INTRODUCTION

Rheumatoid arthritis (RA) can be described as a severe chronic autoimmune disease characterized by joint inflammation, destruction of cartilage and the presence of autoantibodies\textsuperscript{[1,2]}, with approximately 340 genes involved in causing the RA\textsuperscript{[3]}. Statistically, RA affects 1% of the population worldwide\textsuperscript{[4]}. RA is a ubiquitous disease although in the urban area of some countries the prevalence seems to be less\textsuperscript{[5]}.

Pathogenicity of RA comes from both genetic and environmental factors and lead to the response of innate and adaptive immunity of the organism and to systematic inflammation\textsuperscript{[6]} With this, researchers have divided the pathogenicity into chronic and early and suggested that both have more similarities than differences\textsuperscript{[7]}. Many investigators believed that an appropriate genetic background combined with stochastic events, such as activation of innate immunity, can serve as the trigger for RA\textsuperscript{[8]}. Yet several aspects need to be considered\textsuperscript{[6]}. Moreover, low oxygen partial pressure (synovial hypoxia) is highly considered as a potential pathogenic factor and also a constant feature of RA\textsuperscript{[4]}.

Hypoxia occurs when there is an imbalance between demand and supply of oxygen\textsuperscript{[2]}; this can result in tissue dysfunction and even death. Thus under hypoxic condition, cells activate relevant genes in order to control the hypoxic environment\textsuperscript{[9]}, such as hypoxia inducible factor (HIF) as one of the key regulators of the tissue hypoxia\textsuperscript{[9]}. Three different HIF-alpha subunits have been described to date, with the greatest amount of research carried out on the two most closely related HIF-alpha-subunits\textsuperscript{[10]} and were found to play fundamental roles as mediators of transcriptional responses to hypoxia\textsuperscript{[11]}. Thus, the aim of this review is to highlight different regulatory patterns of HIF-1alpha on RA pathogenesis through influence of some regulatory genes under hypoxic condition, as it has been found in other types of arthritis such as osteoarthritis\textsuperscript{[4]}, different types of cancer and also in Retinopathy\textsuperscript{[12-14]}.

Role of HIF-1α in Rheumatoid Arthritis: A Mini Review

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ABSTRACT

Rheumatoid arthritis is an autoimmune disease and also a member of arthritis that can cause joint pain and damage in the body. The pathogenicity of (RA) is not fully elucidated due to its complexity but based on the available data interplay between environmental and genetic factor was reported. Therefore this Review is going to highlight the molecular pathways activated through the influence of Hypoxia inducible factor one alpha (HIF-1alpha) in (RA) and how these pathways might interact with inflammatory signaling, angiogenesis, as well as cartilage destruction via activation of some relevant genes in RA. In conclusion, this review highlighted the role of HIF-1alpha in pathogenesis of RA.
HIF-1alpha Structure

Structurally, HIF-1alpha protein possesses N-terminal transactivation domain (N-TAD) and C-terminal transactivation domain (C-TAD). It has polypeptide chain of 826-amino-acid [15]. Half parts of the C-terminal are involved in activation of the transcriptional process therefore, the C-TAD particularly interacts with CBP/p300 which is (acting as co-activators) to activate gene transcription. The association of HIF-1alpha with co-activators CBP/p300 is inhibited due to hydroxylation of an asparagine residue in the C-TAD [16].

Furthermore, HIF-1alpha also possesses an oxygen-dependent degradation domain called (ODDD) that mediates oxygen-regulated stability [2]. In the presence of normal oxygen tension levels (normoxic), HIF-1alpha become hydroxylase in a proline residue within the same domain, which subsequently binds to ubiquitin and degrade in the proteasome [17]. However, under hypoxic conditions, hydroxylation is inhibited and HIF-1alpha accumulates in the cytoplasm is later become phosphorylated and changes its territory by moving to the nucleus in order to activate transcription of some of it is target genes, such as vascular endothelial growth factor (VEGF), Insulin-like growth factor type 2 (IGF2) and some oxide synthase 2 (NOS2) [15]. The stability of this protein is also enhanced through truncation of the HIF-1alpha at amino acid 390 which resulted in a constitutively stable protein, these explain the concept of HIF-1alpha half-life modulated by oxygen concentration as well as sequences from carboxyl terminal domain to amino acid 390 [9], that as well enable HIF to affect signaling pathways that influence development, metabolism, inflammation, and integrative physiology [18].

HIF-1alpha EXPRESSION IN RA

HIF-1alpha is detected in the sub-lining layer in lower amount and strongly expressed in the intimal layer of the RA synovium, including macrophages [19]. Activation of the HIF transcription factor signaling cascade leads to extensive changes in gene expression, which allow cells, tissues and even organisms to adapt to reduced oxygenation [20]. HIF-1alpha was found up-regulated in RA fibroblast [21]. But a recent research shows that celastrol, a triterpene compound with an antioxidant and anti-inflammatory activity, inhibits hypoxia-induced migration and invasion of synovial fibroblasts through suppression of the HIF-1alpha-mediated CXCR4 in RA Figure 1 [22].

In addition, HIF-1alpha also promotes the activation of some signaling pathways and controls IL-33 production by fibroblasts, which in turn induces expression of HIF-1alpha and generates a regulatory cycle that perpetuates inflammation in RA [4], its co-activation function is enhanced due to presence of several single nucleotide polymorphisms (SNPs) in the oxygen-dependent degradation (ODD) domain and was also reported to be associated with increased of HIF-1alpha activity [23]. At the same time, a factor inhibiting-hypoxia inducible factor FIH-1 is an asparaginyl b-hydroxylase enzyme that was initially found to hydroxylate the HIF-1alpha, preventing its transcriptional activity and leading to adaptive responses to hypoxia [24].

Furthermore, a recent study has found evidence for a functional interaction of HIF-1alpha and some other genes such as Notch-3, and STAT-1 to regulate pro-inflammatory mechanisms in RA synovial a fibroblast during hypoxia [25]. Also, its role under normoxic condition was confirmed through knockdown experiment, the HIF-1alpha results in reducing Glycolytic Metabolism and Induces Cell Death of Human Synovial Fibroblasts [26], an indication of its regulatory role even under aerobic condition.

**Figure 1.** Role of HIF-1alpha in inflammation and destruction of RA joint, via modulating the expression of mediators that are involved in inflammation, angiogenesis, cartilage destruction and bone erosion.
HIF-1alpha and Inflammation in RA

Inflammations have been associated with a number of pathological conditions, in particular, inflammatory diseases such as RA, while hypoxia is mainly associated with the activation of hypoxia-inducible factors (HIFs) including HIF-1alpha sub-unit [27]. Cramer et al. shows the first evidence of HIF-1alpha participation in the inflammatory process by knockout of HIF-1alpha in macrophages which result in a reduction of disease severity in different models of both acute and chronic inflammation. Using fish model, they also demonstrate the role of HIF-1alpha in neutrophil inflammation, by showing the reduction of inflammation as a result of HIF-1alpha activation. Both genetic manipulation and pharmacological approaches suggested that the activation of HIF-1alpha delays the resolution of inflammation and lead to a reduction in neutrophil apoptosis [27] and also increase the retention of neutrophils at the site of injury, therefore delays retention of the neutrophils [38].

Regulatory role of HIF-1alpha in inflammation was also shown in knock-out experiment on mice. The result showed a significant reduction in synovial inflammation, pannus formation, cartilage destruction and histological improvement [29]. Moreover, PI3 kinase/Akt-mediated HIF-1alpha expression has been shown to play a critical role in hypoxia-induced epithelial-mesenchymal transition (EMT), phenotype transformation of fundamental laparoscopic of surgery (FLS), synovial hyperplasia, and inflammatory cell infiltration in vivo in the CIA model [30]. In an in vitro experiment, HIF-1alpha/B-cell activating factor (BAFF) complex was found involved in the production of inflammatory cytokines, which may result in regulating the physiological functions of RA FLS [30]. Moreover, Inhibition of HIF-1alpha signaling can attenuate hypoxia-induced invasiveness of activated FLS from the synovium of RA [31, 32].

Synovitis happens to be one of the most important characteristics of RA. It has synovium which has two layers, the initial lining called (intima) and an underlining loose connective tissue called sub-lining or (sub-intima) layer [33]. It was found that the architecture of the affected synovium is distorted and changes in shape as RA progresses which result in an increase in proliferation in the synovial cell lining to about 10-15 layers and also the sub-intimal layer becomes excessively infiltrated by immune cells which resulted in neovascularization [7].

In addition, a new research indicates the role of some inflammatory factors that found up-regulating the expression of HIF-1alpha [34], such as IL-1 Fig-1, IL-33 which is a newly identified inflammatory cytokine exacerbating the disease severity of RA (Figure 2) and TNF-alpha [35, 36]. Another chemokine (SDF-1) was also found up-regulated in response to hypoxia in RA [19]. It is Co-expression with HIF-1alpha has been identified in both synovial tissue explants and synovial fibroblasts [19]. Moreover, it’s also involved in a number of pathogenic events such as increased Synovitis, angiogenesis, bone erosion, and cartilage destruction (Figure 1) [37].

Up-regulation of HIF-1alpha has also been shown to significantly enhances the expression of IL-33, which is then able to form a complex of HIF-1alpha/IL-33 regulatory circuit which increases HIF-1alpha expression [39]. Furthermore, it has been reported that overexpression of HIF-1alpha does enhances RASF-mediated expansion of inflammatory Th1 and Th17 cells, as well as enhance inflammatory cytokine expression in polyIC-stimulated RASF thereby inducing a shift toward a pro-inflammatory state in RA [17].

Role of HIF-1alpha in Angiogenesis in RA

This is the development of new blood vessels; it is an important process in health and disease including RA. The perpetuation of neovascularization in inflammatory diseases, such as RA may promote the ingress of inflammatory cells into synovium [39]. The regulation of angiogenesis by hypoxia is an important component of homeostatic control mechanisms. It links cardio-pulmonary-vascular oxygen supply to metabolic demand in local tissue [40]. Therefore, in RA, the synovial angiogenesis is likely due to the hypoxia and it was found that nutrients are also being supplied to the pannus due to increase in blood supply and relatively that also increase the transportation of immune cells to the site of inflammation [40]. In addition, HIF-1alpha is an angiogenic transcriptional factor [41] and its role in angiogenesis was found in the local vein through up-regulation in the vein wall and promotes angiogenesis to re-open the veins and resolve the blood clot [37].

Furthermore, expression of a wild type HIF-1alpha in ischemic tissue may stimulate angiogenesis. This has been demonstrated for gene therapy with VEGF and other angiogenic factors [41], but may also promote survival of ischemic cells during the period when vascularization is in progress. A new finding also show more advanced role of HIF-1alpha by improving blood flow recovery as well as improvement of limb revascularization [42]. Research in this field of rheumatology holds out the prospect of understanding fundamental aspects of development and physiology while at the same time, it is also providing novel therapeutic approaches to the most common causes of mortality in the western world [43]. However its association with an angiogenic factors (VEGF) Figure 2 was found by increasing the expression of VEGF in the inflammatory joint regions, as well as in cells that are derived from RA synovium [44], as such that association can be control via the FIH-1 which interact with Notch2 and repress its activity, thereby playing a critical role in controlling the survival of vascular endothelial cells [45], these findings might pave the way toward novel, anti-angiogenic strategies in many diseases including RA. Moreover, a stromal cell derived factor 1 (SDF1, also known as CXC-chemokine ligand 12) was found to have a dual role, both as pro-angiogenic, as well as being a member of the CXC family of chemokine [46].

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Cartilage Destruction and Borne Errosion in RA Influenced by HIF-1alpha

HIF-1alpha serves as a survival factor on healthy cartilage \cite{36}, as well as maintaining cartilage homeostasis \cite{45} \cite{29}. It was found that tryptone soya agar (TSA) significantly decreases the expression of some metalloproteinase (MMP-2 and MMP-9) Figure 1 in RA FLSs induced by hypoxia and also hypoxia-induced invasion was significantly suppressed by TSA treatment. With these, the researchers concluded that their data indicate the role of TSA in an anti-invasive activity in hypoxic RA, largely through down-regulation of MMP-2 and MMP-9 \cite{49}. In addition, angiopoietin-like 4 (ANGPLT4) was overexpressed in RA osteoclasts in a HIF-1alpha dependent manner \cite{47} and promote bone desorption as well especially in RA synovial tissue \cite{39}.

Moreover, the expression of HIF-1alpha was insignificantly involved in MMP-1 and MMP-13 of FLS under nonoxic condition in RA, rather under hypoxic condition via IL-1beta stimulation \cite{18}. IL-17A was found to promote the migration and invasion of RA-FLSs, via NF-κB/HIF-1alpha-induced expression of MMP2 and MMP9, that result in the migration and invasion of the RA-FLSs \cite{30}. This indicates the different role of HIF-1alpha can be influenced by different regulatory genes on metalloproteinase compounds on RA.

![Image](https://via.placeholder.com/150)

**Figure 2.** An overview of the transcriptional activity of HIF-1alpha under hypoxic condition, through activation of an Angiogenic factor, different class of Cytokines and Metalloproteinase group that promote Angiogenesis, Inflammation and Cartilage destruction respectively.

**CONCLUSION**

In conclusion, HIF-1alpha was found playing roles in RA inflammation, angiogenesis, cartilage destruction and bone erosion, through activation of relevant genes. Hence pathogenicity of RA is still not fully clear, although inflammation and angiogenesis are identified as essential players. Identification of new SNPs that help HIF-1alpha during it is transcriptional activity on the mentioned cytokines genes, chemokine, pro-angiogenic factors, metalloproteinase and other proteins that are not yet been reported in RA cases is worth doing. Therefore HIF-1alpha seems to be a key molecule in RA pathogenesis and a promising therapeutic target in the context of RA.

**RECOMMENDATION**

A research needs to be taken with aim of observing the effect of HIF-1alpha SNPs that are found in exon regions on RA patients together with any of cytokines, pro-angiogenic factors, metalloproteinase and or chemokine in order to see their clear activating pathways with respect to inflammation, angiogenesis, bone erosion and cartilage destructions in RA patients as it has been done in some other classes of Arthritis.

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