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The Role of Fibronectin and its Isoforms in the Pathogenesis and Progression of Rheumatoid Arthritis: A Review

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Abstract: Rheumatoid arthritis (RA) remains a desolating and devastating disease with a strong social impact on the world. Current drugs and therapies are showing poor responses toward RA due to its unknown progression. Evidence has shown that Extra Domain A fibronectin, recognized as a damage-associated molecular pattern (DAMPs), interacts with pathogen recognition receptors (PRR), which play a vital role in the erosion and degradation of joints. The post-translational modification and citrullination of fibronectin enhance the expression of EDA fibronectin (EDA+Fn). Fibronectin and its interacting receptors, such as TLR-4 may be a potential target for the treatment of RA. This review critically summarizes the recent discoveries and breakthroughs in the role of fibronectin and its isoforms in the pathogenesis and progression of RA.

Keywords: EDA-fibronectin; rheumatoid arthritis; DAMP; TLR4; NF-kB pathway.

1. Introduction

Rheumatoid Arthritis is a leading autoimmune disease that affects almost 1% of the world population. It is known that RA is an inflammatory disease in which the body's immune system mistakenly attacks its cells, including the joints, resulting in the deformation and erosion of the joints [1]. The disease is more prevalent among the aging population, and women are more susceptible to RA than men, which eventually wrecks the population's healthy life and well-being [2].

In this scenario, scientists play a critical role, and much research is going on in the field of rheumatology to discover the feasible ways that lead to the pathogenesis and progression of RA. The final result of these studies had shown that DAMPs play a pivotal role in the pathogenesis and progression of many inflammatory diseases, including rheumatoid arthritis, osteoarthritis, cancer, Alzheimer's disease, hyperuricemia, atherosclerosis, Parkinson's disease, sarcoidosis, coronary heart diseases, Crohn's disease, gout, obesity, systemic sclerosis, etc. [3]. Targeting the DAMP is one of the main approaches to inhibit the progression of many inflammatory diseases. Nowadays, drugs are designed to block the release or action of the DAMP molecules [4,5,6]. DAMPs are molecules with endogenous cell functions like gene regulation, cell proliferation, tissue repair, etc., and are released as dangerous molecules upon

cell death and injury [7]. Upon release from the cells, these DAMP molecules initiate inflammation by activating the innate immune system [8]. After being released from the cell, these DAMP molecules bind with PRR of both immune and non-immune cells like macrophages, neutrophils, monocytes, and dendritic and epithelial cells. The PRRs include membrane-bound receptors (such as Toll-like receptors TLR, C-type lectin receptor, receptor kinases), cytoplasmic sensor receptors (RIG 1, NOD-like receptors), and inflammasomes (multi-protein complexes) [9,10]. As a result of interaction with the receptors, it produces many pro-inflammatory mediators like cytokines, prostaglandins, histamines, and serotonin that ultimately cause inflammation through vasodilation, vessel permeation, leukocyte migration, and phagocytosis [11,12].

In this review, the role of fibronectin in the pathogenesis and progression of RA is discussed. RA occurs in symmetric joints, so the biggest question has always been, what triggers the disease to originate in symmetry joints? And here, DAMPs may play a significant role in the pathogenesis and progression of RA. This review aims to critically examine the functions of fibronectin, its interacting receptors, inflammatory mediators, and signaling pathways and bring to light the therapeutic targets of RA.

2. Importance of DAMP Molecules

It has been well documented that DAMPs contribute to various inflammatory and immunological disorders [13], as shown in Table 1. Nowadays, researchers are more fascinated by DAMPs, as they are involved in the pathogenesis and progression of many autoimmune diseases. The frontline shield in our body is the innate immune system, consisting of somatic cells like smooth muscle cells, epithelial cells, fibroblasts, and immune cells like macrophages and neutrophils. All these cells are furnished with PRR to secure the host. These cells remove the dead cells, kill pathogens and promote tissue repair through the innate immune system by inflammation. Even though the innate immune system is a protective tool to remove the infection, it contributes to the pathogenesis of various inflammatory diseases [14]. Over the years, the interest of scientists in DAMPs has considerably increased, and of course, targeting the PRR or DAMPs for treating autoimmune diseases will be a potential therapeutic way. It will create a revolution in the scientific world in the forthcoming days [3, 15].

Table 1. DAMP molecules contribute to the pathogenesis of RA.

S.No	Name of the DAMP molecule	Interacting receptors	Inflammatory mediators and their effects	References
1	High Mobility Group Protein B1 (HMGB-1)	TLR 2, TLR 4, TLR 5,TLR 9	Production and release of pro-inflammatory cytokines (tumor necrosis factor (TNF) and IL-1), which causes RA	[16,17]
2	HSP60	TLR 2, TLR 4	Promotes the induction of IL-1β and TNF-α, which mediate inflammation, cartilage and bone destruction	[16,18]
3	HSP70	TLR 2, TLR 4	Activation of the nuclear factor-kappa-B or the Akt signaling pathways or both produces various pro-inflammatory mediators such as TNF, IL-1β, and IL-6	[16,19,20]
4	HSP96	TLR 2, TLR 4	Increased TNF-α and IL-8	[16,21]
5	RNA	TLR7	Release of Interleukin-8 (IL-8) or CXCL8 and matrix metalloproteinase 3 (MMP-3), which leads to RA	[16,22,23]
6	DNA fragments	TLR 9	It enhances JNK, p38 MAPK, and Erk1/2 activation, which contributes to RA	[24]

S.No	Name of the DAMP molecule	Interacting receptors	Inflammatory mediators and their effects	References
7	S100 Protein	TLR 2,TLR 4 and RAGE	Production of matrix-degrading enzymes like MMPs and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs), which are involved in cartilage degradation and the development of RA	[25,26]
8	Serum amyloid A protein	TLR 1,TLR 2	Activates interleukin 17, producing T helper cells	[27]
9	Biglycan	TLR 4 and TLR 2	TNF-α and macrophage inflammatory protein–2 (MIP-2).	[16,28]
10	Heat Shock Protein B8	TLR 4	Activation of dendritic cells and release of pro-inflammatory mediators TNF- α and IL-12.	[29]
11	miR-let-7b8	TLR 7	Production of higher levels of interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α)	[30]
12	Small extracellular vesicles -derived-miR-574-5p	TLR 7,TLR 8	Activates fibroblast-like synoviocytes (FLS), which secret inflammatory mediators such as IL-6 and IL-8 that ultimately degrade the cartilage.	[16,31]
13	Tenascin C	TLR 4, α9β1 integrin	Produces IL-1, TNF-α, and IL-6 that mediate the inflammation	[32]
14	EDA Fibronectin	TLR 4, α5β1	With TLR 4, it produces many inflammatory mediators, and with α5β1, it activates MAPK and NF-kB signaling pathways	[33,34]

3. Fibronectin as a Glycoprotein

Fibronectin is a glycoprotein found on the cell's extracellular matrix that is liable for many regulatory functions such as cell adhesion, proliferation, migration, etc. Fibronectin is the first thoroughly studied glycoprotein [35,36]. Fibronectin is synthesized by various cells chiefly by fibroblast in the form of dimer linked by a pair of disulfide bonds. Fibronectin binds to the Integrin receptor and extracellular components such as fibrin, collagen, heparin, etc. The Integrin receptor comprises of Metal Ion Dependent site (MIDAS) and two subunits, α, and β, each having different receptors for different binding ligands [37]. Fibronectin is classified into two types such as soluble plasma fibronectin and insoluble cellular fibronectin. Hepatocytes synthesize the first one in the liver cell, and the latter is synthesized by various cells, including fibroblasts. Both show different structures, and there are many forms of fibronectin; every one has its function with respect to tissue repair. Based on the amino acid sequence, fibronectin consists of three domains: Type I, Type II, and Type III. Nearly 20 different isoforms of fibronectin are constitutively expressed, alternatively spliced, and non-homologous [38-40].

4. Fibronectin and its Isoforms as a DAMP Molecule

Fibronectin is a dimer linked by a pair of a disulfide bond. Each monomer sequence of fibronectin has 3 repeats, which on alternative splicing generates 15 isoforms, i.e., (FN1-FN15). Synovial fluid collected from RA patients has different FN isoforms. The 3 repeats (domains) of fibronectin include type 1- extra domain A (EDA), type 2- extra domain B (EDB), and type 3- connecting segment (IIICS). Type 1 contains 40 amino acid residues, type 2 contains 60 residues, and type 3 contains 90 residues, as shown in Table 2 below. Type 1 and 2 contain a disulfide bond, while type 3 has no disulfide bond [41]. In a study, synovial tissues

of RA patients were collected and processed to identify the presence of alternatively spliced fibronectin. The study unveiled that EDB fibronectin is expressed highly in the fetal and transformed human tissues, particularly in the CD36-type B cells [42].

Table 2. Fibronectin and its major isoforms.

Domains	Binding domain	Amino acids	Repeating units
FN 1(Type I)	Plasma protein domain	40 residues	Purple rectangles
FN 2(Type II)	Collagen-binding protein domain	60 residues	Green octagons
FN 3(Type III)	Conserved protein domain	90 residues	Red ovals

5. Role of Fibronectin and its Isoforms in the Pathogenesis of RA

The EDA fibronectin arises as a result of alternative splicing. During the post-translational modifications of fibronectin, splicing takes place in the nucleus, where an enzyme called Ca^{2+}-dependent peptidylarginine deiminase (PAD) converts the arginine amino acid of fibronectin to citrulline amino acid, this process is called citrullination which is shown in (Figure 1), and it increases the expression of Extra Domain A-fibronectin (EDA+Fn). This EDA+Fn is an isoform of fibronectin containing the same protein but different amino acids [35,43,44]. Particularly three non-coding sequence (EIIIA, EIIIB, and IIICS) of a fibronectin gene undergoes alternative splicing and increases the expression of the extra domain A-fibronectin (EDA+Fn) [37]. EDA fibronectins are cellular and are released during cell injury, which is conceded as DAMP, and it contributes to the pathogenesis of many inflammatory disorders, including RA [45].

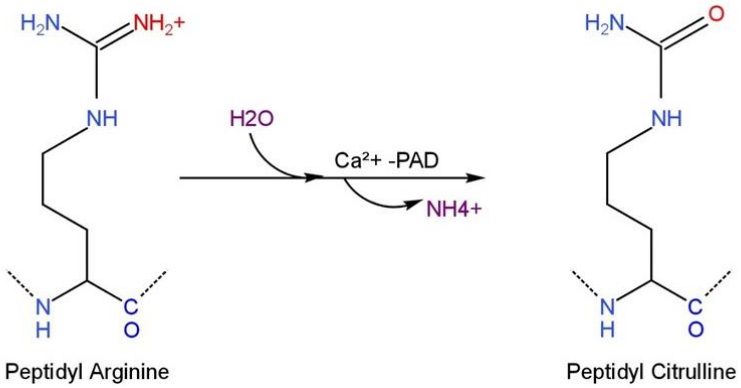

Figure 1. Conversion of peptidyl arginine to peptidyl citrulline by Ca^{2+} dependent peptidylarginine deiminase (PAD)

The enzymatic activity of peptidyl arginine deiminase (PAD) plays an important part in the pathogenesis of RA. Five PAD enzymes have been reported in RA. CFn was detected in the connective tissues especially in the synovial and pannus tissue of RA patients. The production of mediators like cytokines and metalloproteinases by fibronectin fragments has been reported by various researchers [46].

In research demonstrated by a group of scientists, synovial tissues were collected from RA patients and processed for TUNEL assay, quantitative RT-PCR analysis, western blot analysis, and ELISA to elucidate the pathogenic role of citrullinated fibronectin (cFn) in RA. The study found that cFn contributes to the secretion of many inflammatory mediators and concluded its major role in RA [35].

6. Role of Fibronectin and its Isoforms in the Progression of RA

Till now, the exact mechanism behind the progression of RA remains unknown and unclear. However, it is suspected and proven that DAMP molecules also play a crucial role in the progression of RA [47]. The progression of RA is influenced by many factors, including age, sex, genetic factors, and environmental factors like pollution and smoking. RA originates from small joints such as knees and wrists and proceeds with large joints and even internal organs like lungs, kidneys, etc. Currently, there is no cure for RA [48]. It is noteworthy that Rheumatoid Arthritis Synovial Fluids (RASF) activated by fibronectin through the production of MMPs, play a substantial role in the progression of RA [49]. Degrading enzymes like Matrix metalloproteinases (MMPs) and cathepsins produced by the RASFs are devoted to cartilage degradation. It also secretes pro-inflammatory cytokines and chemokines like nuclear factor kappa B ligand (RANKL) that leads to inflammation and causes RA. Initially, the lining of the joints becomes inflamed, and in the fullness of time, it starts destructing the cartilage. This inflammation results in the deformation and erosion of the joints. At last, the portion of the body loses its motion [50].

7. Fibronectin Receptors

Integrins are transmembrane receptors that act as an intermediate between the cell and the extracellular matrix, and various kinds of ligands can bind to this receptor. There are different kinds of integrin receptors such as αIIbβ3, which is a platelet Integrin, IIbIIIa is found in monocytes, and polymorphonuclear neutrophils, Very Late Antigen (VLA-5) or α5β1 is present in the leukocytes, chondrocytes, fibroblasts, and monocytes, α3β1 is found in all synovial cells while α4β1 is present only on the lymphocytes. Among all, nearly 12 integrins can bind to fibronectin [51,33].

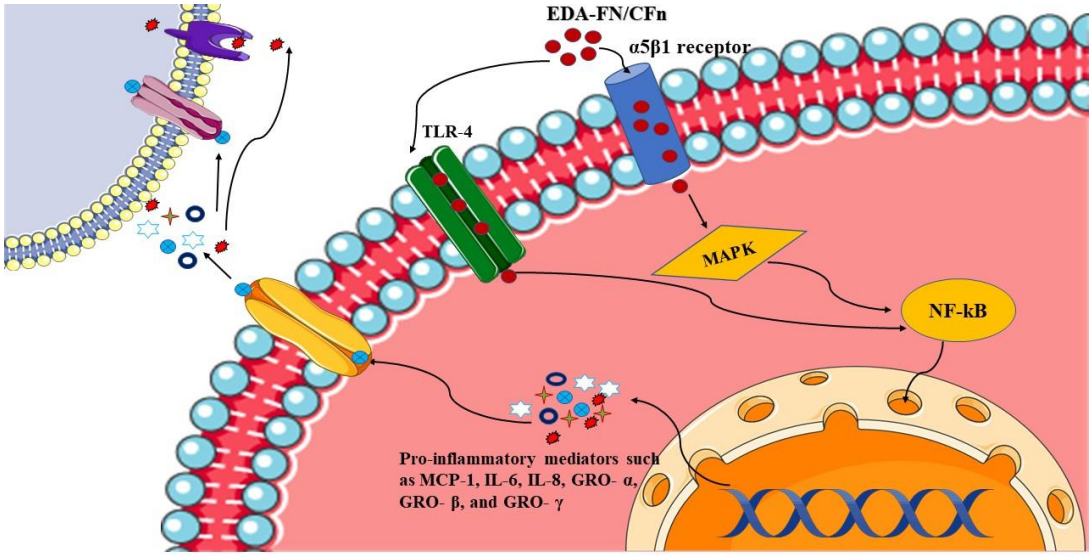

Figure 2. EDA-fibronectin (post-translationally modified fibronectin) and its signaling pathways in RA.

8. Signalling Pathways and Inflammatory Mediators

The EDA+Fn acts on PRR, specifically on the Toll-Like Receptor 4 (TLR 4), and releases pro-inflammatory mediators such as cytokines (TNF- α, IL-1β, and IL-6), Vascular Endothelial Growth Factor (VEGF) and cause RA. Fibronectin on reaction with integrin receptor of the macrophages, secrets IL-1β, IL-6, IL-8, TNF, and MMPs. EDA+Fn also secretes

cytokines through bone marrow mast cells BMMCs, when it acts on the TLR 4 [33,52]. When the fibronectin interacts with articular chondrocytes, NF-κB regulates inflammatory responses by releasing various prostaglandins, MMPs, and chemokines. Fibronectin binds to the VCAM 1 and VLA 4, and this bidirectional property activates the matrix degradation. The fibronectin-integrin interaction often enhances the secretion of cytokines such as TNF and other interleukins [53].

A study was done using human cytokine Ab protein array and semiquantitative PCR to identify the inflammatory mediators accountable for FN-f stimulated RA. They confirmed that FN-f binds to the α5β1 receptor, which unlocks and activates MAPK signaling pathways that further switch on the NF-κB-dependent pathway and release inflammatory cytokines such as IL-6, IL-8, MCP-1, GRO- α, GRO- β, and GRO- γ which is shown in Figure 2 [34].

Fibronectin secreted by FLS (Fibroblast-like synoviocytes) facilitates Wnt signaling pathways and gives rise to MMPs, both of which enhance joint destruction and are liable to RA's pathogenesis. Certain studies have shown that Wnt signaling pathways controlled the production and release of inflammatory mediators such as IL-8, IL-15, IL-6, and RANKL in RA patients. This indicates that RA patients' fibronectin secretion is balanced by Wnt signaling pathways. Several data reveal that fibronectin is responsible for chemokine signaling, and it expedites the cartilage degradation process. There is now ample evidence suggesting that the fibronectin type III domain acts on the TLR 4 and stimulates the NF-κB pathway, which results in the downstream production of inflammatory cytokines [54].

9. Therapeutic Approaches

Bispecific diabody (BsDb) is an antibody secreted by *Escherichia coli* that acts as an antagonist to the EDB fibronectin and inhibits its circulation in inflamed sites. BsDb had shown excellent activity in mice and inhibited the progression of RA. BsDb seems to be a potential therapeutic target for RA [55]. Triptolide, a diterpenoid epoxide, inhibited the production of fibronectin in human tenon fibroblasts (HTFs). It has also been used in Chinese traditional medicine to treat various immunological disorders [56].

Doubtlessly, targeting the PAD enzyme is a great option to treat RA, and it has gained great interest over the years in the research community. As a result, various PAD inhibitors have been developed to treat various inflammatory disorders. The PAD inhibitors include Taxol Sanguinarine, Streptonigrin, F-amidine, Chlortetracycline, 2-chloro-acetamide, GSK121, PAD2-IN-1, BB-F-amidine, NSC95397, and so on [57].

10. Conclusions

The evidence and information in this review put forward that EDA Fibronectin acts as a biomarker in the pathogenesis and progression of RA, which may be a possible target for diagnosing and treating RA. This review unveiled the current perspectives on the pathophysiology of RA. Further studies in fibronectin will help to look deeply into the progression of RA, which may aid in discovering novel drugs against RA.

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Conflicts of Interest

The authors declare no conflict of interest.

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