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Identification of Genetic Markers of Atherosclerosis in Patient with Rheumatoid Arthritis

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Abstract: *Rheumatoid arthritis (RA) is a systematic autoimmune disease characterized by infiltration of synovium with immune cells leading to joint destruction. RA is also a systemic disorder, involving several other organs, such as eyes, blood vessels and heart. Over the past few years, a series of evidence has linked RA to atherosclerosis. RA itself represents an important risk factor for development of atherosclerosis. RA patients are 60% more prone to suffer from atherosclerotic disease compared to age-matched controls. Traditional risk factors (smoking, lipids), inflammatory mediators (TNF-α, IL-1 and auto-antibodies) have been proved to play important roles in the pathogenesis of atherosclerotic disease in RA. Besides, many genetic factors are found to be associated with accelerated atherosclerosis in RA. In this paper, we will summarize genetic markers of atherosclerosis in patient with rheumatoid arthritis.*

Keywords: *Rheumatoid arthritis, atherosclerosis, genetic markers*

1. INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disorder, characterized by synovial membrane inflammation, joint swelling, cartilage destruction and disability. Besdies, RA is a systemic disorder which can cause inflammation in several other organs, including eyes, heart and blood vessels *ec*[1]. In the past few years, a great deal of studies has found a correlation between RA and atherosclerosis. RA patients are 60% more prone to suffer from an atherosclerotic cardiovascular disease (CVD) compared to their age-matched controls[2]. Accelerated atherosclerosis development is also recognized as one of the major cause of morbidity and mortality in patients with RA[3].

Atherosclerosis was traditionally recognized as a lipid-based disorder affecting the arteries. Recently, more and more studies suggest that atherosclerosis is an immune mediated - inflammatory process of the vascular system[4]. Pro-inflammatory cytokines (TNF-α, IL-6, Il-1), immune cells (Th1, Th2 and Th17 cells) play important roles in initiation and development of atherosclerosis[5]. In along with these inflammation-related risk factors, RA is considered as one of the novel inflammation - risk factors. Many researches proved that RA is associated with increased atherosclerosis progression independent of the classical cardiovascular risk factors[6, 7].More importantly, a lot of genetic factors have been found to be associated with increased atherosclerosis progression in RA. In current paper, we will conclude genetic markers of atherosclerosis in patient with RA.

2. THE LINK BETWEEN ATHEROSCLEROSIS AND RHEUMATOID ARTHRITIS

In the last decades, a great deal of evidence has proved that atherosclerotic cardiovascular diseases (CVD) events are significantly increased in patients with rheumatoid arthritis

(RA). Although the underlying mechanisms of the accelerated atherosclerosis in RA remain to be fully addressed, traditional risk factors, inflammation-risk factors, and genetic factors are suggested to be associated with the increased atherosclerosis risk[8].

2.1. Traditional Risk Factors

Traditional atherosclerotic risk factors such as smoking and lipid play critical roles in the initiation and development of atherosclerosis in patients with RA.

2.1.1. Smoking

Cigarette smoking has been suggested as a major cause for atherosclerotic cardiovascular diseases (CVD)[9]. Meanwhile cigarette smoking is also recognized as an independent risk factor for RA development and is closely related to disease activity[10]. Smoking has a doze-dependent relationship with synthesis of auto-antibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated protein (anti-CCP), all of which may be participated in increased CVD event in RA[11].

2.1.2. Lipids

Dyslipidemia is a critical risk factor for atherosclerosis[12]. In RA patient, composition of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) may be disturbed by immune system-mediated inflammation, thus failing their ability to remove cholesterol of atherosclerotic plaques. In addition, the level of oxidized pro-inflammatory HDL is significantly increased in patients with RA. The oxidized pro-inflammatory HDL causes LDL oxidation and leads to the formation of oxidized LDL (OxLDL) which is a central factor in development of CVD. The management of dyslipidaemia is critical to control CVD risk in patients with RA [13, 14].

2.2. Inflammatory Mediators

A large amount of studies have demonstrated that rheumatoid inflammatory mediators, such as proinflammatory cytokines and auto - antibodies, were involved in accelerated atherosclerosis in RA.

2.2.1. Tumor necrosis factor alpha (TNF-α)

TNF-α plays a central role in the development of RA and the level of TNF-α is significantly elevated in patients with RA[15]. Meanwhile, TNF-α is also a key mediator in initiation and development of atherosclerosis. TNF-α might participate in perpetuation of atherosclerotic lesions and increased circulating level of TNF-α was correlated with an increased risk of atherosclerosis [16]. TNF-α may influence the development of atherosclerosis in RA.

2.2.2. Interleukin-1 (IL-1)

IL-1 is a pro-inflammatory cytokine acting as a mediator of inflammation and tissue damage in many diseases. IL-1 has been linked to pathogenesis of RA[17]. Many studies also showed that IL-1 might be involved in development of atherosclerosis. IL-1 play a proatherogenic role by regulating many critical events involved in the atherosclerotic plaques formation[18].

2.2.3. Interleukin-6 (IL-6)

The level of IL-6 is significantly increased in RA patients and is colosely correlated to clinical features. IL-6 plays a critical role in pathogenesis of RA[19]. Moreover, IL-6 is a critical modulator in accelerated atherosclerotic plaques formation and inhibition of signaling pathways that can clear plaque in the carotid artery[20]. IL-6 may participate in initiation and development of atherosclerosis in patient with RA.

2.2.4. Interleukin-17 (IL-17)

IL-17A, a novel pro-inflammatory cytokine, has been increasingly considered as an instigator in the pathogenesis of many autoimmune diseases including RA[21]. Besides, IL-17A is a critical factor in atherosclerotic plaque formation by promoting monocyte/macrophage recruitment into the wall of carotid artery[22]. Blockade of IL-17A lead to suppression of atherosclerotic plaque formation in apolipoprotein E–deficient (*Apoe*$^{-/-}$) mice[23]. IL-17A may play a critical role in inducing atherosclerotic plaque formation in patients with RA.

2.2.5. Interleukin-32 (IL-32)

IL-32, a novel human cytokine, plays an important role in the pathogenesis of RA[24]. Meanwhile, a recent study reported that IL-32 expression is detectable in arterial vessel wall of atherosclerotic patients. More important, IL-32 transgenic mice exhibited symptoms of ather osclerosis[25]. Taken together, these results indicated that IL-32 is also involved in pathogenesis of atherosclerosis and might participate in atherosclerosis development in RA.

2.2.6. TNF-like protein 1A (TL1A)

TL1A is a novel TNF super-family cytokine. TL1A can bind to death receptor 3 (DR3), induce cell apoptosis and cause inflammation response. A recent study reported that disturbed TL1A - induced signaling is associated with atherosclerosis progression in RA[26].

2.2.7. Autoantibodies

A lot of studies have shown that auto-antibodies like RF and anti-CCP antibodies which is commonly detected in RA, could be identified as risk factors for atherosclerosis. These results indicate that RA-related auto-antibodies may also play a critical role in atherosclerosis progression in RA[27].

3. GENETIC FACTORS

Apart from traditional atherosclerotic risk factors and inflammation mediators, various genetic factors have been proved to be the important contributing factors in pathogenesis of atherosclerotic disease in RA.

3.1. CD40-CD154

CD40-CD40 ligand (CD40L/CD154) interaction which will lead to inflammation process, is considered as a critical step in autoimmune disease pathogenesis. A pilot study found a potential association of rs1883832 CD40 gene polymorphism with susceptibility to RA. Also, the CD40 rs1535045 gene variant is thought to be involved in atherogenesis and plaque rupture in RA[28].

3.2. Interleukin 33 rs3939286

RA patients carrying the TT genotype of the IL33 rs3939286 polymorphism had lower intima-media thickness (cIMT) values compared to those homozygous for the CC genotype. IL33 rs3939286 allele T exhibits a potential protective effect in the risk of subclinical atherosclerosis in patients with RA [29].

3.3. TNFRSF11B

Osteoprotegerin is encoded by *TNFRSF11B* gene and it is a member of the TNF receptor family which can recognize activator of nuclear factor KB ligand (RANKL). A study identified a polymorphism of the TNFRSF11B gene, which encodes osteoprotegerin, is associated with the presence of coronary atherosclerosis in patients with RA[30].

3.4. MTHFR

C677T polymorphism in the gene coding for MTHFR enzyme has been proved to be a new candidate genetic risk factor for CV disease in the general population. Another research further demonstrated that the MTHFR 1298 A>C gene polymorphism is an increased risk for atherosclerosis in patients with RA[31].

3.5. 11q23.3 genomic region-rs964184

The 11q23.3 genomic region-rs964184 polymorphism has been found associated with coronary artery disease in caucasian individuals. Recently, another research demonstrated that RA patients carrying rs964184 GG genotype was more prone to suffering from CVD than those carrying CC genotype. rs964184 polymorphism may be participated in CVD development in patients with RA[32].

3.6. NFKB1-94ATTG ins/del polymorphism

Previous research showed that NFKB1-94ATTG ins/del polymorphism is associated with higher risk of coronary heart disease in healthy caucasians. A recent study further disclosed that NFKB1-94ATTG ins/del polymorphism was also associated with increased CVD events in patients with RA[33, 34].

3.7. TNF-α gene

As TNF-α play a critical role in pathogenesis of RA and atherosclerosis, many polymorphisms of this cytokine have been studied in RA patients with atherosclerosis development. Among of them, TNF-*α* 308 and TNF-*α* 1031 T/C polymorphisms has been identified as involved factors[35, 36].

3.8. HLA-DRB1

Several HLA-DRB1 alleles have been found to be associated with RA susceptibility. A recent study demonstrated that *HLA-DRB1*04* SE alleles, especially the *HLA-DRB1*0404* was associated with the increased cardiovascular events and cardiovascular mortality in patients with RA[37].

4. DISCUSSION

In the last decades, a great deal of evidence has proved that atherosclerotic cardiovascular disease events are markedly increased in patients with RA. Therefore optimal management is needed in order to minimize vascular complications and atherosclerotic cardiovascular diseases (CVD) events in RA

treatment. Traditional atherosclerotic risk factors and inflammation mediators have been proved to be associated with increased CVD events in RA, besides various genetic factors have also be identified as critical contributors in this process. These genetic factors might provide a new way to detect atherosclerosis progression in RA.

5. ACKNOWLEDGEMENTS

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