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Insights of rheumatoid arthritis risk factors and associations

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A B S T R A C T

Rheumatoid arthritis (RA) is a defective post-translational modification of citrullinated peptides which cause synovial inflammation in joints. The present review elaborates the basic mechanisms of RA and the root causes of molecular mechanisms. The gender-based differentiation and probabilitiesof RA causes were discussed. Many report studies supporting that females are more prone to RA than males maybe suspected that circulating estrogen hormones 16a-hydroxy estrone, 2-hydroxy estrogens involvement in the RA pathogenicity. Other important aspects like environmental factors and air pollutants like (SO2 and NO2) were also impacted and enhances the risk of RA were discussed. The root cause of pathomechanisms of peptidylarginine deiminase (PAD) enzymes in RA and autoimmunity factors were poorly understood, however, Ati-citrullinated peptides (ACP) are the powerful markers to diagnose the RA disease. This review discusses three main risk factors of RA to understand the RA pathogenesis and disease-modifying mechanisms, may provide a unique opportunity to determine disease prevalence and RA associations.

1. Introduction

Autoimmune diseases caused due to dysfunction of the immune system have now unequivocally regarded as the most significant clinical problem, as they affect nearly 23.5 million Americans and with increasing prevalence [1]. The dysfunction of the immune system leads to the production of autoantibodies against the healthy cells, tissues and organs. Based upon the impact, severity, and the organs affected, more than 80 autoimmune diseases have been identified. Rheumatoid arthritis (RA) is one of the major autoimmune diseases, with an estimated incidence rate of 5–50 of 100,000 persons per year, and it gains insight due to its distinct pathogenetic mechanisms [2]. The chronic inflammation of the joints is a hallmark of RA. The immune system attacks joint tissue for pathogenic citrullinated peptides causing inflammation in synovium, leading to RA. Citrullination, also termed as deamination, is a modification of arginine side chains catalyzed by peptidyl arginine deaminase (PAD) enzymes. This post-translational modification has the potential to alter the structure, antigenicity, and the function of vimentin proteins, Inflammation synovium is known as synovitis. This leads to symptoms of warmth, redness, swelling, and pain. The chronic inflammation of RA causes the normally thin synovium to become thick and joints to become swollen and puffy. The inflammation of synovium invades and destroys the cartilage and bone within the joint, about 1.3 million adults have RA, and researchers studying rheumatoid arthritis now believe that it begins to damage bones during the first year or two that a person has the disease. Genetic influences are estimated to be responsible for around 50–60% of the risk of developing RA [3]. Arthritic conditions that are different individual illnesses, with differing features, treatments, complications, and prognosis that's one reason why early diagnosis and treatment are so important. They are similar in that they have a tendency to affect the joints, muscles, ligaments, cartilage, and tendons, and many have the potential to affect internal body areas as well. There are many forms of arthritis (over 100 have been described so far, and the number was growing). The forms range from those related to wear and tear of cartilage (such as osteoarthritis) to those associated with inflammation as a result of an overactive immune system (such as rheumatoid arthritis) (Fig. 1). Recent research has uncovered a complex interplay between the hormonal, nervous, and immune systems in rheumatoid arthritis [4]. Researchers are also trying to learn why rheumatoid arthritis often improves during pregnancy. One review suggests that certain proteins passed between the mother and unborn child may be responsible for the improvement. These are proteins that help the immune system tell the difference between the body's own cells and foreign ones. This exchange of proteins may change the mother's immune system during pregnancy in some way.

2. Autoimmune disorders

An autoimmune disease like rheumatoid arthritis, something goes awry. The white blood cells overreact to stimuli inside the body. Instead of protecting the body from infection or disease as it normally does the immune system attacks and destroys the body's healthy tissue. It does this by producing antibodies against the body's tissue. When the disease affects many organs, as in lupus, it's called a systemic autoimmune

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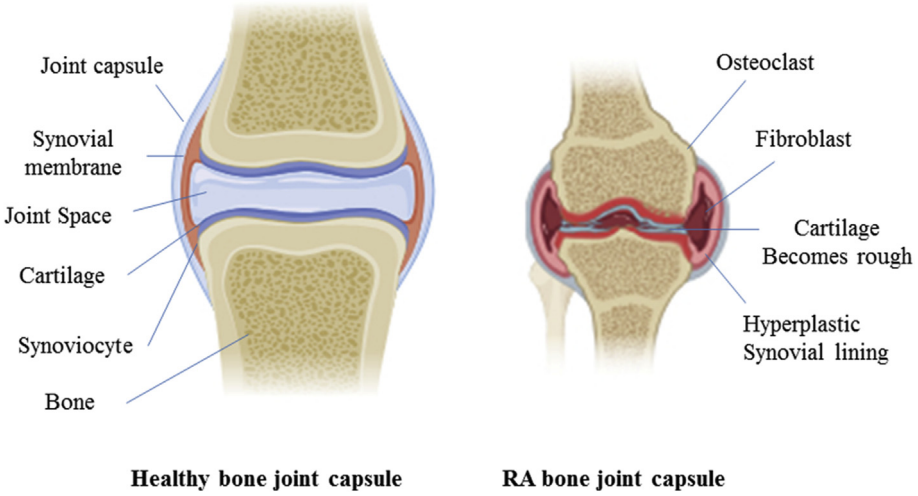

Fig. 1. Bone joint differentiation of normal and Rheumatoid arthritis the pathophysiological mechanism of rheumatoid arthritis (RA) and the immune response involves a sequence of events.

disease. If it affects a single organ or type of tissue, such as in type 1 diabetes, it's known as a localized autoimmune disease. Different autoimmune diseases often cluster in families and may affect almost any organ in the body. When they do so, they may cause abnormal growth or changes in function. The body overreacts and response to citrullinated proteins, as they are true auto-antigens in RA [5]. The cyclic citrullinated peptides (CCP) as surrogate target antigens, are routinely used in RA diagnosis. The first generation anti-CCP assay (anti-CCP1) was based on citrulline-containing peptides from the filaggrin sequence [6,7]. This test had a diagnostic sensitivity of approximately 70% with a disease-specificity of 96% because filaggrin, a protein which is involved in epidermal differentiation and hydration, is found only in epithelial cells but not in the joint [8]. It was known that citrullinated filaggrin acted as a surrogate antigen and that other citrullinated protein were more likely to be driving the autoimmune response in RA. To improve the diagnostic sensitivity and specificity of the anti-CCP1 test, the anti-CCP2assay was developed and is now widely used in diagnostic laboratories.

3. Sex-linked RA

There are many interesting machanisms attached to RA, one of them is, we do not know what actually triggers sex linked deformities associated with RA. One of the major female sex hormones is called estrogen in females and androgen in males. Gender is a well-known risk factor for RA, in which females in general have a 2.5-fold higher risk [9–11]. Genetic factors of sex chromosomes, factors related to pregnancy and hormones, and also environmental factors obviously differ between the two sexes. However, there are some evidences which seem to point to the role of female sex hormones impact on its pathological development and expressions in RA [12,13]. There is an increased estrogen concentration observed in RA of both sexes are characterized by the hydroxylated forms, in particular 16a-hydroxyestrone and 4-hydroxyestradiol [12]. Several groups have investigated the effects of estrogen and other sex-related factors in RA reviewed in Refs. [14,15], and both the estrogen synthase locus and the estrogen receptor gene have been weakly associated [16]. In a recent study, urinary levels of 2-hydroxylated estrogens were found 10 times lower in RA patients than in healthy controls, whereas the ratio 16 a-hydroxy estrone and 2-hydroxy estrogens were found 20 times higher in RA patients than in healthy controls(Straub in press). The relative loss of 2-hydroxylated estrogens in relation to the mitogenic 16 a-hydroxyestrone might thus be an important switch to support the proliferative state of the synovial cells in RA [12]. In another study of tandem CAG repeats in the androgen receptor exon 1, it was suggested that male patients with an early onset of RA had significantly fewer repeats than did age-matched controls or late-onset male RA patients [17]. This feature indicates that arthritis suggests that female sex hormones, like estrogen may be playing an important role in RA (Fig. 2). Specific effects of estrogen hormones are due to effects on cells within the body. They, therefore, gave the mice a chemical endocrine disrupting chemicals such as bisphenol A (BPA) which blocked the effect of estrogens on cells [18]. The arthritis in these mice was, as you would expect, worsened therefore this report is very interesting, however, the doses of estrogen and of inhibitor used were such that they did not interfere with the normal female cycle in these mice. These experiments provide some the information that these estrogen hormonal effects on rheumatoid arthritis by a mechanism that is independent of their ability to act as sex hormones [19].

4. Citrullinated proteins

Pathological protein citrullination is associated with inflammation, not just in RA, but also in other forms of inflammatory arthritis [20–22] and unrelated inflammatory diseases, such as multiple sclerosis [23], glaucoma [24], myositis [25], and Alzheimer's disease [26]. In psoriasis, citrullination is down regulated in keratinocytes, possibly reflecting their failure to undergo terminal differentiation in the formation of the cornfield layer of the skin [27]. In inflammatory arthritis, including RA, it is assumed that inflammation and the resulting release of pro-inflammatory stimuli and increased cell death, allowing PAD activation in a calcium-rich environment, might account for the accumulation of citrullinated proteins. The previous reports shown that the synovial fluid is an extracellular compartment within the joint with a particularly abundant expression of citrullinated proteins [28]. The dominating enzyme PAD4 was detected in all three disease groups, while detection of PAD2 was mainly restricted to the inflammatory synovial fluids, this provides some evidence that the extracellular (and therefore Ca^{2+} rich) environment is able to support the activity of PADs and that PAD2 may be inducible by inflammation. However, intracellular citrullinated proteins in inflammatory arthritis were also observed by a number of investigators [29–33] results from a controlled or increase in intracellular Ca^{2+} concentrations, for example, in response to specific ion pump activation influence the formation of citrullination in RA (Fig. 2).

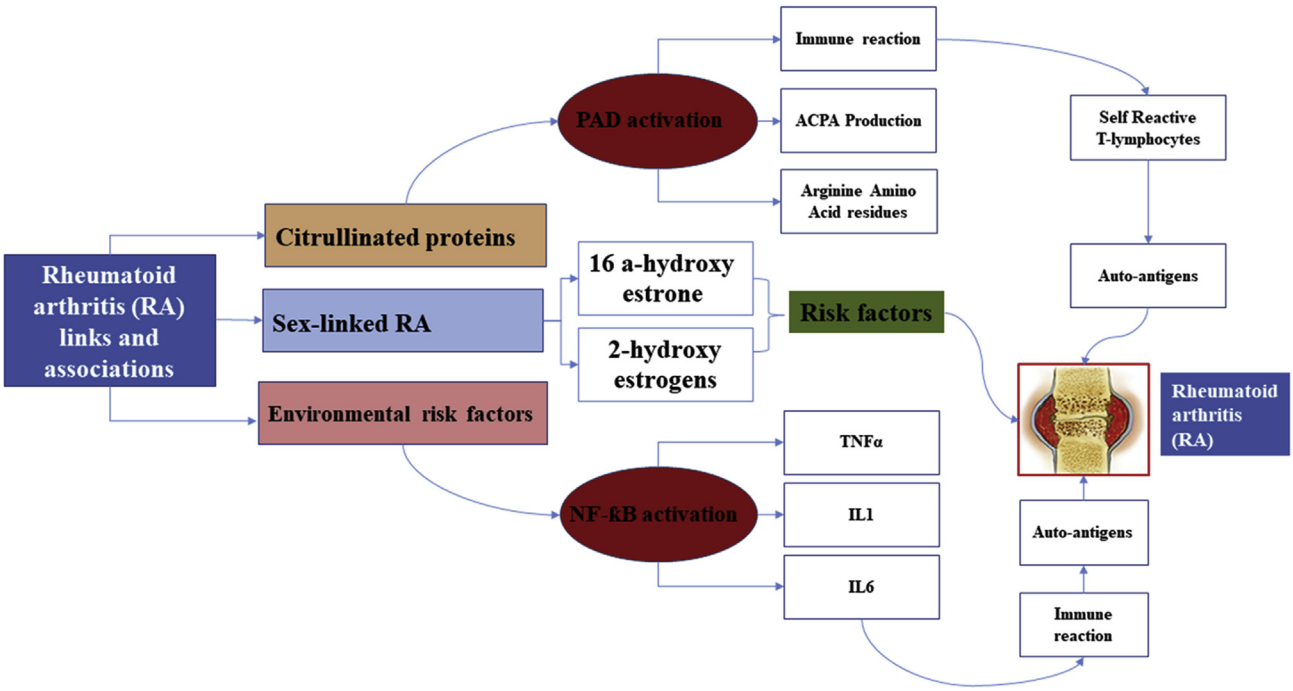

Fig. 2. Schematic representation of mechanisms putatively influencing rheumatoid arthritis through links and associations. Three main risk factors are represented in mechanistic ways (light yellow, light blue and light pink). Light yellow: Citrulinated peptides activated by peptidylarginine deiminase (PAD) activation leads to immune reaction, anti-citrunilated peptides (ACP) production, Arginine amino acid defects. These three factors collectively lead to self-reactive T-cells finally auto-antigens which makes the synovial inflammation in joints. Light blue: Sex linked hormones like circulated 16a-hydroxy estrone, 2-hydroxy estrogens and Light pink: Environmental risk factors inhaled activates the nuclear factor kappa B (NF-kB) that stimulates the production of tumor necrosis factor alpha (TNF-α), interleukin 1 (IL1) and interleukin 6 (IL6) by T helper lymphocytes type 1 (Th1) these cytokines stimulate immune system in adverse ways to leads auto-antigens and finally inflammation at joints causes Rheumatoid arthritis (RA). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5. Citrullinated vimentin in RA

Vimentin is an abundant intermediate filament protein, involved in the dynamic organization of the cytoskeleton, with a vital function in organelle transport, cell migration, and proliferation. Citrullinated vimentin was first described as the Sa antigen, detected by immunoblotting using placenta and spleen extracts [34]. Anti-Sa antibodies were detected in approximately 40% of rheumatoid serum samples and were predictive of a more severe disease [35]. The identity of the Sa antigen was subsequently suggested [36] and later confirmed [20] to be citrullinated vimentin. Citrullinated vimentin is expressed in vitro in macrophage-like cells after ionophore induced Ca^{2+} influx [20,37]. As these ionophores and the concomitant Ca^{2+} influx cause apoptosis, it was suggested that citrullination of vimentin is associated with apoptosis. Later, two independent groups [38,39] demonstrated the presence of citrullinated vimentin in the inflamed joint. In one of these studies, citrullinated iso-forms lacking the amino-terminal region were detected in synovial tissue of patients with various arthritis [38]. These particular isoforms could be the result of caspase-3 cleavage, as it is known that vimentin is cleaved by various caspases during apoptosis [40,41] and that the amino-terminal cleavage products promote apoptosis. In the other study, Bang et al. [38] reported various citrullinated and mutated isoforms of vimentin in cellular synovial fluid from RA patients and their reactivity with serum antibodies by immunoblotting. The mass-spectrometry analysis demonstrated that the vimentin isoforms contained certain amino acid mutations and modifications, in particular mutations of glycine residues in arginine residues at positions 16, 59, 145, and 147 citrullination of a number of arginine residues [42]. Based on these findings, recombinant human vimentin was expressed, mutated at positions glycine-16 and glycine-59 into arginine and at arginine-50 into histidine, and citrullinated in vitro. The commercial test using this antigen is known as the anti-modified citrullinated vimentin (anti-MCV) assay and was found to be of superior diagnostic sensitivity (82%) compared with the anti-CCP2 assay (72%), without loss of specificity [39]. A similar difference in sensitivity was also found in patients with early RA (anti-MCV: 70.7% versus anti-CCP2: 57.9%) [43], while another study reported that anti-CCP2 was superior [44]. In a systematic review of 14 studies comparing the two assays [45], the authors concluded that the anti-MCV assay could be used as an alternative to the anti-CCP2 assay for diagnosis, though importantly, all studies found a handful of samples which were positive for anti-MCV but negative for anti-CCP2 or vice versa. This means that it is best to adopt one of the assays as a 'gold standard' for the purposes of epidemiological studies, and, for most, this choice has tended to be anti-CCP2 [46]. The high diagnostic sensitivity and specificity of anti-MCV as well as its predictive value for erosive disease provide indirect evidence for citrullinated vimentin as an important molecule for driving the pathological immune response in RA. These earlier reports of RA demonstrate that at least one citrullinated peptide, but not its arginine-containing counterpart, can drive a T-cell response in the context of the HLA-DRB1*0401 molecule [47]. However, unlike citrullinated fibrinogen, citrullinated vimentin has yet to be demonstrated to be arthritogenic in an *in vivo* animal model. The proven the fact that the human and murine vimentin are highly conserved (97.4% sequence identity), animal models using antibodies to human citrullinated vimentin could provide important insights into the pathogenicity of these auto-antibodies. Furthermore, a potential role for vimentin in the pathology of RA is beginning to emerge from studies of extracellular vimentin in inflammation. A recent study showed that extracellular vimentin mediates TGF-b activation [48,49] reported that during the inflammatory response to bacteria, cell-surface expression and secretion of vimentin in monocyte-derived macrophages was enhanced by TNF-α stimulation and mediated killing of internalized *E.coli*. Other

studies have shown extracellular vimentin fragments on endothelial cells [48] and on inflammatory cells, including apoptotic T cells [50], neutrophils [51], activated platelets [52], and macrophages [50,51]. Interestingly, various bacteria use cell-surface vimentin as an attachment receptor [49–53]. Taken together, the extracellular location and the data demonstrating *in vivo* citrullination of vimentin support a role for citrullinated vimentin in pathogenesis and, in the presence of additional risk factors such as bacterial infection, possibly priming of an autoantibody response.

6. Environmental risk factors in RA

The non genetic factors such as smoking, air pollution and silica and asbestos is the dominant environmental risk factor and doubles the risk of developing rheumatoid arthritis [54]. Its effect is restricted to patients with ACPA-positive disease [55,56]. Although patho-genetically very important, on a population level, the risk is too low to be clinically relevant. Other potential environmental risk factors include alcohol intake, coffee intake, vitamin-D status, oral contraceptive use, and low socioeconomic status, although supporting evidence for these other factors associated with RA [57]. Air pollution, a mixture of suspended particulate matters (PM) of different diameters and gases nitrates (NO2), sulphur dioxide (SO2), ozone (O3), and carbon monoxide) have recently been paid more attention in the field of RA [58]. The main sources for these pollutants are heavy traffic, industry, stationary fuel burners, forest fires, and solid fuel combustion. In this aspect, free reactive oxygen species released by fine/ultrafine PM or gaseous pollutants inhaled into the respiratory tract are capable of activating nuclear factor kappa B (NF-kB), a key regulator for pro-inflammatory cytokine production in RA patients [59, 60]. The excess T helper lymphocyte type 1 (Th1) production of tumor necrosis factor alpha, interleukin-1 and interleukin-6 (Fig. 2). These cytokines stimulate resting monocytes to mature dendritic cells, which then present auto-antigens, co-stimulating self-reactive T lymphocytes that migrate to target tissues synovial joints, and cause destruction of cells expressing auto-antigens. Moreover, reactive oxygen species are capable of worsening with adverse environmental risk factors in RA.

7. Conclusions

RA is often characterized by progressive joint damage that, often leads to to cartilage and bone destruction. It is evident that the nature of progressive joint damage varies considerably, linking with several factors including genetic, sex, and environmental pollutents in RA risk. We review the basic understanding of RA pathomechanisms linking these environmental factors to disease risk. Understanding the exact role of action and risk factors of RA is especially important given the prevention of RA. Consequently, the identification of risk factors, exposure consequences with ongoing joint damage may limit cartilage degradation and is important in preventing irreversible synovium damage. Present biological markers and clinical measures can be used to help with identity in early RA, including elevated CRP levels and the number of swollen and tender joints. Additional application of biochemical markers, which are able to sensitively detect ongoing joint damage, may facilitate the appropriate use of targeted therapy in RA and help reduce the progression of joint damage in patients.

Conflict of interest

None.

Funding

Nill.

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