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REVIEW

Focus on the Multimodal Role of Autophagy in Rheumatoid Arthritis

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Abstract— Autophagy exerts its dual role in eukaryotic cells and exerts its cytoprotective action through degradation mechanism and by regulating catabolic processes which results in elimination of pathogens. Under suitable conditions, autophagy is associated with recycling of cytoplasmic components which causes regeneration of energy whereas deregulated autophagy exerts its implicated role in development and pathogenesis of auto-immune diseases such as rheumatoid arthritis. The immune, innate, and adaptive responses are regulated through the development, proliferation, and growth of lymphocytes. Such innate and adaptive responses can act as mediator of arthritis; along with this, stimulation of osteoclast-mediated bone resorption takes place *via* transferring citrullinated peptides towards MHC (major histocompatibility complex) compartments, thereby resulting in degradation of bone. Processes such as apoptosis resistance are also regulated through autophagy. In this review, the current knowledge based on role of autophagy in pathogenesis of rheumatoid arthritis is summarized along with proteins associated.

KEY WORDS: auto-immune; autophagy; rheumatoid arthritis; immune response.

INTRODUCTION

Autophagy can be defined as a degradation pathway which can be characterized *via* isolating the specific cytoplasmic material in a double membrane vesicle termed as autophagic vacuole (autophagosome), followed *via* the fusion of autophagic vesicle with that of lysosome which ensures destruction of organelles as well as misfolded proteins, further carried inside vesicles [1]. Autophagy can be defined as a physiological process which is required for the degradation of proteins and is restricted towards tissue. It can be considered as a physiological process which is involved in turning over of basal organelles and is required for removing the protein aggregates [2]. The process of autophagy is considered as cellular housekeeping pathway, pro-survival mechanism which exerts its major action of removing or eliminating damaged organelles and aggregates of proteins [3, 4]. Along with the removal of aggregated proteins, it serves and provides energy that is employed for synthesizing macromolecules as in case of starvation and during excessive oxidative stress. Thus, it can lead to recycling of intracellular

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components which leads to ATP formation and helps in the maintenance of essential and normal cell functions [5, 6]. Under normal conditions, it maintains homeostasis as it prevents premature aging by means of inhibiting the accumulation of protein aggregates, acting as tumor suppressive [7, 8]. The autophagy can be categorized into macro-autophagy and chaperone-mediated autophagy as well as micro-autophagy. Along with the cytoprotective effect, process of autophagy exerts its contributable actions *via* cell death of numerous cells [9, 10]. The process of dysregulated autophagy can be responsible for diseases such as auto-immune diseases, cancer, cardiovascular disease, and neuro-degeneration. Studies have shown that autophagy mainly alters and put forth its role in the pathogenesis of autoi-mmune disorders including rheumatoid arthritis which is discussed in this review. Rheumatoid arthritis can be defined as systemic auto-immune disorder, chronic in nature, and is responsible for the destruction of bones and articular cartilages, thereby altering the quality of life and thus leads to disability [10]. It is a chronic auto-immune disorder which comprises of progressive destruction and is marked through chronic inflammation in joints, bones, and cartilages which are characterized with severe pain. Various evidences show that attenuated levels of autophagy can be responsible for pathogenesis of rheumatoid arthritis and are described in this review [11].

GENERAL CONSIDERATIONS OF AUTOPHAGY AND ITS BIOGENESIS: DYSREGULATED AUTOPHAGY

Autophagy is an energy-producing/catabolic process which is linked/associated with movement and targeted delivery of protein aggregates as well as intracellular organelles towards lysosome so that its degradation takes place [12]. Along with degradation of protein aggregates, autophagy can also lead to degradation of pathogenic microorganism (comprising of bacteria and protozoa as well as viruses) in eukaryotic cells [13]. The process of autophagy is responsible for maintaining cellular homeostasis. The screening processes lead to the discovery of genes which are accountable for process of autophagy and include genetic screening carried out in yeast which comprises of 37 autophagy-associated genes (Atg) [14]. The activation of autophagy machinery in mammals is carried out *via* mammalian target of rapamycin complex 1 (mTORC1) and thus, it acts as sensor. The up-streaming of signals is carried out from enzymes such as phosphoinositide-3-kinase (PI3K) which stimulates the process of autophagy. Triggering of autophagy can also be due to starving conditions which leads to dissociation of mTORC1 [15]. The various factors responsible for suppression of autophagy comprises of amino acids along with numerous growth factors. Amino acid is responsible for the inhibition of mTORC1 which in turn suppresses autophagy *via* formation of ULK1 (unc-51-like kinase 1) complex [16, 17]. The process of autophagy is categorized and distinguished on the basis of cell functioning as well as mode of transportation towards lysosomes and is differentiated into macro-autophagy and chaperone-mediated autophagy as well as micro-autophagy [18]. Biogenesis is mediated *via* appearance and formation of flat membranous sheet inside cytoplasm which is known as isolation membrane, subsequently followed *via* its expansion and elongation which leads to formation of double membrane bound spherical structure termed as autophagosome, and its further fusion with lysosome to form auto-lysosome [19].

The autophagosomes are derived using perautophagosomal structure which is double membrane and termed as phagophore, originating *via* endoplasmic reticulum, golgi complex, and from plasma membrane. The nucleation of phagophore is carried out through activity of PI3K-III complex (phosphatidylinositol-3-kinase complex belonging to class III) which comprises of p150 (serves as an analogue of yeast Vps15; acts as serine/threonine protein kinase), Beclin-1 (mammalian analogue of Atg6), and Atg-14 like proteins [20, 21]. Beclin-1 is associated with triggered autophagic activity and this activity is influenced *via* its binding with antiapoptotic protein Bcl-2 (encoded by BCL2 gene) which inhibits the process of autophagy. Beclin-1-regulated autophagy protein 1 or AMBRA1 (autophagy and beclin 1 regulator 1) acts as positive regulator of autophagy as it induces Beclin-1-associated autophagy and thus transmits the protein *via* action of class III PI3K complexes [22, 23]. The further steps of expansion as well as closure of autophagy are carried out under influence of ubiquitin-conjugates system such as microtubule-associated protein-1 light chase kinase-3 (LC3)-phosphatidylethanolamine as well as Atg12-Atg5-Atg16L. The process of expansion is carried out *via* means of binding to Atg16 (acts as autophagic protein) to form a heterotrimer complex; this organizes itself at outer side of autophagasomal membrane which leads to growth of membrane and further promotes binding of light chain kinase III with phosphatidyl ethanolamine (PE). The cleavage of LC3 is carried out *via* Atg4 (acts as cysteine protease) which produces LC3-I, it gets activated *via* Atg7 and further under the influence of Atg3, and conjugation of

LC3-I occurs with PE leading to the conversion to LC3-II. LC3-II acts as a marker for testing autophagic activity as it serves like protein which is in close association with maturing autophagosome. The matured and formed autophagosome fuses with that of lysosome in order to form autophagolysosome which comprises of lysosomal hydrolase and is responsible for hydrolysis of vesicular content and is depicted well through Fig. 1. The products such as amino acids as well as lipids are exported to autophagosomal compartments for degradation along with the process of development of new products [24, 25].

Dysregulated autophagy can serve its major role in pathogenesis of numerous diseases that are linked with various pathological conditions. The cells can undergo numerous changes such as DNA mutation and protein aggregation accumulation as well as damages [26, 27]. The facts and data suggest that level of autophagy decreases with that of age; along with this, Atg proteins and its over expression can be responsible for altering and attenuating life span of human beings. Autophagy serves the degradation of misfolded proteins and this process is carried out in neurons and thus, the failure of autophagy can be responsible for neurodegenerative disease such as Parkinson disease (mainly due to accumulation of α-synuclein) [28, 29]. The studies suggest that inhibiting autophagy leads to reduced levels of 3-methyladenine which cause an increase in level of α-synuclein [29]. A controversial link is there between autophagy and cancer as process of autophagy leads to removal of mitochondria which comprises of reactive oxygen species (ROS) and thus exerts cytoprotective action [30, 31]. Studies demonstrate that deletion in an autophagic gene Beclin-1 is responsible for development of malignancy in mouse models [32]. Despite the above studies, it has been reported that autophagy can serve its tumor-supporting function, allowing the tumor cells to respond from external stress stimuli conditions comprising of hypoxia as well as nutrient deficiency conditions. From various studies, the role of autophagy is observed in rheumatoid arthritis as well as systemic lupus erythematosus [33, 34].

ROLE OF CYTOKINES IN AUTOPHAGY

Autophagy plays its major role in adaptive and innate immunity *via* elimination of bacteria present intracellularly. They are required for presenting and processing of

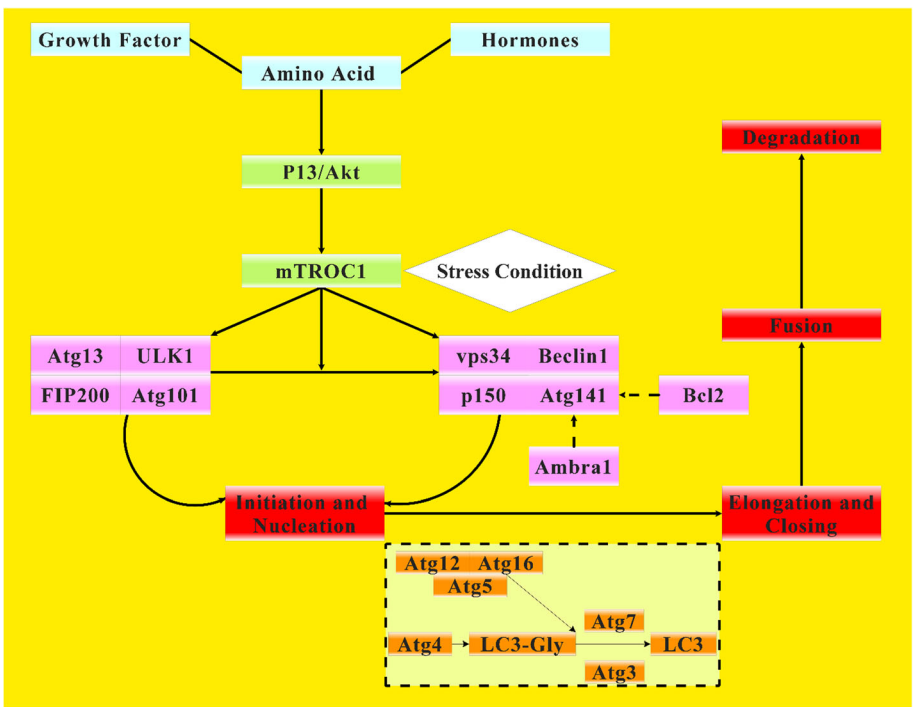

Fig. 1. Normal process of autophagy.

endogenous antigens *via* MHC class I and II molecules, thereby serving its immune response [35]. Cytokines such as NOD-like receptor ligands (NLR) perform as potent inducers of autophagy. Various studies are elucidated in order to ensure the role of cytokines in regulating autophagy *via* checking response of macrophages to *Mycobacterium tuberculosis* [36]. Production of IL-12, IFN-α, and TNF-α along with predominant and directive effect of Th-1-based response is essential for protection of host from responses produced by M. tuberculosis [37]. Human macrophages, murine macrophage, and IFN-c (interferon-c) activation are responsible for induction of autophagy in Irgm1 (immunity-related GTPase family M protein1)-dependent manner. Similarly, pre-treatment provided with IFN-c in macrophages that are infected with mycobacteria results in attenuated killing of bacillus along with engulfment of mycobacterium-comprising phagosomes *via* autophagosomes which further fuses with lysosomes [38]. The macrophages that are initially infected with H36Ra strains of M. tuberculosis does not stimulate autophagy in murine macrophages and can be induced only if treated with IFN-c. The silencing of Beclin-1 carried out in murine macrophages with siRNA has abrogating effect on IFN-c and blocks maturation of BCG-containing phagosomes, ensuring that the process is completely autophagy dependent. TNF blockers can be responsible for abrogating and blocking IFN-c-induced phagosomal maturation in M. tuberculosis-infected human macrophages [39, 40]. This suggests that IFN-c-induced phagosomal maturation is dependent on autophagy as well as TNF-α. It can be demonstrated from numerous studies that TNF-α possesses its stimulating effect on autophagy carried out in cells (human T lymphoblastic cells, skeletal muscle cells, human vascular smooth cells, murine, and human macrophages). The autophagic elimination of *Toxoplasma gondii* is aided in murine macrophages when CD40 ligation is coupled with TNF-α signaling. TNF-α levels inside rat intestinal epithelial cells are responsible for attenuating mitochondrial dysfunctioning, amplified mitochondrial ROS along with reduced level of mitochondrial membrane potential as well as oxygen consumption which leads to attenuated and amplified autophagy of mitochondria referred to as mitophagy [40–43]. Archetypal Th1 cytokines (TNF-α, IFN-c) are responsible for induction of autophagy whereas the classical Th2 cytokines (IL-3 and IL-4) are responsible for inhibition of autophagy [44]. IL-4 as well as IL-13 in human macrophages infected with M. tuberculosis is responsible for abolishing IFN-c-induced autophagosomal action and the process of inhibition occurs *via* two major pathways:

1. *Via* inhibiting autophagy that occurs by means of Akt pathway
2. Inhibiting IFN-c-induced phagosomal formation leading to reduced maturation and thus enhanced maturation of bacillus [45, 46].

IL-13 acts as potent inhibitor of autophagy in HT-29 cells (human epithelial cells) which is induced *via* starvation and acts through the activation of Akt pathway. IL-10 can be responsible for inhibiting starvation-induced autophagy in murine macrophages *via* Akt and STAT3 (signal transducer and activator of transcription 3) pathway and can serve its role in context with infection [47, 48]. Along with the mentioned cytokines, other factors comprise of chemokines and citrullinated peptides as well as growth factors that control the process of autophagy. Chemokines such as monocytes chemo-attractant protein-1 (CCL2) and IL-6 mainly influence *via* upregulating autophagy and amplify antiapoptotic proteins in human CD11b + mononuclear cells. CCL2 along with IL-6 allows transportation of CD11b + cells towards CD205+ tumor promoting M2 type phenotype which shows its conflicting role in tumourigenesis. A negative feedback is exerted *via* IL-1b and IL-1a which have a stimulating effect on autophagy inside human macrophages. Transcription of Atg5, Atg12, LC3B, and beclin 1 is attenuated *via* pro-inflammatory cytokines (TWEAK/TNF-like weak inducer of apoptosis) and this can lead to atrophy in C2C12 cell cultures. The autophagy is induced *via* IL-2 inside CD4+ T lymphocytes and there it serves cell protective action [49–52].

The process of autophagy is co-related with process of secretion, processing, and transcription of numerous cytokines. The autophagic pathways are mainly linked with disruptive processes and can lead to increased and attenuated levels of pro-inflammatory cytokines such as interleukins (IL-18, IL-1b, and IL-1a). Autophagy is co-related with production, regulation, and secretion of IL-1b which is dependent on activation of caspase 1 followed by a subsequent formation of inflammasome. This process occurs in mainly two steps:

1. Induction of transcription of pro-IL-1b.
2. Assembly of inflammasome as well as activation of caspase 1 which requires the stimulation through various signals such as uric acid, ATP, and ROS [53, 54].

The autophagy is responsible for the regulation of IL-1b secretion and its inhibition *via* autophagy inhibitors or loss inside macrophages and dendrites *via* downregulation

of Beclin 1, Atg7 can lead to enhanced secretion under the influence of TLR (Toll-like receptor) agonist. Inside macrophages and dendrites, the whole process of secretion is dependent on TIR-domain-containing adaptor inducing interferon-b, mitochondrial DNA, and ROS while inside peripheral blood mononuclear cells, the same is dependent on p38 MAPK signaling (mitogen-activated protein kinases). The level of pro-IL-1b decreases inside the macrophages when rapamycin was administered and macrophages treated with TLR agonist, IL-1b was observed inside the autophagosomes suggesting that autophagy targets the pro-IL-1b for its lysosomal degradation [55–57].

PATHOGENESIS OF RHEUMATOID ARTHRITIS AND ROLE OF AUTOPHAGY IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis is considered as an autoimmune disease, chronic in nature, and is marked with inflammation in joints, bone, and synovial fibroblasts; it is not only restricted to joints but comprises of other organs including lungs, skin, heart, and vascular system. The risk factors associated with development of rheumatoid arthritis comprises of genetic factors as well as environmental factors such as lifestyle and smoking. The cells that are responsible for the process of initiating an auto-immune and chronic response comprises of dendritic cells or DC, activated β cells, and macrophages as well as antigen-presenting cells. The progressive destruction of articular structures follows synovial hyperplasia; bone destruction and the same is carried out *via* auto-antibodies (comprising of antibodies (Abs); anti-cyclic citrullinated peptide (anti-CCP)) as well as pro-inflammatory cytokines and thus acts as markers for the disease. Along with this, inflammatory mediator is released from macrophages, chondrocytes, and osteoclasts as well as T and B cells and this leads to a chronic inflammatory response [58–60]. Various evidences suggest that autophagy has a role in the pathogenesis of rheumatoid arthritis and acts at numerous levels which are depicted in Fig. 2:

1. Role of autophagy in immunological tolerance conditions, citrunillation peptides, and in CD4+ cells.
2. Autophagy and its relation with numerous cells: chondrocytes; pro-inflammatory cytokines [61, 62].

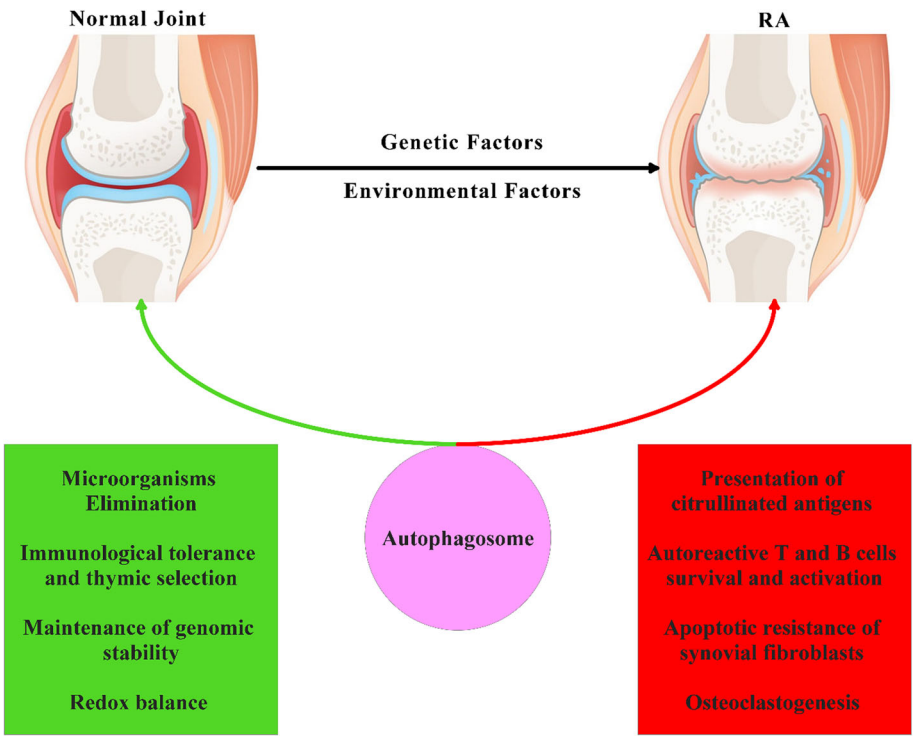

Fig. 2. Role of autophagy in rheumatoid arthritis.

3. Connection between autophagy and synovial fibroblasts [63, 64].
4. Relation between autophagy, joint destruction, and osteoclasts [65, 66].

Role of Autophagy in Immunological Tolerance Conditions

Autophagy has a significant contribution towards production and presentation of numerous cytosolic antigens which are in close association with MHC class II molecules and thus helps in maintenance of acquired immune response and in self-tolerance. The development of T cells takes place inside thymus where the presence of MHC molecules on surface of thymic epithelial cells (TECs) is responsible for ensuring restriction of thymocytes with MHC molecules and thus are specific for foreign antigen. The process of autophagy is involved in maintenance of tolerance mechanism; the level of autophagy is higher in TECs and involved in development of lymphocytes [67–69]. Autophagy deficiency can be a reason of the removal of self-tolerance and thus can lead to the development of diseases such as arthritis. Th1 cells exhibit their predominant role in pathogenesis of rheumatoid arthritis but recently, crucial role of Th17 is observed. Th17 acts as principal source required for production of pro-inflammatory cytokine (IL-17), and this acts synergistically with IL-1 and TNF-α, promoting towards bone destruction. The T cells and B cells are responsible for production of RANKL (receptor activator of nuclear factor kB), when it binds to RANK inside monocytes and macrophages lead to stimulated production of matured osteoclast from precursor cells [70–72]. Autophagy serves its role in osteo-clastogenesis which causes bone erosion and bone tissue degradation and ultimately leads to rheumatoid arthritis. The inhibition of autophagy can be used for preventing above processes in patients with rheumatoid arthritis [73].

Antibodies respond towards citrullinated self-proteins during the state of auto-immune diseases as in arthritis and thus serve their role of diagnostic indicator. Citrullination is defined as the chemical conversion of arginine into citruline *via* influence of peptidyl arginine deiminase (PAD) enzyme. Anti-CCP antibodies act by targeting epitopes of citrullinated auto antigens and serve their role in the development of rheumatoid arthritis. Anti-CCP antibodies that are extracted from patients of rheumatoid arthritis are capable of differentiation of human osteoclast, thereby promoting bone loss and destruction. Studies illustrate that antigen-presenting cells require the process of autophagy in order to present the citrullinated proteins and this process gets inhibited as soon as the process of autophagy is inhibited. The expression of PAD is highly expressed inside autophagy compartments and related stimulus such as nutrition-deprived cells and thus, it serves as biochemical marker of autophagy. Studies have also demonstrated that the concentration of citrullinated proteins get enhanced after its treatment with rapamycin (acting as autophagy inducer) in patients with rheumatoid arthritis [74, 75]. Chondrocytes are termed as critical attributes which enhances chronic inflammatory stimulus in the patients with rheumatoid arthritis and exhibit property of extensive clonal expansion. These cells undergo activation and produce cytokines in larger amounts. The activated cells enhance catabolism and induce autophagy in order to regulate the process of homeostatis. From studies, it is shown that in T cells of patients with rheumatoid arthritis, the autophagy is inhibited mainly due to action of 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 3 (PFKFB3) which acts as glycolytic enzyme. Normally, it is responsible for the process of upregulating autophagy but in rheumatoid arthritis as no T cells are upregulated, therefore no autophagy takes place [76–78].

Autophagy and Its Relation with Numerous Cells: Pro-inflammatory Cytokines

IL-1 along with TNF-α is responsible for chronic inflammation that takes place *via* destruction of bone and cartilage, acting as inflammatory cytokines. IL-1b belongs to family of IL-1 and injection of the same in knee joints of rabbit can induce rheumatoid arthritis [79]. Autophagy is involved in production of pro-inflammatory cytokines in ATG16L1-deficient mice macrophages, as stimulation with TLR4 (Toll-like receptors) ligands can lead to amplified and attenuated levels of TNF-α [80, 81]. Inhibition of autophagy in human macrophages enhances production and secretion of IL-1b. Another interleukin responsible for inflammation is IL-23 which acts *via* promoting enhanced secretion of IL-17 from Th17 cells. IL-23 secretion is based on inhibition of autophagy-induced secretion and depends on factors such as IL-1 and nuclear factor kappa B signaling. Autophagosome formation takes place in macrophages due to attenuated levels of IL-1b, IL-1a, and IL-23 [82]. As discussed above, autophagy is responsible for production of pro-inflammatory cytokines such as TNF-α, which expresses itself inside rheumatoid arthritis synovium and further induces rheumatoid arthritis synovial fibroblasts allowing the proliferation and production of proteinases and pro-inflammatory cytokines as well as

adhesion molecules. This subsequently stimulates the process of osteo-clastogenesis. Inhibition of process of autophagy can abolish the secretion and production of TNF-α and thus from above, it can be indicated that autophagy can serve its role in pathogenesis of autoimmune disease such as rheumatoid arthritis and employs treatment with IL-1 receptor antagonist such as anakinra, TNF-α inhibitors, glucocorticoids, and steroidal therapy which downregulates production of pro-inflammatory cytokines [66, 80–83]. Numerous cytokines and cell surface receptors are responsible for regulating autophagy and acts *via* activating NF-Kb, TNF-α, IFNγ, CCL2, CD40, and DC46. The various inhibitors of autophagy are insulin like growth factor-1, CLCF1 (cardiotrophin like cytokine factor 1), IL-4, and IL-13. IFNγ acts as Th1 cytokine and helps in inducing autophagy whereas IL-4 belonging to Th2 cytokines can lead to the inhibition of autophagy and it can be elucidated that autophagy is an effector of both Th1/Th2 polarization. It is also observed that pro-inflammatory cytokines can be responsible for disrupting the balance of autophagy. Along with this, it is also suggested that autophagy is responsible for the secretion, production, and proliferation of numerous pro-inflammatory cytokines including IL-18, TNF, and adipokinocytes [82, 84].

Chondrocytes mainly participate in cartilage and matrix destruction in patients of arthritis *via* release of various proteinases as well as pro-inflammatory cytokines. From various studies, a relation between chondrocytes and autophagy is observed and demonstration reveals that autophagy gets attenuated during rheumatoid arthritis and OA in response to various conditions such as catabolic stress and nutritional stress which causes enhanced degradation of cartilage. Inhibition of autophagy can lead to production of reactive oxygen species [85–87]. The conflicting results were obtained from studies where downregulation of autophagy was related with enhanced signaling of mTOR (mammalian target of rapamycin) which causes cartilage destruction and a conclusion can be withdrawn that varied result may be due to degenerative stages of arthritis. The earlier stages are implicated with less degenerative chondrocytes leading to enhanced autophagy and with the progressive stages leads to reduced autophagy [88, 89].

Autophagy and Rheumatoid Arthritis Synovial Fibroblasts

Synovial cells are mainly classified into fibroblast and macrophages like synoviocytes and serves as dominating cells that are densely found in joints of patients with rheumatoid arthritis. The pro-inflammatory mediators are produced through macrophages like synoviocytes whereas destruction of bone and cartilage is carried out *via* matrix degrading enzymes and inflammatory mediators are produced from fibroblast like synoviocytes. Joint destruction is observed experimentally when implantation of synovial fibroblast is carried out along with cartilage (obtained from healthy mice) and lead to a condition of combined immunodeficiency and is thus considered as a hallmark which is associated with rheumatoid arthritis and joint destruction. The development, proliferation, and expansion of rheumatoid arthritis associated synovial fibroblast (RASFs) are carried out *via* stimulation of cytokines and TNF-α [90, 91]. Synovial fibroblasts are also responsible for production of matrix degrading enzymes and chemokines as well as inflammatory cytokines which are inflammatory in nature and are related with joint destruction and serve its role in pathogenesis of rheumatoid arthritis. The relationship between autophagy and synovial fibroblast can be demonstrated from numerous studies and it can be concluded that upregulated level of autophagy is observed in arthritis patients which leads to the activation, development, and proliferation of synovial fibroblast. The process of apoptosis is reduced, downregulated, and thus has major contribution towards inflammation and chronic destruction [92]. Rheumatoid arthritis synovial fibroblasts also lead to increased resistance against apoptosis. The increased expression of Beclin1 and LC3 is attenuated inside synovial fibroblasts and is co-related with decreased levels of C/EBP homologous protein (CHOP) and enhancer building proteins (CCAAT-enhancer binding proteins). CHOP is pro-apoptotic transcription factor which is employed as an anti-oxidant and protects cell from oxidative stress. The influence of autophagy and ubiquitin proteasomal pathway on RASFs was investigated and drawn with a conclusion that higher levels of these activities are active inside synovial fibroblast. No synergistic effect is observed when inhibition of both autophagy and ubiquitin proteasome pathway is carried out, suggesting that compensatory mechanism is proposed by RASFs for degradation of proteins. Dual role of autophagy-mediated cell death is observed; under normal conditions, they promote cytoprotective action whereas induced level causes cell death [92–94].

CONCLUSION AND FUTURE PROSPECTIVE

The various feedback mechanisms have evaluated the role between autophagy, its protein, and inflammation. Various studies have shown the role of autophagy in rheumatoid arthritis. Hyperactive autophagy is consistent with

Table 1. Drugs Used in Autophagy induced Rheumatoid Arthritis

Drugs	Role in treatment of rheumatoid arthritis	References
Rapamycin	Acts as autophagy activator and leads to decreased in progression of disease.	[95]
Chlorquine and hydroxychlorquine	Inhibits the presentation of antigen towards T cells in patients of arthritis. Also inhibits differentiation of precursor osteoclasts into matured and thus inhibits the process of osteo-clastogenesis.	[96]
TNF-α inhibitors	Inhibits the activity of TNF-α in patient of rheumatoid arthritis.	[97, 98]
Etanercept	Acts as TNF-α b	
Infliximab	Possesses high affinity for TNF-α locking agent	
Adalimumab		
3-MA	Inhibits autophagy at an earlier stage and further inhibits formation of autophagosome.	[99]
Methotrexate	Protects synovial cell from apoptosis; the proposed therapy is methotrexate + autophagy inhibitor	[100]
Glucocorticoids	Exerts its immunosuppressive and anti-inflammatory action	[101]
Everolimus	Acts *via* inhibiting mTOR signaling	[102]
Temsirolimus		
Wortmannin	Possesses anti-inflammatory activities; acts *via* inhibiting autophagy but leads to irreversible binding	[103]
AZD8055	Inhibits mTOR signaling and is given in combination with SAR405 acting as autophagy inhibitor.	[104]

RASF hyperplasia as well as apoptosis resistance which enhances the release of inflammatory cytokines leading to rheumatoid arthritis. Enhanced activation of autophagy inside the inflammatory cells is responsible for the development, growth, and proliferation of numerous cells such as IL-17 and IL-1b inside synoviocytes which exert its role in processes such as osteo-clastogenesis and citrullination. Autophagy also exerts its cytoprotective action and thus, its suppression can lead to development of malignancy and premature aging as well as infections. The chronic inflammation and hyperplasia associated with enhanced autophagy causes joint destruction which results in increased autophagy proteins inside the osteoclasts and further osteoclast-associated bone resorption takes place, leading to articular destruction of bone as well as cartilages. The transportation of citrullinated proteins to the CD4+ cells is responsible for triggering an immune response and thus serves as molecular aspect in pathogenesis of rheumatoid arthritis which needs to be treated.

Biological agents have been introduced and are implied clinically for treatment of rheumatoid arthritis. Drugs that can potentially treat arthritis are chlorquine, DMARDs (disease-modifying anti-rheumatic drugs), and glucocorticosteroids, and autophagy inhibitors act *via* interfering with attenuated level of autophagy and are tabulated in Table 1. Improved therapy and customized medicine can be provided with continuous research and identifying and exploring the molecular aspects of the disease [105]. The future prospective in the field of autophagy-induced rheumatoid arthritis can be treated using 3-MA (3-methyladenine) which mainly acts as suppressor of autophagy and can abolish the formation of autophagosome at an earlier stage. This can further lead to reduced presentation of citrullinated protein along with activation of apoptosis pathway. 3-MA exerts its atheroprotective role and leads to downregulation of inflammation. Another aspect employed in treatment of rheumatoid arthritis can take place *via* inhibition of mTOR signaling and inhibitors such as everolimus. Combination of everolimus with methotrexate can be implied for enhanced action.

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