



Implication of LncRNAs MEG3 and LINC00305 in Pathophysiological Mechanisms Associated with Rheumatoid Arthritis

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Abstract

Received on: 14. 06. 2020

Revised on: 16. 07. 2020

Accepted on: 19. 07. 2020

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Rheumatoid arthritis (RA) is a joint destructive disorder with great morbidity. Early diagnosis and early and effective therapy may prevent joint damage and lead to better long-term results. Therefore, reliable biomarkers and outcome measures are needed. Complex interplay between multiple risk factors contributes to RA. These risk factors include environmental factors, genetic factors and epigenetic modifications. Long non-coding RNAs (lncRNAs) are involved in these epigenetic mechanisms. Accumulating evidence has shown that lncRNAs participate in the processes of inflammation, aberrant proliferation, apoptosis and angiogenesis. They also play roles in autoimmune diseases, such as SLE, Sjogren syndrome, RA and multiple sclerosis. Maternally expressed gene 3 (MEG3) is a maternally expressed lncRNA of the imprinted DLK1–MEG3 locus located on human 14q32 chromosome. It functions as a tumor suppressor. Decreased MEG3 expression has been observed in various human cancers, both type 1 and type 2 diabetes, osteoarthritis and in RA. Decreased serum levels of lncRNA MEG3 in RA could be attributed to MEG3 promoter hypermethylation induced by hypoxia. This downregulation was associated with increased inflammation, cell proliferation and cell invasion and decreased apoptosis. Long intergenic non-Protein coding RNA 00305 (LINC00305) was identified as a pro-inflammatory atherosclerosis-associated lncRNA. RA was associated with increased LINC00305 which served as a regulator of inflammatory, hypoxic, invasive, apoptotic and proliferative mechanisms associated with RA.

Keywords: Rheumatoid arthritis; MEG3; LINC00305.

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease triggering joint inflammation combined with extra-articular involvement and profound disability (Guo et al., 2018). The formation of autoantibodies is a typical characteristic of RA specially rheumatoid factors

and anti-citrullinated protein antibodies (Alarcon et al., 1982). Advances in understanding the pathogenesis of the disease led to greatly improved RA treatment, emphasizing early intervention soon after diagnosis and escalating the therapy based on disease activity assessment and treatment response in pursuit of clinical remission (Lao and Xu, 2020).

Genetic, environmental factors and epigenetic modifications have been identified to play a role in disease initiation and progression. The human leukocyte antigen (HLA) genes have greater influence on RA. Smoking and infection are environmental factors that affect the development, and severity of RA (Arend and Firestein, 2012). The epigenetics study revealed that DNA methylation, histone modification, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) directly affect genes associated with inflammation and/or tissue destruction. lncRNAs are implicated in a wide range of biological processes from chromatin remodeling to transcriptional and posttranscriptional modifications (Strietholt et al., 2008; Lao and Xu, 2020).

2. Rheumatoid arthritis pathogenesis

Complex interplay between multiple risk factors is often required leading to initiation and propagation of autoimmunity against modified self-proteins which can occur years before the onset of subclinical synovitis (inflammation of the synovium) and clinical symptoms (Smolen et al., 2016) (Figure 1).

2.1. Preclinical RA

The interaction between the previous causative factors triggers protein citrullination and production

of autoantibodies. Following citrullination, the altered peptides bind to major histocompatibility complex (MHC) protein heterodimers, especially those containing the shared epitope. This leads to antigen presentation to T cells, which in turn stimulate B cells to synthesize a range of antibodies that recognize self-proteins, including RF (targeting IgGs) and ACPAs (targeting citrullinated proteins). The stage is called loss of tolerance (Muller and Radic, 2015).

2.2. Early RA

Clinical synovitis is initiated due to inflammatory cells infiltration into the synovium (Arend and Firestein, 2012). Fibroblast-like synoviocytes (FLSs) interact with the immune cells producing a large set of inflammatory cytokines and chemokines and thereby actively contribute to the inflammatory state in RA owing to activation of the notch and nuclear factor- κ B (NF- κ B) pathways (McInnes and Schett, 2011; Lao and Xu, 2020). NF- κ B is a major inflammatory mediator functioning in different cell types. NF- κ B consists of a group of inducible transcription factors (TFs), which controls multiple genes that play a role in cellular immune and inflammatory processes (Liu et al., 2017).

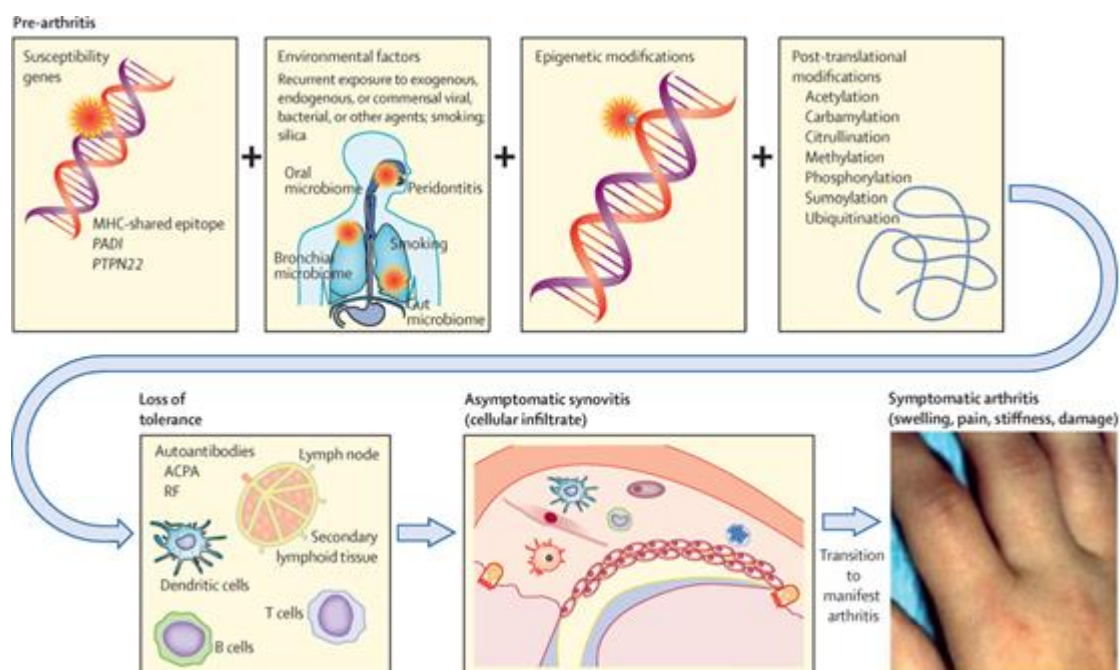


Figure 1: Development and progression of rheumatoid arthritis (Smolen et al., 2016).

2.3. Established RA

Progression to established RA occurs as fibroblast-like synoviocytes (FLSs) secrete cytokines, growth factors and enzymes (matrix metalloproteinases (MMPs) and collagenase), promoting synovial hyperplasia and cartilage destruction (**Guo et al., 2018**). MMPs are zinc-dependent endopeptidases which mediate basement membrane and extracellular matrix protein degradation, promoting tissue damage. Thus, their enhanced production in RA contributes to loss of cartilage and joint integrity (**Ni et al., 2019**). Synovial hyperplasia results from cellular proliferation, influx of cells from the circulation and reduced apoptosis through B-cell lymphoma-2 (Bcl-2) family proteins dysregulation (**Li and Wan, 2013**), leading to inadequate oxygenation and local hypoxia (**Chimenti et al., 2015**). The main factor mediating the response to hypoxic stress is hypoxia inducible factor (HIF)-1, which transactivates a series of genes such as vascular endothelial growth factor (VEGF) that participates in angiogenesis (**Hu et al., 2014**).

3. Long non-coding RNAs function and mechanisms

The importance of lncRNA molecules in different biological processes is beginning to be appreciated. LncRNAs interact with RNA or DNA through complementary base-pairing and interact with protein via direct interaction (**Rutenberg-Schoenberg et al., 2016**). Interactions between lncRNA and RNA, DNA, and proteins enable lncRNAs to regulate gene expression at multiple levels, including transcription, post-transcription, translation, post-translation, and epigenetic modification. LncRNAs were shown to interact with protein coding genes and their transcripts to regulate gene expression. Nuclear lncRNAs interact with chromatin remodelling factors and TFs to regulate the expression of neighbouring or distal genes. Also, they regulate transcription and several other transcriptional events of RNA processing. Cytoplasmic lncRNAs were shown to interfere with post-transcriptional regulation such as mRNA stability and degradation as well as translational regulation of mRNAs (**Hadjicharalambous and Lindsay, 2019**) (Figure 2).

4. Long non-coding RNAs and rheumatoid arthritis

Accumulating evidence has shown that lncRNAs participate in the processes of inflammation, aberrant proliferation, apoptosis and angiogenesis. They also play roles in autoimmune diseases, such as SLE, Sjogren syndrome, RA and multiple sclerosis (**Liang et al., 2019**). LncRNAs regulate gene transcription via interactions with chromatin-modifying proteins and TFs and they potentially regulate mRNA stability and translation in the cytoplasm (**Carrieri et al., 2012; Liu et al., 2015**).

4.1. Long non coding RNA maternally expressed gene 3 (MEG3)

MEG3 is a maternally expressed lncRNA of the imprinted DLK1–MEG3 locus located on human 14q32 chromosome. It functions as a tumor suppressor (**Benetatos et al., 2011**). Imprinted loci comprise both maternally- and paternally expressed genes. Reciprocal parental expression occurs between protein-coding genes and non-coding RNAs through epigenetic modifications such as DNA methylation at imprinting control regions (**Barlow, 2011**).

The imprinted Delta-like homolog 1(DLK1)–MEG3 locus contains paternally expressed protein-coding genes (DLK1, retrotransposon-like protein 1 (RTL1), thyroxine 5-deiodinase (DIO3)), maternally expressed non-coding RNAs consisting of the lncRNA MEG3, several miRNAs and small nucleolar RNAs (**da Rocha et al., 2008**). Methylation of two differentially methylated regions (DMRs) on the paternal allele, one located upstream of the MEG3 transcription start site (IG-DMR), and the other overlapping with the promoter of the MEG3 (MEG3-DMR) maintains reciprocal imprinting (**Benetatos et al., 2011**).

MEG3 is expressed in many normal tissues. Previous research demonstrated that MEG3 overexpression inhibits proliferation and invasion and induces apoptosis (**Zhang et al., 2019**). On the other hand, decreased MEG3 expression has been observed in various human cancers (**Benetatos et al., 2011**), both type 1 and type 2 diabetes (**Motterle et al., 2016**), osteoarthritis (**Su et al., 2015**) and in RA (**Lu and Qian, 2019**).

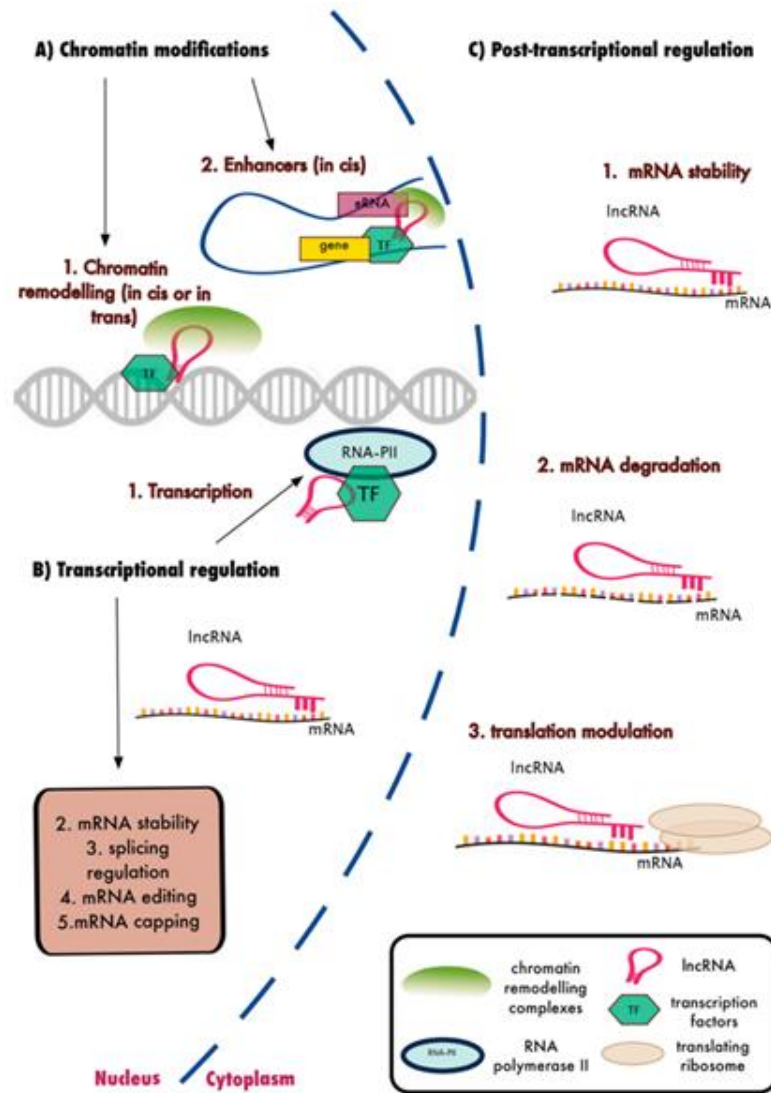


Figure 2: Cellular functions of lncRNAs (Hadjicharalambous and Lindsay, 2019).

Recent studies have demonstrated that the lack of MEG3 expression is involved in RA progression. It was reported that MEG3 promoter hypermethylation might account for its loss in the synovial tissues (Liu et al., 2019). This epigenetic effect on the MEG3 promoter is induced by hypoxia. Hypoxia up-regulates DNA methyltransferases which mediate methyl group transfer to cytosine within a CpG, forming 5-methylcytosine. This causes DNA hypermethylation. This hypoxia-induced epigenetic alteration consequently leads to gene silencing by preventing binding of TFs to DNA or by modifying chromatin structure through recruitment of methyl-DNA binding proteins, thereby making them inaccessible to transcriptional machinery (Hu et al., 2017; Mann, 2017).

Biswas et al. (2019) reported that MEG3 exerts anti-inflammatory activity through NF- κ B signaling pathway by specifically targeting important epigenetic regulators, sirtuin (SIRT) 1, miRNA-34a and miRNA-9. MEG3 positively regulates SIRT1 by directly sponging its negative regulator, miRNA-34a and miRNA-9 (Takayama et al., 2009; Cieřlik et al., 2020). SIRT 1 inhibits NF- κ B transcription by deacetylating the RelA/p65 subunit of NF- κ B at lysine 310 (Yeung et al., 2004).

MEG3 can repress cell proliferation and angiogenesis (He et al., 2017). Also. It was demonstrated that MEG3 induces apoptosis that is associated with the downregulation of the Bcl-2 protein and the upregulation of the Bax protein (Luo et al., 2015).

The pro-apoptotic activity together with the anti-proliferative activity of lncRNA MEG3 is attributed partly to stimulating the anti-proliferation protein p53 accumulation by blocking p53 degradation through inhibition of murine double minute 2 (MDM2). MEG3 has been shown to interact with p53 and stimulate p53-mediated transcription (Al-Rugeebah et al., 2019). The p53 protein can negatively regulate VEGFA transcription through binding to its promoter (Qin et al., 2006). Also, MEG3 modulation of Bcl-2/Bax signaling pathways could be attributed to its ability to act as miRNA-34a and miRNA-9 sponge, activating SIRT1 which regulates mitochondria-related apoptotic signals (Takayama et al., 2009).

In addition, MEG3 suppresses cell invasion by downregulating the expression of MMP-3, MMP-9 and VEGF. It also reduced epithelial-mesenchymal transition, which is reported to reduce intercellular adhesion and promote cell migration and invasion through negatively regulating miRNA-21 expression which functions as an onco-miRNA (Xu et al., 2018) (Figure 3).

4.2. Long intergenic non-protein coding RNA 00305 (LINC00305)

Recent study demonstrated that LINC00305 promotes monocyte inflammation and production of inflammatory cytokines by activating the aryl hydrocarbon receptor repressor (AHR)-NF- κ B pathway in human monocytes. LINC00305 overexpression has been found in atherosclerotic plaques and monocytes implying its role in monocytes inflammation (Zhang et al., 2017b). Recently, it was demonstrated that RA was associated with increased LINC00305 which served as a regulator of inflammatory, hypoxic, invasive, apoptotic and proliferative mechanisms associated with RA (Wahba et al., 2020).

LINC00305 expression was markedly increased in hypoxia (Zhang et al., 2017a). However, the precise mechanism by which hypoxic conditions affect LINC00305 expression needs further investigation.

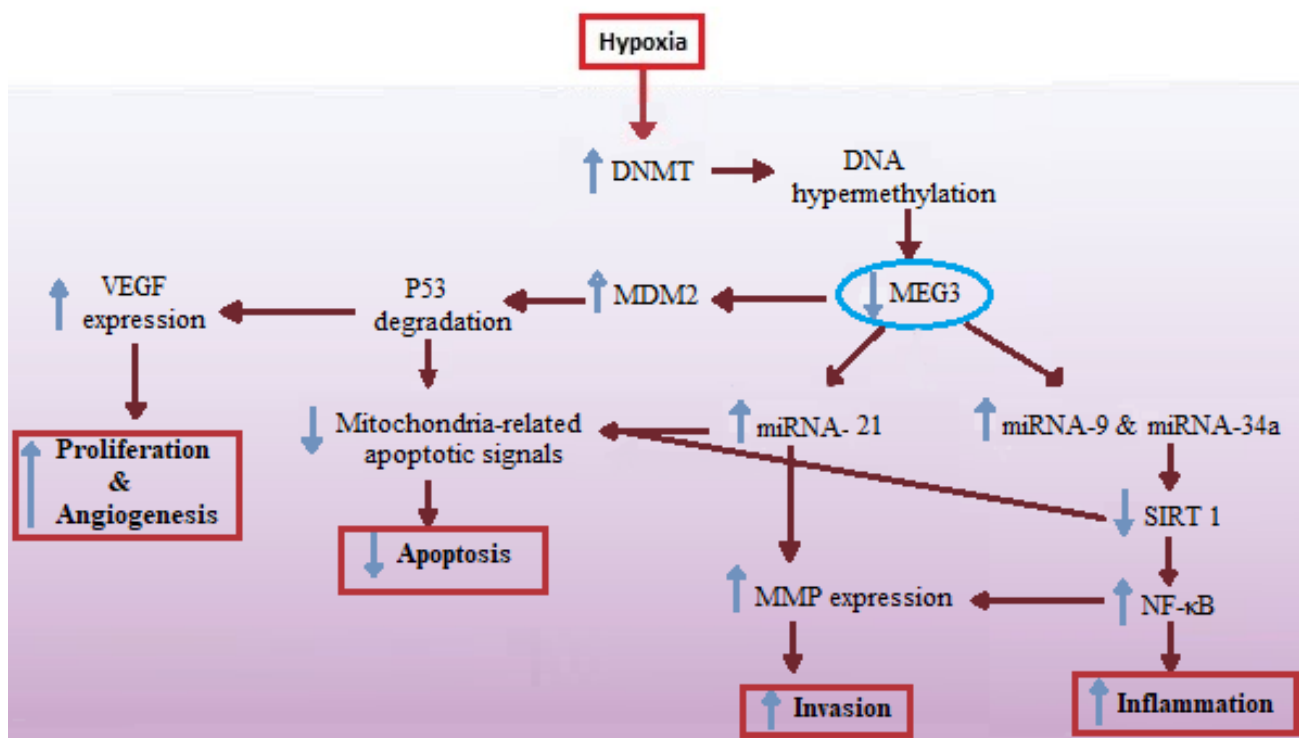


Figure 3: Implication of lncRNA MEG3 in RA pathogenesis. MEG3= maternally expressed gene 3, DNMT= DNA methyltransferases, MDM2= murine double minute 2, SIRT 1= sirtuin 1, NF- κ B = nuclear factor-kappa beta, MMP = matrix metalloproteinase, VEGF = vascular endothelial growth factor.

LINC00305 promotes monocyte inflammation and production of inflammatory cytokines by activating the AHRR-NF- κ B pathway in human monocytes. LINC00305 binds to lipocalin-1 interacting membrane receptor (LIMR), promoting the interaction between LIMR and aryl-hydrocarbon receptor repressor (AHRR), the repressor of AHR, leading to enhanced expression and nuclear localization of AHRR which positively regulates NF- κ B activity (Zhang et al., 2017b). LINC00305 activates Notch/NF- κ B pathway by down-regulating miRNA-124 (Li et al., 2019), whose levels are decreased in RA synoviocytes (Ceribelli et al., 2011). In addition, it was reported that miRNA-124 directly binds to the 3'-UTR of NF- κ B p65 inhibiting its expression, thus suppressing pro-inflammatory cytokine production (Qiu et al., 2015).

MiRNA-124 was confirmed to be involved in the pathogenesis of RA. MiRNA-124 modulates cell growth and invasion by negatively regulating the inhibitory member of the apoptosis stimulating protein p53 (iASPP) which is a key inhibitor of tumor suppressor p53 (Dong et al., 2015). iASPP up-regulation has a confirmed pathogenic role in RA, reduces the expression of p21, a cell cycle inhibitor regulated by p53, leading to activation of activator protein-1 (AP-1) which plays a role in the regulation of MMP secretion in RA FLSs (Zeisel et al., 2004; Chen et al., 2017).

Other miRNA-124 target proteins, cyclin-dependent kinase-2 (CDK-2) and monocyte chemoattractant protein-1 (MCP-1), are up-regulated, which leads to increased synovial proliferation, angiogenesis and chemotaxis (Nakamachi et al., 2009). In addition, a previous study hypothesized that miRNA-124 might inhibit the proliferation and invasion of RA synovial fibroblasts (RASFs) through suppressing the expression of NF- κ B (Li et al., 2018), which mediates transcriptional activation of several genes including VEGF and MMPs (Okamoto et al., 2007). Another study reported that miRNA-124 inhibited the proliferation and invasion of RASFs through downregulating the expressions of MMP3 (Li et al., 2018). Thus, LINC00305 alters regulation of its target proteins through down-regulating miRNA-124.

It was reported that p53 was down-regulated by iASPP, followed by the up-regulation of anti-apoptotic protein Bcl-2 and the down-regulation of

pro-apoptotic proteins Bax and caspase-3 (Ma et al., 2017) (Figure 4).

5. Conclusion

Accumulating studies have implicated ncRNAs in inflammation and autoimmune regulation, including miRNA, lncRNA, and circular RNA. LncRNA is an emerging area of focus in RA pathology. Many lncRNAs such as MEG3 and LINC00305 are aberrantly expressed in RA. The exploration of their underlying molecular mechanisms will offer a new direction to understand the pathogenesis of RA. It is also promising as a novel diagnostic and therapeutic strategy for RA. Decreased serum levels of lncRNA MEG3 could be attributed to RA-associated hypoxia. LncRNA MEG3 downregulation was associated with increased inflammation, cell proliferation and decreased apoptosis. On the other hand, RA was associated with increased LINC00305 which served as a regulator of inflammatory, hypoxic, invasive, apoptotic and proliferative mechanisms associated with RA.

6. Conflict of interest

The authors report no declaration of conflict of interest.

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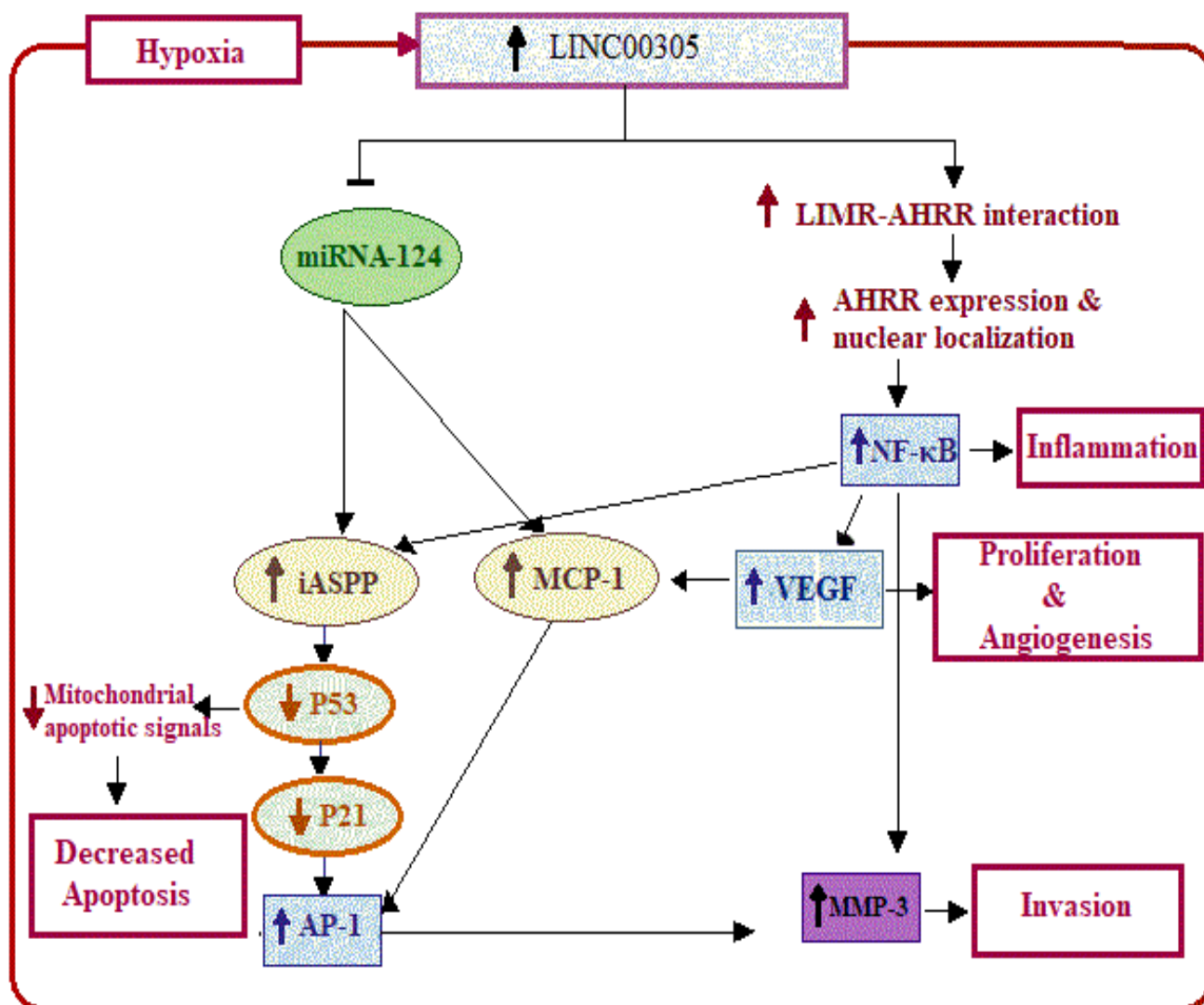


Figure 4: Implication of lncRNA LINC00305 in RA pathogenesis. LIMR= lipocalin-1 interacting membrane receptor, AHRR= aryl-hydrocarbon receptor repressor, iASPP= inhibitory member of the apoptosis stimulating protein p53, MCP-1= monocyte chemoattractant protein-1, NF-κB = nuclear factor-kappa beta, VEGF = vascular endothelial growth factor, AP-1= activator protein-1, MMP-3 = matrix metalloproteinase-3.

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