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The Role of Novel Genes in Rheumatoid Arthritis Pathogenesis

Shaimaa A. Fattah [a*], Maha A. Abdel Fattah[b], Eman T. Mehanna[a], Noha M. Mesbah[a],

Samy M. Saleh[a], Dina M. Abo-elmatty[a]

[a]*Department of Biochemistry, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt,* [b]*Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Suez Canal University, Ismailia, Egypt*

Abstract

Rheumatoid arthritis (RA) is a debilitating disease characterized by chronic symmetric polyarthritis involving peripheral small joints. Heterogeneity in RA pathophysiology extends to a molecular level. Understanding the complicated interaction between genetics, environment, and autoimmunity, and their function in pathogenesis, is necessary for getting further insight into the mechanisms and outcomes that manage disease development and progression. Pharmacogenomics emphasizes the relations of numerous genetic signatures with responses to traditional disease-modifying drugs and biologics. More than 100 genetic susceptibility loci have been recognized for RA through studies directed on patients with longstanding RA compared with healthy controls. So the interaction between genes and the environment may determine who is more susceptible to develop RA. This review pays attention to some recently discovered genetic risk loci in RA; ZNF804a, CDK1, YWHAH 14-3-3 η, and IL-17A. Also, their involvement in the etiology, pathogenesis, and outcome of the disease is explained, aiming to provide new insights into the pathogenesis of RA and the possibility to develop novel therapeutic approaches through targeting these genes.

Keywords: Rheumatoid arthritis; ZNF804a; CDK1; 14-3-3 η; YWHAH; IL-17A.

1. Introduction

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease that induces prolonged synovial inflammation, ultimately generates disabling joint injury as well as systemic complications (**Smolen and Steiner, 2003**). Several epidemiologic types of research show that the prevalence of RA is 0.5% – 1.0% (**Cribbs et al., 2015**). 70% and 80% of RA patients possess autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) (**Smolen and Steiner, 2003**).

The RA pathological process represents an autoimmune inflammation of the synovial joint membrane with proliferation of synovial cells and the formation of pannus. This pannus granulation tissue causes bone deterioration and articular cartilage erosion. Synovial tissue dysfunction facilitates the penetration of macrophages, fibroblasts, and lymphatic cells inside it. Pro-inflammatory cytokines; mainly tumor necrosis factor (TNF), interleukin (IL) superfamilies, and growth factors; are produced by T-lymphocytes (**Nemtsova et al., 2019**).

B-lymphocytes are involved in RF and ACPA autoantibodies production. Variances in ACPA and RF expression, disease manifestation rate and therapeutic response variability cause heterogeneity of RA patients that indicate the involvement of different pathophysiological mechanisms in the progression and development of the disease.

Most rheumatic diseases involve complicated features in which various genetic and environmental factors associate. Twin studies have concluded that the heritability of RA is ~60% (**MacGregor et al., 2000**). These results refer principally to RA patients with positive ACPA, whereas the heritability of RA patients with negative ACPA seems to be lower. Since 2007, genome-wide association study (GWAS) technologies have aided the description of genetic risk factors for numerous miscellaneous disorders (**Consortium, 2007**). More than one hundred genetic loci have been linked to RA (**Okada et al., 2014**).

Figure 1 illustrates the complicated interaction between the "Bermuda triangle" of genetics, environment, and autoimmunity in RA

pathogenesis. Environmental factors as smoking, bacteria, and viruses, cause epithelial damage which leads to an inflammatory response that activates cytokines, chemokines, and growth factors as tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and interleukins (ILs). These contribute to differentiation and proliferation of fibroblasts, increased synthesis, and activity of matrix metalloproteinases (MMP) that cause cartilage damage. Both genetic and environmental risk factors are associated with increased citrullination of proteins which lead to the production of ACPAs antibodies and allow an autoimmune response which also activates cytokines, chemokines, and growth factors causing inflammation of the synovial membrane of joints with synovial cells proliferation and pannus formation.

As a genetic factor is obviously implicated in RA, it is necessary to understand the recently associated genes and their pivotal roles in RA. This review will describe recent genes associated with RA, envisaging a more reliable understanding of RA pathogenesis.
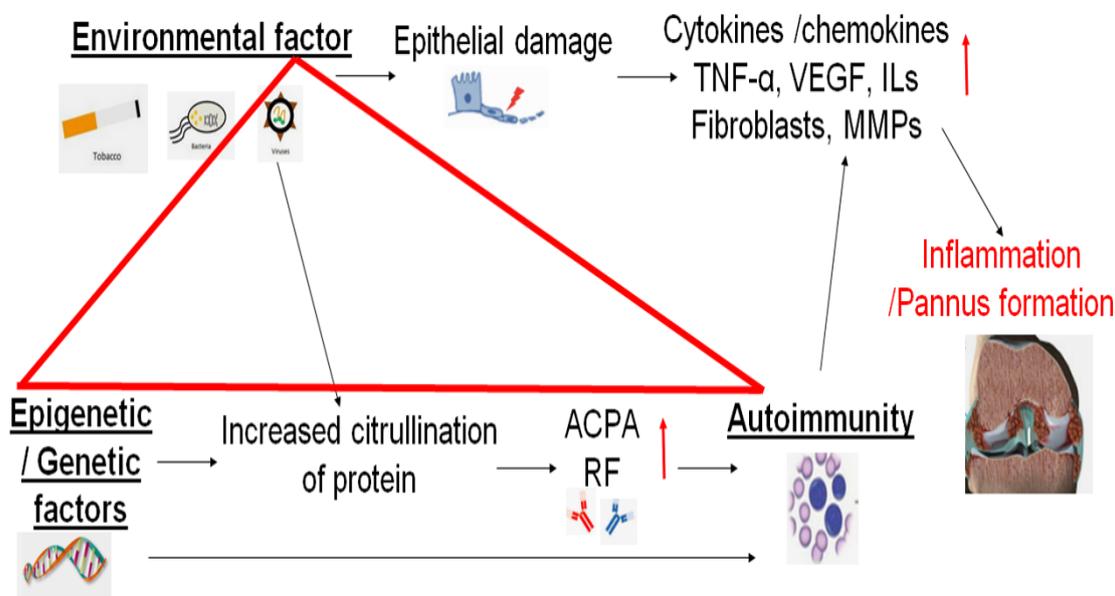

Figure 1. Bermuda triangle of rheumatoid arthritis: genetics, environment, and autoimmunity. TNF- α tumor necrosis factor-alpha. VEGF vascular endothelial growth factor. ILs interleukins, MMPs matrix metalloproteinases, ACPA anti-citrullinated protein antibodies, RF rheumatoid factor.

2. ZNF804a gene

Zinc-finger proteins (ZNFs) are abundant protein aggregations that have a broad molecular variety. As ZNFs have deeply divided domains, they can combine with DNA, RNA, poly-ADP ribose (PAR) and other proteins (**Gibson et al., 1988; Vrana et al., 1988**). ZNFs are also associated with the organization of multiple cellular processes. ZNFs functions include transcriptional control, cell migration, actin targeting, DNA repair, signal transduction, ubiquitin-mediated protein degradation, and many other approaches (**Linke et al., 2008**).

Four exons and three introns on human chromosome 2q32.1 are found in ZNF804a gene which encodes a ZNF804a protein of 1210 amino acids (137 kDa) (**Walters et al., 2010**). While ZNF804a 's molecular function remains unknown, the sequence of amino acids contains the C2H2 zinc-finger domain, indicating that ZNF804a plays a role in binding and transcribing DNA (**Girgenti et al., 2012**).

ZNF804a gene has been associated with bipolar disorder (BD) and schizophrenia (SZ) (**Rao et al., 2017**). ZNF804a is also distinguished as an important gene for anxiety disorder (**Talkowski et al., 2012; Blake et al., 2014**), autism spectrum disorder (**Griswold et al., 2012**), developmental disabilities and psychosis (**Steinberg et al., 2011**). In addition to the correlation of this gene with central nervous system diseases, it was recently identified as a systemic lupus erythematosus (SLE) vulnerability factor (**Almlof et al., 2017**).

There is a well-known link between the ZNF804a gene and RA pathogenesis, where phosphodiesterase 4B (PDE4B) protein that is involved in inflammatory processes is downregulated by this gene (**Girgenti et al., 2012**). PDE4B suppression can increase the cyclic AMP (cAMP) intracellular level and thus maintain immune balance and alter inflammatory actions (**Maurice et al., 2014**). One efficient therapy for RA is PDE4B antagonists that reduce TNF-α secretion (**Li et al., 2018**). The ZNF804a gene can therefore decrease TNF-α in RA by decreasing PDE4B proteins (**Figure 2**). In a recent study, we established the correlation between ZNF804a expression and RA activity and severity. Our study reported the down-regulation of ZNF804a in RA patients. Expression of ZNF804a was negatively associated with serum TNF-α levels in the RA patients. ZNF804a gene downregulation is expected to raise the levels of TNF-α that is considered an essential cytokine involved in the pathogenesis of RA (**Fattah et al., 2020**).

Higher serum levels of TNF-α enhance RA disease activity, and severity as it is positively associated with levels of c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity score (DAS)-CRP, DAS-ESR, RF, and ACPA (**Wei et al., 2015**) In our above-mentioned work; RA patients with lower expression of ZNF804a had considerably higher serum levels of CRP, DAS-CRP, and RF, suggesting an impact of ZNF804a expression on the disease activity and severity– (**Fattah et al., 2020**).
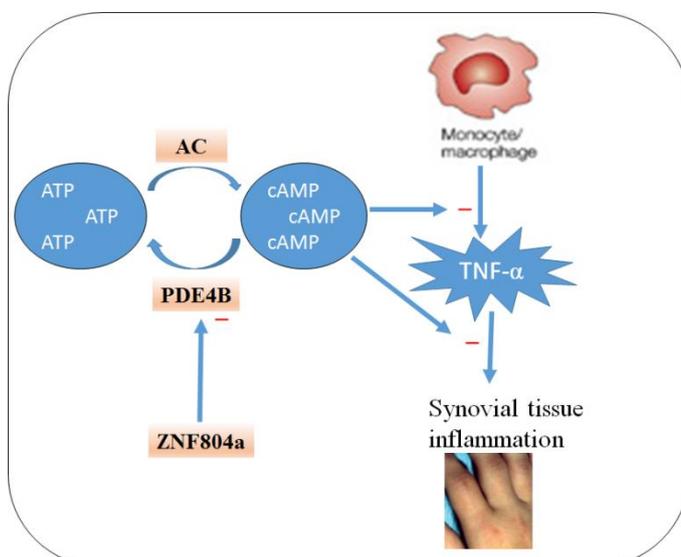

Figure 2. The relation of ZNF804a and RA pathogenesis. ATP adenosine triphosphate, cAMP cyclic adenosine monophosphate, AC adenylate cyclase, PDE4B phosphodiesterase4 B, ZNF804a zinc finger 804a, TNF- α tumor necrosis factor-alpha. - Indicates an inhibition (**Fattah et al., 2020**).

3. CDK1 gene

Cyclin-dependent kinases (CDKs) control the phases of cell division, commencing with quiescence, the G1/S phase transition, DNA replication in S phase, nuclear breakdown, chromosome condensation, segregation, and cytokinesis **(Crosby, 2007)**. CDK1, the first CDK identified in all species **(Nurse and Thuriaux, 1980; Lohka et al., 1988)**, is retained and performs essential functions throughout mitosis. The S phase is triggered by CDK1 **(Aleem et al., 2005)**.

CDK1 gene forms 9 exons on human chromosome 10q21.2, encoded as CDK1 enzyme (https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=983). The development of fibroblasts in the synovium is correlated with CDK1 to generate a hyperplastic RA pannus **(Sekine et al., 2008)**. Also, CDK1 activates the interferon (IFN) type I-induced phosphorylation of signal transducer and transcription 1 (STAT1) and enhances the up-regulation of interferon-stimulated genes which leads to improvement of IFN-1 signaling **(Wu et al., 2016)**, that is involved in RA pathogenesis **(Gordon et al., 2012)**. IFN-1 cytokines were found in RA synovium **(Hu et al., 2008)**. IFN-1 was also observed in SLE patient's sera **(Petri, 2006)**.

The CDK1 gene is overexpressed in SLE **(Wu et al., 2016; Almlof et al., 2017)**. We reported CDK1 gene overexpression in RA patients. The serum levels of IFN-1 were significantly higher in RA patients **(Fattah et al., 2020)**.

There was an association between CDK1 overexpression and abnormal amplification of IFN-1 signaling in SLE **(Wu et al., 2016)**. A significant positive correlation between CDK1 expression and IFN-1 serum levels was observed in our study. Consequently, CDK1 gene overexpression may contribute to an increase in the IFN-1 serum levels in RA patients, which is essential for RA pathogenesis **(Figure 3)**. CDK1 expression was positively correlated with ACPA in RA patients while CRP, ESR, DAS-ESR, DAS-CRP and RF had no association. This suggests that the CDK1 gene may impact the RA disease severity but not the activity **(Fattah et al., 2020)**.

4. YWHAH 14-3-3 Eta gene

There are seven isoforms: α/β, γ, δ/ζ, ε, η, θ/τ and σ, in the 14-3-3 regulatory proteins **(Maksymowych et al., 2014)**. Generally, these proteins are ubiquitous intracellular adapters (or chaperones) that interact with more than 200 intracellular proteins and regulate their activities **(Kilani et al., 2007)**.

Serum 14-3-3 η, first described in 2007, is noticeable at a significantly higher serum and synovial fluid levels in RA patients than healthy people and those with other autoimmune diseases and viral/bacterial infections **(Kilani et al., 2007)**. Extracellular 14-3-3 η in RA patient serum is an indicator for cell damage that extremely stimulates pro-inflammatory cytokines and bone-degrading enzymes **(Maksymowych and Marotta, 2014).**
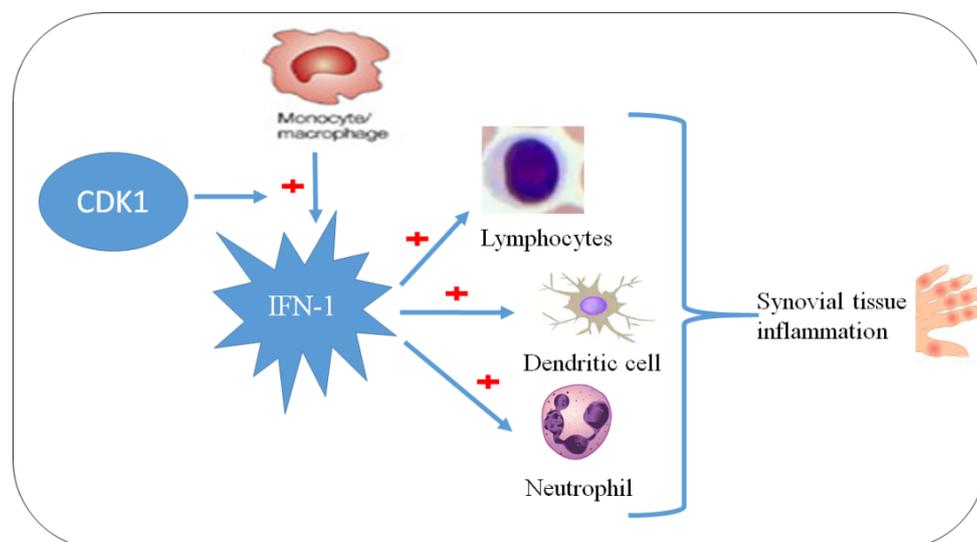

Figure 3. The relation of CDK1 and RA pathogenesis. CDK1 cyclin-dependent kinase 1, IFN interferon. + indicates stimulation.

14-3-3 η expression was strongly correlated with MMPs. ZMMPs are serine proteases, which play a significant role in tissue homeostasis. In the condition of RA, the discrepancy between these proteolytic enzymes expression and their cognate antagonist's triggers cartilage disintegration (**Siebuhr et al., 2013**). It has been defined that MMP expression is controlled by transcription factor Activator Protein 1 (AP-1) that determines intracellular signals, including Mitogen-Activated Protein Kinase (MAPK) (**Kook et al., 2011**). The extracellular regulated kinase (ERK), p38MAPK and Jun N-terminal kinase/stress-activated protein kinases JNK/SAPK, have been widely noticed in RA (**Kyttaris, 2012**).

In early RA patients with gradual joint destructions, **de Launay et al. (2012)** reported significant changes in ERK and JNK activation, but not in P38MAPK activation, stressing their potential importance to RA etiology.

Cell stimulation experiments have shown 14-3-3 η stimulation of the innate immune system, leading to the activation of major signals such as MAPK/ ERK, SAPK/JNK, and the JAK-STAT pathway which regulates the inflammatory and degradative factors production (**Maksymowych et al., 2014a**). Various RA associated transcriptional factors such as receptor activator of nuclear factor Kappa-B ligand (RANKL), joint degradation factors such as MMP-9, and pro-inflammatory cytokines, IL-1β, IL-6, TNF-α are upregulated by 14-3-3 η (**Maksymowych et al., 2014b**). CRP and fibrinogen synthesis can be triggered in the liver by IL-6 (**Rhodes et al., 2010**).

YWHAH gene spans 10 kb and encodes a protein 246 amino acids long (**Muratake et al., 1996**). It consists of a long 8 kb intron and two 741 kb exons and is located on human chromosome 22q12.1– q13.1 (**Muratake et al., 1996; Takahashi, 2003**). It codes the η of the 14-3-3 family of proteins, which are primarily found in the brain (**Grover et al., 2009**). This gene has been associated with SZ and psychotic BD (**Wang et al., 2005; Grover et al., 2009**). The YWHAH gene is expressed in synovial tissue (**Kilani et al., 2007**). YWHAH gene has been studied as a susceptibility gene for RA due to its action in joint deterioration. YWHAH 14-3-3 η was upregulated by 4.7 fold in synovial fluid from RA patients (**Balakrishnan et al., 2014**). YWHAH was reported to be overexpressed by 3.27 fold in synovial membrane and by 2.37 fold in peripheral blood cells from psoriatic arthritis patients (**Dolcino et al., 2015**).

5. IL-17A gene

Interleukin (IL)-17A is a cytokine that is involved in many autoimmune and inflammatory disorders (**Miossec and Kolls, 2012**). It is produced by Th17 cells as well by cytotoxic CD8+ T cells (Tc17 cells), invariant natural killer T cells (iNKT cells), lymphoid tissue inducer cells (LTi cells), γδ T cells, and other hematopoietic and non-hematopoietic cells (**Kim and Jordan, 2013**). Experiments in vitro and in vivo have recognized the function of IL-17 in several cell types, which illustrate its relationship with the early and late chronic phases of many disorders. In keratinocytes, for example, IL-17A induces several chemokines expression, contributing to the mobilization of immune cells which characterize psoriasis (**Beringer et al., 2016**). Also, IL17A works locally on synoviocytes and osteoblasts leading to synovitis or joint damage in RA (**Hot and Miossec, 2011; Ndongo-thiam and Miossec, 2015**), which is one of the most severe chronic inflammatory diseases (**Smolen et al., 2016**).

The immunostaining of RA patients' synovial tissues has demonstrated that an IL-17 group of CD4+CD45RO+ T-memory cells has not been observed in synovial tissue from osteoarthritis (OA) patients. In comparison, the synovial fluid content of IL-17 is greater in RA patients than in OA, trauma and gout patients (**Kotake et al., 1999**). In the lymphocytic infiltrate and the hyperplasic lining of the RA synovium, the IL-17A-producer cells are detected (**Kotake et al., 1999**). Th17 cells and synoviocytes interactions are critical, as they generate IL-17 massively (**Noack et al., 2016**).

IL-17A partly contributes to cartilage injury. Sample synovial RA studies show that the production of leukemia inhibitory factor (LIF), macrophage inflammatory protein (MIP)-3α/chemokine (C-C motif) ligand-20, and IL-6 by RA synovium are triggered by IL-17A (**Chabaud et al., 1998; Chabaud et al., 1999; Chabaud et al., 2000**). Additionally, the discovery of RA synovium anti-IL-17 antibody considerably impaired the development of MMP-1, collagenases but not of MMP (Timp)-1 tissue inhibitors, indicating the clear interaction with mutual degradation of IL-17 (**Chabaud et al., 2000**).

Several cytokines and chemokines, especially IL-6 and IL-8, are massively produced by synoviocytes which are activated by IL-17A and IL-17F (**Zrioual et al., 2008; Hot and Miossec, 2011; Hot et al., 2011**). Also, IL-17 is responsible for inducing tissue destruction through migration of synoviocyte and fostering a tissue- invasive phenotype (**Hot et al., 2012; Bottini and Firestein, 2013; Li et al., 2013**). The injury to the tissue involves degradation of the cartilage matrix and bone deterioration. The major source of matrix disruption is MMP. Amongst such, MMP-1, 2, 9, and 13 synoviocytes and chondrocytes are caused by IL-17 in RA (**Chabaud et al., 2000**).

IL-17A gene, which is located on chromosome locus 6p12, encodes the IL-17A cytokine (**Jakubiuk-Tomaszuk et al., 2015**). The IL17A gene occupies a total of 4252 bp composed of three exons and two introns and encodes a protein of 155 amino acids (http://atlasgeneticsoncology.org/Genes/GC_IL17A.html). The retinoid-related orphan receptor (ROR) γ T and RORα transcription factors regulate IL-17A expression. ROR γ T is expressed primarily by Th17 cells and drives their differentiation (**Khan and Ansar Ahmed, 2015**). The expression of IL-17A gene and growth of Th17 cells are surprisingly guided not just by microorganisms and tumors, but also by several environmental factors including nutrients, metabolites, hypoxia, toxins, NaCl, and circadian rhythm (**Kleinewietfeld et al., 2013**). IL-17 expression is increased in number of pathological disorders as asthma, pneumonitis and pulmonary fibrosis (**Gurczynski and Moore, 2018**). Also, the IL17A gene has been upregulated in breast cancer (**Benevides et al., 2013**) and gastric adenocarcinoma (**Chen et al., 2011**). Upregulation of IL-17A mRNA was reported in synovial fluid from RA patients (**Chen et al., 2020**).

5. Conclusion

ZNf804a and CDk1 genes have been identified as pivotal genes in various autoimmune diseases. These genes are implicated in RA progression through their effects on the expression of various cytokines as TNF-α and IFN-1. 14-3-3 η is a relatively novel biomarker for RA. Overexpression of YWHAH 14-3-3 η gene is associated with RA. IL-17A is considered an important cytokine in RA as it is produced by several immune cells. There is an increase in IL-17A gene expression in synovial fluid from RA patients, which may contribute to

synovitis. Yet, large scale studies are recommended to confirm the association of these novel genetic factors with inflammatory rheumatic diseases.

6. Conflict of Interest

None of the authors have any conflicts of interest.

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