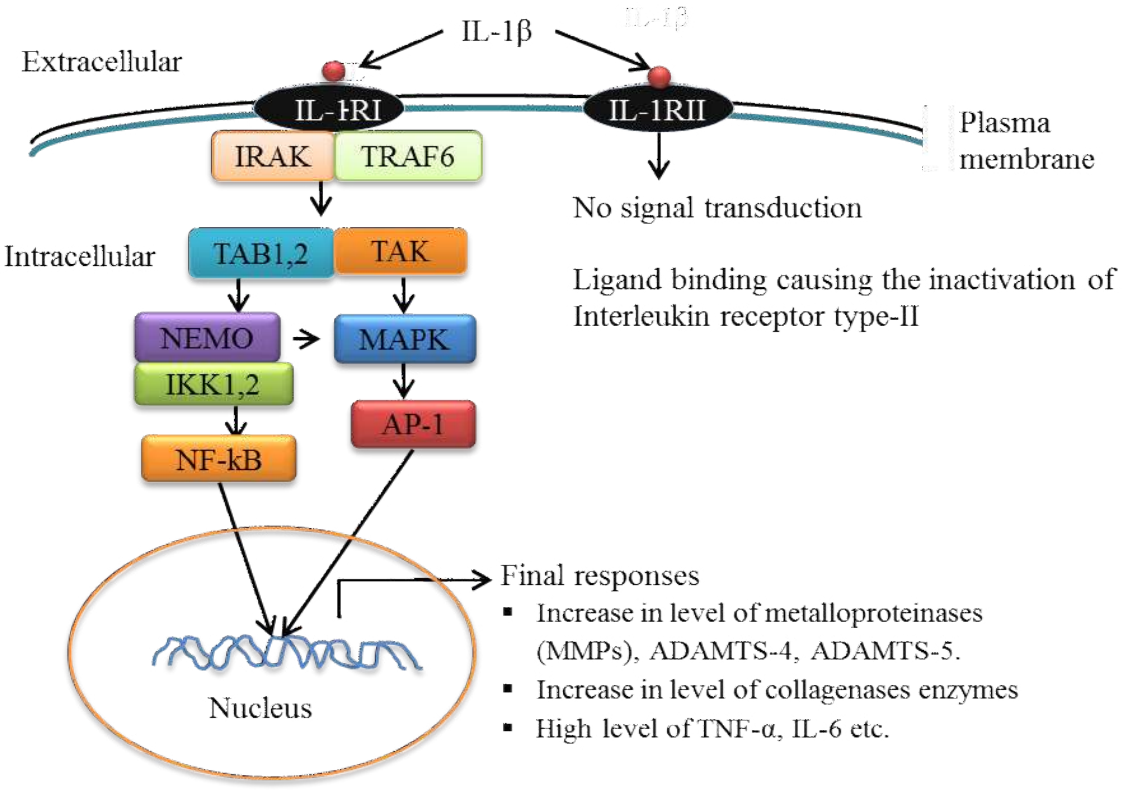

Fig. 2 Intracellular signal transduction of IL-1β ligand and receptor complex downstream towards nucleus. Interleukin type-I receptor (IL-1RI); Interleukin type-II receptor (IL-1RII); Interleukin-1 receptor associated kinase (IRAK); TNF receptor associated factor-6 (TRAF-6); TAB1 is also known as mitogen activated protein kinase kinasekinase 7 inactivating protein 1(MAP3K7IP1) and TAB2 is also known as mitogen activated protein kinase kinasekinase 7 inactivating protein 2(MAP3K7IP2); TAK is a mitogen-activated protein kinase kinasekinase 7(MAP3K7); NF-kB essential modulator/NF-kB inhibitor kinase1,2(NEMO/IKK1,2); mitogen activated protein kinase (MAPK); basal transcription activating protein called activator protein-1 (AP-1).

proIL-1β resides inside the cell whereas after maturation, it is secreted to extracellular environment of the secretary cell. IL-1β, a well-studied cytokine involved in production of ECM proteinases primarily type-II collagenase and aggrecanase. These proteolytic enzymes are impaired the homeostasis of cartilage metabolism and cause anabolism shift towards catabolism. Apart from over catabolism, IL-1β is also triggering the production of miRNAs in the extra cellular environment (Miyaki *et al.,* 2009). A recent study points out that the miRNAs are associated with breakdown of joint cartilage (Akhtar *et al.,* 2010).

5. IL-1RN:

It directly inhibits inflammatory response of IL-1 cytokine without any cytosolic signal induction and transduction (Carter *et al.,* 1990). IL-1RN compete with IL-1 for recognising to IL-1R (Vigers *et al.,* 1997) thus making an antagonistic effect. IL-1RN has same binding affinity to IL-1R as in case of IL-1α and IL-1β (Dinarello, C.A., 1994). Neutrophils and macrophages produce a 16 to 18 IL-1RN (Granowits *et al.,* 1991). IL-1RN bears about 20 to 30 percent similarity with IL-1α and IL-1β in their acid residues composition of the protein chain. It has been reported in *in vivo* and *in vitro* studies that IL-1RN shows anti-inflammatory properties (Mclntyre *et al.,* 1991). IL-1RN gene contains specific sequence repeats of 86 bp called Variable Numbers of Tandem Repeat (VNTR) in their polymorphic region of intron-2. Three potential transcription factors binding sites present in VNTR region may increase the level of expression of gene transcription and translation (Arnalich *et al.,* 2002).

6. IL-1R:

It also belongs to IL-1 super family which interact with different members of IL-1 and regulates its activity. IL-1R is broadly divided into two forms, type-I (IL-1RI) and type-II (IL-1RII), whereas IL-1RII is further divided into two sub forms the soluble IL-1RII (sIL-1RII) and membrane bound IL-1RII (mIL-1RII) (Dinarello *et al.,* 1991). IL-1RI primarily helps in response to IL-1 ligand induced signal whereas IL-1RII could suppress the effect of IL-1.

7. IL-1R-AcP:

It is a member of IL-1 super family which alsocalled IL-1R3. It is a multi-pass membrane protein encoded by *IL-1RAP-gene* (Gay, N. J. and Keith, F. J., 1997). Two different transcript variants of IL-1RAcP results from alternative splicing mechanism, a membrane bound form and a soluble form which are known to enhance the inflammatory property of IL-1 and help in subsequently signal transduction (Sims, J. E., 2002).

8. IL-18:

It is recently defined member of the IL-1 super family that regulates the immune responses. It has reported that the its expression occur in various kind of cells such as synovial fibroblast, macrophases, dendric cells , kupffer cells, microglial cells etc (Conti, B., 1997; Prinz, M. and Hanisch U.K., 1999).

9. Association of IL-1β with Osteoarthritis:

IL-1β is a pleotropic proinflammatory (Yuyan *et al.,* 2017) catabolic mediator that plays a pivotal role in pathogenesis of OA by ECM degradation. In OA, high level of IL-1β is found in synovial membrane, synovial fluid, and cartilage etc. (Gordon *et al.,* 2008). It causes intracellular signal transduction by binding with IL-1β receptor and induces inflammatory reactions. IL-1β inducing kinins and prostanoids to trigger the nociceptive sensitization pathways. (Sommer, C., 2004; Hassett *et al.,* 2012).

IL-1β induces various cell surface adhesion molecules such as Inter Cellular Adhesion Molecules (ICAM), L-selectin, Vascular Endothelial Cell Adhesion Molecule (VCAM) (Tsang *et al.,* 1997) which belongs to Immunoglobulin Super Family (IgSF). Apart from these functions, IL-1β has shown to influence the release of other catabolic mediators such as IL-6, IL-8 and other small inflammatory factors such as chemokine ligand 5, also called RANTES (encoded by CCL5 gene), monocyte Chemoattractant Protein-1 (MCP-1) (Alaaeddine *et al.,*2001; Villiger *et al.,* 2001) which exhibit additive or synergistic effect on cartilage breakdown.

Binding of IL-1β to its Type-I receptor initiates signal transduction intargeted cell. The receptor IL-1RI also has binding affinity with IL-1α and IL-RN (Symons *et al.,* 1995). IL-1β also recognised by Type-II receptor and causes inactivation of ligand receptor complex thus no subsequent intracellular signal transduction occurs (Boraschi, D., 2013) (Fig. 2). It has been observed that chondrocyte

and synoviocyte cells shows expression of IL-1RI receptor in OA patients (Martel-Pelletier *et al.,* 1992; Sadouk *et al.,* 1995). After activation of IL-1RI, it binds with cytosolic Interleukin-1 Receptor Associated Kinase (IRAK) which subsequently activates TNF Receptor Associated Factor-6 (TRAF-6) through serine threonine kinase property and further recruits the TAK, TAB1 and TAB2 proteins. Furthermore, TAK phosphorylates the IKK1 & IKK2 and successively activate the NF-kB (Kawai, T. and Akira, S., 2007). The final activation of cascade of cytosolic proteins result in expression of inflammatory mediators, matrix degadating enzymes, chemokines and other cell surface adhesion molecules (Roman-Blas J. A. and Jimenez S. A., 2006). The effects of IL-1β on chondrocyte cells include production of matrix proteases, decrease in extracellular components production and other inflammatory cytokines production. MMPs are notable markers to destroy the ECM such as collagens. Both IL-1β and TNF-α are responsible for expression of ADAMTS-4, whereas ADAMTS-5 production occurs constitutively without triggering of these cytokines (Koshy *et al.,* 2002; Verma, P. and Dalal, K., 2011). It has been described that IL-1β inhibits receptor R-SMAD (Regulated-SMAD) mediated TGF-β signaling pathways. (Bauge *et al.,* 2008).

10. Summary

OA is a most complex disorder that difficult to describe pathophysiological events involved in disease development. Certain catabolic factors have supplementary role in degeneration of joint supportive muscles and cartilages that lead to joint inflammation, reduction in joint motion and pain. These symptoms irreversibly appear at higher frequencies as a person gets older (Bijlsma *et al.,* 2011; Madry, H. and Cucchiarini, M., 2013).

OA exhibits progressive but gradual loss of ECM. IL-1 has considered as primary catabolic mediator in evolution of the disease by inducing synthesis of ECM degradative enzymes include MMP-1, MMP-13, Aggrecanases (ADAMTS-4 & 5, MMP-3), and hyaluronidase. These enzymes are responsible for degradation of most abundant glycoprotein such as collagen type-II. The production of proteolytic enzymes from chondrocyte is under the influence of IL-1β induced intra cellular signaling down to nucleus. IL-1β primarily induces signal transduction through binding with its type-I receptor whereas binding with type-II receptor leads to inactivation of the receptor and inhibition of further signal transduction. Number of cytosolic kinases and transcription factors are positively associated in signal transmission towards nucleus. Apart from above role of IL-1β, it also induces the nociceptive pathway and leads to pain.

Other studies suggest that IL-1β has strong association in regulation of cytokine and expression of different growth factor in chondrocyte (Moos *et al.,* 1999). Previous studies do not clearly mention the role and significant association of IL-1 family cytokine in Osteoarthritis. Therefore, further study is needed to find out the exact role of IL-1 family cytokines in OA. It may be an unpredictable task to know the overall effect that will be positive.

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