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The role of protein SUMOylation in rheumatoid arthritis

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ABSTRACT

Small ubiquitin-like modifier (SUMO) proteins, as a subgroup of post-translational modifiers, act to change the function of proteins. Through their interactions with different targets, immune pathways, and the responses they elicit, can be affected by these SUMO conjugations. Thus, both a change to protein function and involvement in immune pathways has the potential to promote an efficient immune response to either a pathogenic challenge, or the development of an imbalance that could lead to an autoimmune-based disease. Also, a variety of changes such as mutations and polymorphisms can interfere with common functions of these modifications and move an effective immune response in the direction of an autoimmune disease. The present review discusses the general characteristics of SUMO proteins and focuses on their involvement in rheumatoid arthritis as an autoimmune disease.

1. Introduction

Although strong genetic associations have been found in different autoimmune diseases, no unique genetic mechanism, which can lead to immune tolerance breakdown, has been identified and thoroughly discussed. Increasingly, evidence has shown that mutations and sequence alterations in DNA is not sufficient to explain the variable manifestations of these diseases and how epigenetic changes can affect the severity of this class of diseases [1]. Changes in gene expression, which are heritable and different from mechanisms that can affect DNA sequences, is defined as epigenetics. Epigenetics includes dynamic addition or removal of functional groups or proteins by specific enzymes, which can cause changes in the structure and function of various targets.

Post Translational Modifications (PTMs) are a diverse mechanism used by cells to control and regulate their biological functions [2]. The reversibility of these modifications enable proteins to participate in different functions and regulate their properties in response to changes in environment or a cell's state without interference in either their synthesis, or turnover rates [3]. As one of the post-translational modifications, SUMOylation is implicated in autoimmune diseases especially rheumatoid arthritis, and this is the main aim of our review.

2. SUMO (small ubiquitin-like modifier) proteins

SUMO proteins participate in post-translational modifications that have important roles in the diversity of biologic processes in eukaryotes such as activation of protein functionality. The Ubl family (ubiquitin-related protein modifiers) are similar to ubiquitin in architecture and enzymatic conjugation, but have completely different and non-overlapping functions [2]. While SUMO has no role and function on its own, SUMOs are capable of specifically regulating thousands of protein targets [4]. These proteins are highly conserved in different species [5] and the binding of SUMO to these target proteins is a reversible and dynamic process [4,6]. To date, four SUMO genes have been discovered in human that are different in their local expression and structure [7]. SUMO2 and SUMO3 are so similar in their sequence that they are sometimes referred to as SUMO2/3. SUMO1 is the most prominent

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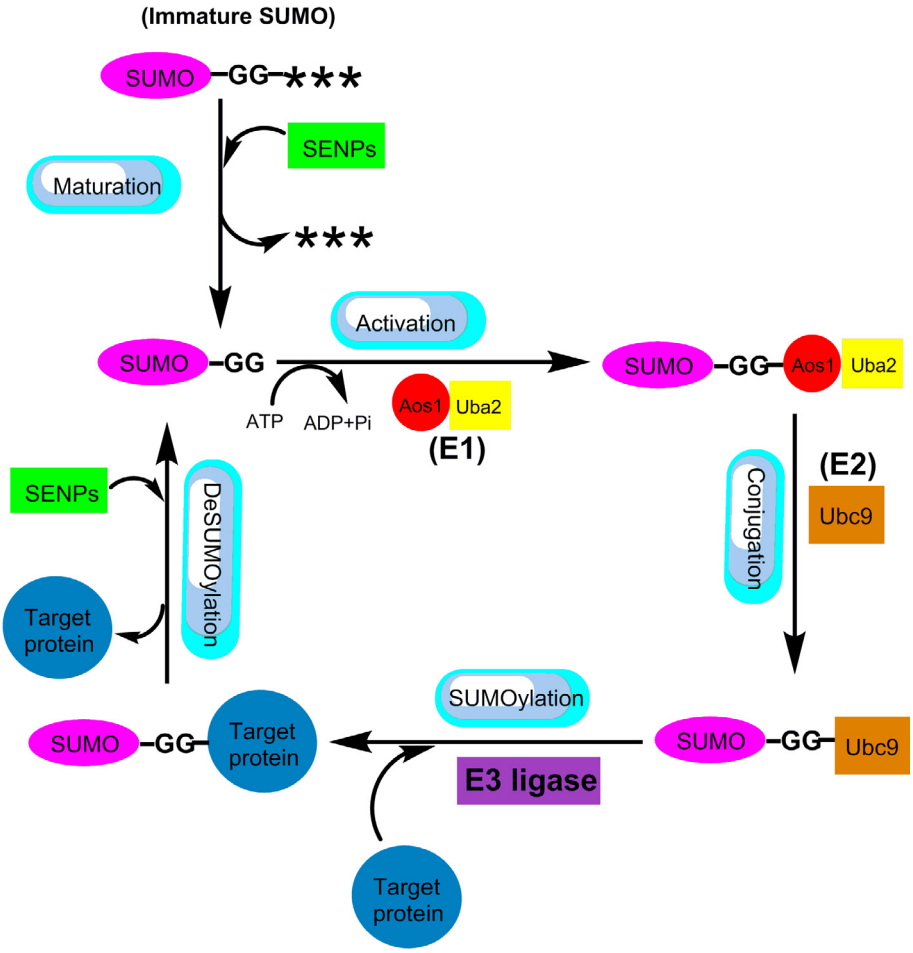

Fig. 1. SUMOylation pathway. SUMO is described as an immature precursor, which is matured by a member of the SENP family and has a C-terminal di-glycine motif in the mature structure. Then this form of SUMO is activated by E1 enzyme, a heterodimer of Aos1 and Uba2. This activated SUMO then passed to the active site of E2 conjugation enzyme, Ubc9. Finally, with E3 ligase SUMO is transferred to target protein. DeSUMOylation of the substrate is happened by SENP family proteases.

isoform, which is conjugated under normal physiological conditions *in vivo*, while SUMO2/3 is free under normal physiological conditions, but conjugated to proteins under disturbed physiological conditions such as heat shock and oxidative stress [5,8,9]. SUMO4 is a unique form of SUMO in the human genome and has its strongest expression in kidney, lymph nodes, and spleen. Unlike SUMO1, types 2, 3 and 4 have a SUMO attachment site and can form SUMO chains both *in vivo* and *in vitro* [2,7,10]. The binding of SUMO protein to the target is termed SUMOylation and occurs *via* a three-step pathway, which is mediated by three groups of enzymes (Fig. 1). Within these enzymes, 1) SUMO-activating enzyme (E1) is heterodimer of Aos1 (SAE1, Sua1) and Uba2 (SAE2) that has similar structure to ubiquitin-activating enzymes and activating SUMO proteins *via* attachment to them [4,5,11,12]. 2) SUMO-conjugating enzyme (E2), which transfers the activated SUMO from the Uba2 part of the E1 subunit to a part of the E2 subunit, which is termed Ubc9 [5,11]. And 3) SUMO ligase (E3), including PIAS, RanBp2, and Pc2; all, of which, interact with Ubc9 and form a covalently-bonded conjugate of the SUMO to the lysine residue of the target protein both *in vivo* and *in vitro* [4,5,11–14].

Multiple proteomic investigations have shown that SUMO substrates are specifically recognized and conjugated by specific enzymes [9,15]. Removal of the SUMO from the target protein is catalyzed by a deSUMOylating enzyme called SENP and includes types 1, 2, 3, 5, 6 and 7, which are specific peptidases [4,13,14,16]. SUMOylation targets in mammals, which modulate different physiologic pathways, includes proteins that are involved in cell cycle regulation, signal transduction, response to stress, regulation of transcription, subcellular localization, chromosome segregation, repair of damaged DNA, and modulation of inflammation [2,5,11,17].

2.1. Association of SUMO and SUMOylation with inflammation and autoimmunity

Activation of innate immunity receptors due to the production of antimicrobial and inflammatory mediators leads to activation of transcription regulator factors such as NFκB and IRF [18], which are tightly regulated by SUMOylation [19,20]. SUMOylation plays a role both in the activation and negative regulation of these pathways, hence, it can impede hyper-responsiveness of the immune system and inhibit the development of inflammatory and autoimmune disorders [21,22].

NFκB is a transcription factor that is involved in the induction of an inflammatory response and ubiquitously inhibited by IκB-α. This inhibitor binds to NFκB and mediates its translocation to the cytoplasm, where it is retained. When activated, ubiquitin binds and degrades IκB-α, which leads to activation of NFκB [2]. The role of SUMO as an antagonist that inhibits the degradation of IκB-α *via* ubiquitin was first introduced in a study on mammalian IκB-α [4]. When SUMO1 binds to the dephosphorylated form of IκB-α, it becomes resistant to ubiquitin attachment and degradation. Subsequently, this process causes NFκB to remain inactive [2,4]. A SNP in SUMO4, which has been termed M55V and leads to a substitution of valine for methionine, can affect NFκB activation. Consequently, this further leads to overexpression of heat

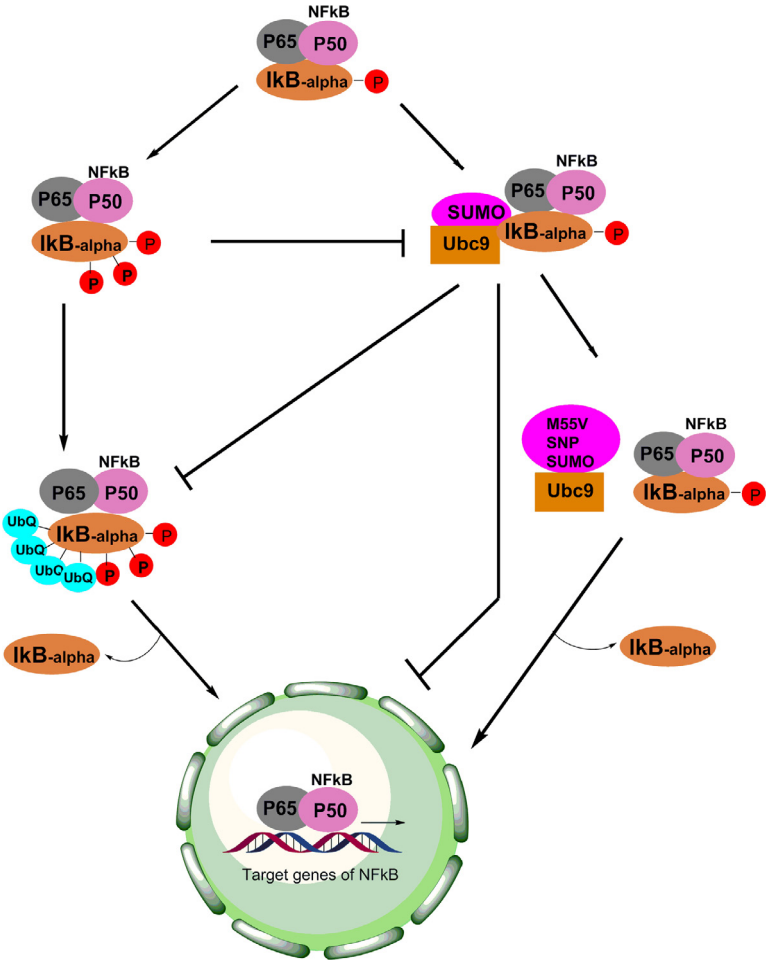

Fig. 2. Regulation of inflammation by SUMO. The NFκB is inhibited by IκB-α in cytoplasm. Upstream activating signal such as binding of TNFα to its receptor may cause phosphorylation of IκB-α, subsequently leads to ubiquitination of this protein and finally degradation of IκB-α. Thus, NFκB migrate to the nucleus and begin to transcription of target genes that mediate inflammation. But SUMO with Ubc9 through binding to IκB-α prevents NFκB from ubiquitination and migration to nucleus and production of inflammatory mediators. Also, some polymorphisms such as M55V in SUMO result in inhibition of binding to IκB-α and induction of inflammation. The SUMO may provide a mechanism which the cells can regulate the quantity of NFκB for activation of transcription.

shock proteins and an increased risk for autoimmune-based type-1 diabetes [9,13,23]. This polymorphism leads to inhibition of IκB-α SUMOylation and, subsequently, NFκB activation [24–26]. A meta-analysis study proved its association with susceptibility to inflammatory and autoimmune diseases, especially in the Asian population. Allelic analysis has shown that A and G alleles have protective and susceptible associations, respectively [27]. Conjugation of SUMO1 to TANK downstream in the IRAK1/TRAF6 signaling pathway of NFκB leads to an abolishment in the inhibitory effect with TLR signaling. Additionally, attachment of SUMO3 to NEMO (IKK-γ) in the IKK complex leads to the formation of a complex with IKK-α and IKK-β. Subsequently, phosphorylation occurs and IKβ-α is degraded as an NFκB inhibitor, which, in turn, leads to NFκB activation [4] (Fig. 2). Also, PIAS1, as a member of the STAT1-activated inhibitor protein family, possesses E3 SUMO ligase activity [28] and is a factor that inhibits transcription for STAT1 and NFκB. Inflammation stimulating factors such as LPS and TNF-α lead to phosphorylation and activation of PIAS1. Additionally, these factors serve to recruit PIAS1 to the promoter region of inflammatory genes to inhibit STAT1-and NFκB-mediated transcription [29], which then functions to inhibit PPAR-γ-mediated inflammatory gene transcription by promoting PPAR-γ SUMOylation [30]. The importance of SUMO proteins stems from their role in the avoidance of overexpressed immune responses that lead to autoimmune disorders. This was proven due to their role in the regulation of T-lymphocyte modulation. Selective deletion of Ubc9 in cells is lethal and followed by early signs of autoimmune-based disease similar to what has been observed with FoxP3 mutation in mice [31]. SUMOylation can also affect the response of RASFs (rheumatoid arthritis synovial fibroblasts) to Fas-induced apoptosis and, with RA, SUMO have been overexpressed in synovial fibroblasts [32]. Moreover, it seems that Ubc9 plays an important role in the stimulation of fibroblastic-like synovial cells and their proliferation and migration in affected joints [33]. Also, different studies have shown that production of autoantibodies against SUMO peptidase 2 and other important antigens of the centrosome is associated with an increased risk of breast cancer [34]. It is noteworthy that drugs which target global SUMOylation are not suitable for the restriction of inflammation, because this modification is necessary for the modulation of various biological processes and there is no clear correlation between the level of global SUMOylation of proteins and inflammation [11,35].

2.2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common chronic inflammatory disorder that has been shown to be a prototype of autoimmune-mediated joint disease and results in progressive destruction of articular structures, particularly cartilage and bone. Subsequently, RA leads to deformation and loss of function in the joints. To date, two types of RA have been identified, which are categorized as RA-positive or RA-negative based on the presence, or absence, of antibodies against citrullinated peptide antigen (ACPA), respectively [36,37]. Synovial inflammation and hyperplasia, infiltration of inflammatory cells, and increased levels of inflammatory cytokines by activated B- or T-cells and other cell populations are the hallmarks and key pathological events in RA. Destructive pro-inflammatory cytokines including IL-1, IL-6, and TNF-α are secreted by macrophages and resident cells. These cytokines stimulate synovial fibroblasts (SFs) and chondrocytes to express matrix-degrading enzymes such as metalloproteinases and

cathepsins [38–41]. RA SFs are the most common and frequent cells at the site of invasion and have been shown to actively participate in the destruction of joints by producing matrix metalloproteinases (MMPs) including MMP-1, 3, 9 and 13. These cells have been characterized as having a unique morphology, aberrant expression of anti-apoptotic molecules, proto-oncogenes, and a lack of tumor suppressor gene expression and interaction with endothelial cells, lymphocytes, and macrophages that ultimately results in tissue-specific responses. Additionally, they have been shown to possess a feature characteristic of tumor cells, because they switch inflammation from acute-to-chronic by 'stable activation' [42–47].

Evidence has shown that fibroblast-like synoviocytes (FLSs) are major participants in the pathogenesis of RA and is found frequently in the synovium of RA patients. The FLSs migrate to the cartilage and bone and play a critical role in pannus formation (a hyper-proliferative intimal lining layer), as well as interact (both *in-vitro* and *in-vivo*) with T-cells important for the progression of RA [48–52]. FLSs obtained from RA patients exhibit an aggressive phenotype and potentially act as starting point for the initiation of inflammation. Also, it has been shown that FLSs isolated from RA patients have the ability to degrade cartilage in a SCID mouse model. Thus, this finding demonstrates that FLSs are not mere 'passive responders' to inflammatory mediators secreted from immune cells, but that they manifest their aggressive features independently from the inflammatory environment in the synovium of RA patients [53]. The etiology of RA is still not completely understood, but a preclinical phase and the absence of ACPA may precede the clinical signs of RA for several years [54].

Environmental factors such as smoking and silica exposure (with associated changes to the human microbiota) may potentially lead to epigenetic and post-translational modifications in a genetically-predisposed individual during the development of RA. This process ultimately results in a decrease in the immune system to maintain 'self-tolerance' and, consequently, leads to asymptomatic synovial membrane inflammation and apparent joint inflammation [55]. Two common epigenetic modifications with significant influence on the function of DNA include DNA methylation and post-translational modification of histones [56,57].

SUMO/SUMOylation, as a post-translational modification, profoundly affects chondrocyte and SF biology, including such physiological processes as the body's response to inflammation, cell survival, matrix metabolism, and hypoxic reactions [58]. For example, Frank et al. showed that SUMO-1 can influence osteoclastogenesis process in mice and owing to a decreased number of functional osteoclasts, SUMO-$1^{-/-}$ mice have a higher bone mass, so this regulatory role of SUMO may be an interesting target for treatment of diseases that are associated with bone loss [59]. When one, or several, of these biological pathways in SFs and chondrocytes is/are impaired, it leads to pathological changes in the joints of RA patients [58].

Reports indicate that although the gene expression of both SUMO-3 and SUMO-4 was barely detected in RA or OA FLSs, SUMO-1 and SUMO-2 expression was elevated in RA FLSs and the SUMO-1 is most prominent. Also, in RA patients SUMO-1 proteins are mostly localized in the synovial sublining cells and subcellular distribution of SUMO-1 in FLSs showed that they are localized mainly in the nuclei. SUMO-1 expression was increased in FLSs from RA patients compared with osteoarthritis (OA) patients and it was up-regulated when treated with TNF-α, IL-1β and IL-17α [60].

2.3. Regulation of apoptosis by SUMO/SUMOylation in RA

Fas-mediated apoptosis is one of the most common cell death pathways in RASFs [61]. Apoptosis is a mechanism that occurs in SFs with Fas to maintain hemostasis. In RASF, cell death is often deregulated, thus, pannus formation occurs, which increases the rate of proliferation of synovial cells and results in exacerbation of the disease. Fas/CD95, TRAIL-R1 and R2, and TNFR1 are some of the death receptors on SFs [58,62]. SUMO-1 or sentrin-1 is an anti-apoptotic molecule and exerts its function by binding to the cytoplasmic domain of the Fas receptor and tumor necrosis factor receptor 1 (TNFR1) [63]. Franz and colleagues observed that the expression of sentrin-1 mRNA was increased in RASF predominantly at sites of invasion and rheumatoid synovial tissue, but not in normal or synovial tissue of patients with osteoarthritis (OA). Since it has been demonstrated that SUMO-1 is overexpressed in RASFs, it would suggest that the function of this protein appears to be protective against Fas-/TNFR1-induced programmed cell death and to also increase the formation of the aggressive phenotype of SF [64]. Additionally, SUMO-1 contributes to RASFs being resistant to Fas-induced apoptosis by SUMOylation and binding to promyelocytic leukemia (PML) protein in a reversible and phosphorylation-dependent manner with subsequent trapping of DAXX (a pro-apoptotic adaptor molecule) in nuclear bodies (NBs). In contrast, SENP1 (SUMO- specific protease), which is down-regulated in RASFs, has a role in reversing the anti-apoptotic effects of SUMO-1 by deSUMOylation of PML, which releases DAXX from PML NBs and, thus, promotes receptor-mediated cell death [32].

2.4. Regulation of cartilage-degrading enzymes by SUMO/SUMOylation in RA

MMPs play a key role in inflammation and degeneration of cartilage [65]. MMP-1 is one the most important enzymes that participates in cartilage and joint destruction by cleaving type-II collagen. The activated phenotype of RASFs is characterized by excessive production of MMP-1, increased expression of SUMO-1 protein, and decreased levels of SENP1. In fact, one study has shown that the balance between histone acetyl transferase and histone deacetylase (HAT/HDAC) activity is changed to histone acetylation in RASFs. Histone deacetylase 4 (HDAC4) is a SUMO-1 substrate, which is modified with this protein and results the in acetylation of histone 4 and subsequently initiates the transcription of MMP-1 promoter. SENP1 acts oppositely to SUMO-1 and leads to the accumulation of HDAC4 on the MMP-1 promoter, decreased H4 acetylation, and downregulation of MMP-1 mRNA and protein levels. Consequently, this biochemical cascade of events significantly alleviates the aggressive properties of RASFs. Indeed, in RASF, the promoter of MMP-1 is hyper-acetylated in the distal region when compared to OASF [66].

MMP-3 is another disease-specific matrix metalloproteinase, which has been shown to be regulated by SUMO-2/3. In one study, Frank and colleagues measured the expression of MMP-3 and MMP-1 in synovial fibroblasts of RA and OA patients by MMP ELISAs. They found that knockout of SUMO-2/3 by specific siRNA leads to a further increase in TNFα- and IL-1β-induced MMP-3. However, there was no effect on MMP-1 expression. These data suggest that SUMO-2/3 is involved in the regulation of MMP-3 in RASF [67].

Regulation of proliferation, invasiveness, and migration by SUMO/SUMOylation in RA.

As mentioned above, FLSs have a crucial role in the development of RA after their migration to bone and cartilage. Cell migration is a complex process and controlled by several pathways [68]. Mammalian protein inhibitor of activated STAT (PIAS), including PIAS1, PIAS2, PIAS3, and PIAS4, have a key role in proliferation, migration, invasion, and apoptosis. PIAS proteins contain four conserved motifs and domains consisting of a SAP region for binding to chromatin, PINIT motif for localization, and RING for E3-SUMO ligation (a SUMO-binding motif) [69–71]. PIAS3, by SUMOylation of Rac1, has been reported to control cell migration [72]. To illustrate the effect of the PIAS family on FLS motility, knockdown of PIAS3 by short hairpin RNA (shRNA) was investigated. Results showed that PIAS3 knockdown significantly suppressed cell migration and the invasive behavior of RA FLSs. Additionally, secretion of MMP-3, MMP-9, and MMP-13, as well as activation of the cell-motility regulator Rac1, p-21-activated kinase 1 (PAK1), and c-Jun N-terminal kinase (JNK) was decreased by PIAS3

Table 1
Characteristics of studies on SUMO and SUMOylation effects on rheumatoid arthritis.

	SUMO finding/pattern	Functional consequences of SUMOylation	Species	Results	Ref.
Li et al. (2014)	Overexpression of SUMO1 and Ubc9 in SFs	Promotes proliferation and migration of FLSs	CIA model in DBA/1 mice and FLSs from RA patients	Treatment with siRNA against Ubc9; Reduced the arthritis score and joint destruction, decreased anti-collagen (CII) antibodies, VEGF-A, MMP-3, and MMP-9 in CIA mice. Inhibited the secretion of VEGF-A, MMP-3, and MMP-9 and significantly attenuated proliferation and migration of TNF-α-stimulated human RA-FLS.	[33]
Franz et al. (2000)	SUMO1	Resistance of RASFs to Fas-induced apoptosis	RASFs	Increase of SUMO1 mRNA expression in RASFs compare to OASFs and normal fibroblasts	[64]
Meinecke et al. (2007)	SUMO1	Trapping of the pro-apoptotic adaptor molecule DAXX in nuclear bodies (NBs) and resulting in resistance of RASFs against Fas-induced cell death	RASFs	Overexpression of SENP1; sensitizes RASFs to Fas-mediated cell death by releasing the transcriptional repressor DAXX from PML NBs	[32]
Maciejewska-Rodrigues et al. (2010)	High levels of SUMO1 paralleled by decreased levels of SENP1 in RASFs	Aggressive phenotype of RASF, increase level of MMP-1 and acetylation of histone H4	RASFs	Overexpression of SENP1 leads to an accumulation of HDAC4 on the MMP-1 promoter and decrease of MMP-1 expression, global level of H4 acetylation and invasiveness of RASFs	[66]
Frank et al. (2010)	SUMO2/3	Resistance of RASFs to Fas-induced apoptosis and regulation of TNFα- and IL-1β-induced MMP-3 production	SFs of hTNFtg mice	SUMO2/3 have specific feature in stable activation of RASFs and overexpressed in hTNFtg mice compare to wild-type	[67]
Duarte et al. (2016)	Overexpression of PIAS3, a protein with E3-SUMO ligation and SUMO-binding motifs	Not mentioned	FLSs from RA patients	Suppression of PIAS3, reduced FLS migration, invasion and activation capacity *in vitro*, with potential implications for FLS-mediated joint destruction	[79]
Orozco et al. (2006)	SUMO4	Not mentioned	Spanish RA patients	No significant association was detected between SUMO4 polymorphisms with RA	[78]
Fakhfakh et al. (2011)	SUMO4	Not mentioned	Tunisian RA patients	Protective effect of +163 G allele in Tunisian RA patients	[77]
Frank et al. (2017)	SUMO1	Influences osteoclastogenesis process	Mice	SUMO-1$^{-/-}$ mice have a higher bone mass owing to a decreased number of functional osteoclasts	[59]
Lao et al. (2019)	SUMO1	Role in aggressive behavior of RA FLSs	RA patients	Suppression of migration, invasion, MMP-1 and MMP-3 expressions as well as lamellipodia formation in RA FLSs due to the SUMO1 knockout by siRNA	[60]

Abbreviation: SUMO, Small Ubiquitin Modifier; **RA**, Rheumatoid Arthritis; **Ubc9**, SUMO-conjugating enzyme; **SF**, Synovial Fibroblast; **FLS**, Fibroblast-like synoviocytes; **CIA**, Collagen-induced Arthritis; **VEGF-A**, Vascular Endothelial Growth Factor-alpha; **MMP**, Matrix Metalloproteinase; **TNF-α**, Tumor Necrosis Factor-α; **OASF**, Osteoarthritis synovial fibroblasts; **HDAC4**, Histone deacetylase 4; **PIAS3**, Protein Inhibitor of Activated STAT 3.

knockdown [73]. Similar results reported by Lao et al. showed that when SUMO-1 knockdown was carried out by small interfering RNA (siRNA), migration and invasion as well as MMP-1 and MMP-3 expressions were suppressed. Also, the activity of Rac-1, as a critical protein of Rho family that control cell motility, was reduced [60]. Rac-1 is a central regulator of cell motility. Although activation of Rac1 promotes the organization of actin cytoskeleton at the leading edge, particularly formation of lamellipodia [74,75], SUMO-1 knockdown inhibited lamellipodium formation in RA SLFs that reduced aggressive behavior of them [60].

Another study revealed that the expression of SUMO-1 and SUMO-conjugating enzyme, Ubc9, was increased in an experimental collagen-induced arthritis (CIA) model. Using siRNA against Ubc9 in the CIA model resulted in a significant reduction in the arthritis score, histological damage, anti-collagen (CII) antibody, vascular endothelial growth factor A (VEGF-A), MMP-3, and MMP-9. Moreover, in-vitro studies have shown that migration and proliferation of human RA FLSs, as well as the production of VEGF-A, MMP-3, and MMP-9, decreased after UBC9 silencing. These findings suggest that inhibition of Ubc9 activity may be a novel therapeutic strategy for the treatment of RA by attenuating FLS proliferation, migration, and invasion [33].

2.5. Association of SUMO-4 polymorphism with susceptibility to RA

SUMO-4 participates in the NFkB signaling pathway, which regulates the production of pro-inflammatory mediators in the immune system [10,76]. Assessment of SUMO4 (+163A/G) single-nucleotide-polymorphism (SNP) in a Tunisian population revealed that the SUMO4 +163 G allele occurs more frequently in controls than it does in RA patients and that there is a protective effect of allele +163 G in RA patients [77]. In another different study in a Spanish population, it was uncovered that there was no significant difference between RA patients and controls with regard to SUMO-4 polymorphism and susceptibility to RA [78].

3. Conclusions

RA is a chronic inflammatory disease and our current knowledge on its etiopathology suggests that the development of RA is a multistep process. Increased levels of proinflammatory cytokines lead to the production of cartilage-degrading enzymes and finally culminates in the destruction of joints. Several studies in this field have shown that epigenetic modifications contribute to the invasion and activated phenotype of RASFs. However, more information needs to clarify which modifications trigger the disease or which modifications occur during the disease chronic conditions. In recent years, increasing amount of *in vivo* and *in vitro* studies strongly support this hypothesis that epigenetic and post-translational modifications, especially SUMOylation, have a critical role in the development of RA (Table 1). SUMOylation, either directly or indirectly, affects the genes involved in inflammation or tissue destruction that are important players in joint hemostasis. Dynamic SUMOylation regulates inflammation, apoptosis, survival, migration and invasiveness in cell populations of joint. It is worth noting that these biological processes are closely interconnected. Therefore, deregulation of SUMO modifications potentially results in the pathogenesis and development of arthritis. By the evolution of research tools for SUMOylation studies and continuous efforts in this area, one can define the role of SUMOylation in joint hemostasis and arthritis. Although treatment of RA has progressed in recent years, current therapies are limited in providing the patients with remission and the symptoms will flare up after discontinuous of immunosuppressive drugs. Also, many of the patients do not respond to available therapeutic agents which reflect permanent deregulation of involved cells. The available data provides a new insight into complex pathogenesis of rheumatic diseases and may enable the researchers to develop novel therapeutic strategies and molecular-based targeted therapies. The pivotal role of SUMO in immune system modulation and modification of protein substrate and biological pathways by SUMOylation suggest a new therapeutic landscape for the development of therapies against arthritis. Moreover, continuing efforts in this field might lead to the development of epigenetic screening panels that can potentially be used for diagnostic and prognostic purposes. Thus, in the future, experiments on SUMO modifications in joint biology will provide potential targets for the design of novel drugs.

Conflicts of interest

None.

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