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The role of autophagy in systemic lupus Erythematosus

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Abstract

The aetiology of Systemic Lupus Erythematosus (SLE), a chronic autoimmune disease that can affect every organ and tissue in the body, is unknown. However, complex interactions among genetic, environmental (such as infectious agents, ultraviolet light, drugs), and hormonal factors are likely to play a role. Human leukocyte antigen regulation, T- and B-cell signalling, Toll-like receptor/interferon signalling, nuclear factor-kB signalling, and immune complex clearance are a few immune system-related pathways that are primarily dysregulated in SLE pathogenesis.

A lysosome-mediated catabolic process called autophagy allows cells to recycle nutrients and break down undesirable cytoplasmic components. Along with being involved in both innate and adaptive immune responses, autophagy is crucial for contacts with microorganisms, processing of antigens for MHC presentation, and the growth, survival, and proliferation of lymphocytes. Macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy are the three primary kinds of autophagy. The most often researched of them, known as autophagy in general, is macroautophagy.

More than 100 loci related with SLE susceptibility have been found by hypothesis-free genome-wide association studies (GWAS). Five autophagy-related genes were found to be linked to SLE susceptibility using this method. These include ATG5, CLEC16A (C-type lectin domain containing 16A), DRAM1, CDKN1B (cyclin dependent kinase inhibitor 1B), and ATG16L2. These findings resoundingly confirmed the idea that autophagy is crucial to the genetic aetiology of SLE. Combining with additional follow-up investigations, it was shown that a number of variations in other autophagy-related genes, including ATG7, IRGM, LRRK2, MAP1LC3B, MTMR3, and APOL1, were linked to SLE susceptibility.

Key words: Autophagy,systemic lupus erythematosus. therapy targets

Introduction:

Chronic systemic autoimmune illness: systemic lupus erythematosus (SLE) is characterized by a propensity for flare-ups and varies in severity and course. Both innate and adaptive immune responses are actively involved in SLE [(1)] Numerous immunologic changes brought on by gene-environment interactions eventually lead to persistent immune reactions to autologous nucleic acids. Autoantibodies or immune-complex depositions induce tissue damage in the kidneys, heart, arteries, central nervous system, skin, lungs, muscles, and joints,

which significantly increases morbidity and death [1].

Epidemiology and causes:

Nearly 10 women suffer with SLE for every guy who has the illness, a startlingly high female predominance. The prevalence has increased over the past 40 years and ranges from 0.3 to 31.5 cases per 100,000 people annually. This increase is likely attributable to the increased detection of cases in their early stages and with milder presentations; the majority of patients are middle-aged women, and about 50% of cases are mild when they first manifest. However, a portion of individuals may worsen, resulting in an equal split of mild, moderate, and severe cases over time, with one-third in each group [2].

Depending on heritage, the disease's severity may vary, but it tends to be worse in those with African and Latin American ancestry. Health-related life quality is greatly impacted. The severity of the condition and the organ(s) affected are closely connected with the annual direct (healthcare-related) expenses, which are expected to range between US$3000-$12000 [3].

It is well established that environmental factors including UV rays, medicines, and smoking have an impact on the pathophysiology of SLE. While infliximab, adalimumab, and etanercept have been associated with the emergence of anti-DNA antibodies, procainamide and hydralazine, two specialised anti-tumor necrosis factor medicines, have been linked to caused lupus. Among all lupus-related autoantibodies, smoking has been connected to antiphospholipid (aPL) and anti-DNA antibodies [4].

Environmental factors were responsible for 30.3% of SLE susceptibility, and among those who have a first-degree relative with the condition, the relative risks (RRs) for many autoimmune diseases range from 5.87 for primary Sjögren's syndrome (SS) to 5.40 for systemic sclerosis to 2.95 for myasthenia gravis to 2.77 for inflammatory myositis to 2.66 for rheumatoid arthritis (RA) to multiple sclerosis to 2.58 These results can promote family therapy and serve as a starting point for additional research into the connection—or lack thereof—between different autoimmune illnesses. Whole-exome sequencing was used to rule out the familial aggregation of primary SS, SLE, and RA in 31 families with autoimmune rheumatic diseases. Uncommon genetic mutations in the T-cell receptor signalling pathway appear to be the source of this.

Systemic lupus erythematosus (SLE) diagnosis can be difficult and delayed by months or years [6], increasing patient uncertainty, referrals, and healthcare use. Poor prognosis in the form of more frequent flare-ups and organ dysfunction has been associated with delays in diagnosis and therapy beginning [7].

The ability of doctors to diagnose SLE frequently depends on their intelligence, and it is frequently hampered by the presence of "high-yield" characteristics or numerous, less-specific results. As a result of the lack of diagnostic criteria, categorization criteria—which were created to make it easier to include homogeneous illness groups in clinical studies—are frequently utilized as a diagnostic tool [8].

A greater percentage of patients can be classified early thanks to the Systemic Lupus International Collaborating Clinics (SLICC) and European League against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria. The EULAR/ACR 2019 criteria also have the best sensitivity to specificity

ratio. Better categorization hasn't made diagnosis any simpler, particularly in the early stages [9].

Delays in diagnosis and the start of treatment have been linked to a poor prognosis manifested as more frequent flare-ups and organ failure [10]. A difficult and protracted diagnosis of systemic lupus erythematosus (SLE) can increase patient uncertainty, referrals, and usage of healthcare services [11].

Autophagy:

Autophagy is a critical cellular system that eliminates molecules and subcellular components such nucleic acids, proteins, lipids, and organelles via lysosome-mediated degradation in order to promote homeostasis, differentiation, development, and survival. Although there are connections between autophagy and health, it is yet unclear how autophagy, ageing, and illness are related. This article examines a few novel elements of autophagy and ponders their potential relevance to the development and progression of disease [12].

Molecular regulation of autophagy:

A large network of proteins called autophagy-related proteins (ATGs), which includes more than 30 molecular species previously discovered in yeast, controls mammalian autophagy. The fact that so many similar mammalian homologues have been found shows how highly conserved the route is. Nutritional and growth factor-sensitive signalling mechanisms, such as the mTOR (mammalian target of rapaamycin) and AMPK (AMP-activated protein kinase) signalling pathways, tightly control autophagy [13].

Through the suppression of mTOR, a multiprotein complex known as mTORC1, nutrient deprivation triggers autophagy. Unc-51 like kinase-1/2 complex is adversely regulated by mTORC1 in response to stimulation from nutrition or growth stimuli, which inhibits autophagy [14] Adenosine monophosphate (AMP) buildup, a sign of decreased cellular energy charge, triggers autophagy by activeating AMPK, which controls mTORC1 and ULK1/2 [15].

Class III phosphatidylinositol-3-kinase (PI3KCIII), Beclin 1 (Atg6) interacting, and other proteins like ATG14L or UVRAG regulate autophagy (UV radiation resistance associated; Ambra1, Rubicon). Both the Class I PI3K/Akt pathway and members of the anti-apoptotic Bcl-2 family negatively regulate the Beclin 1 complex. It generates phosphatidylinositol-3-phosphate (PI3P), which controls how autophagosomes are formed [16]

Recent research has shown how the Beclin1 complex and ULK1/2 (Unc-51 like autophagy activating kinase) interact. Autophagy can start by phos-phorylating Ambra1 by ULK1, which uncouples the Beclin1 complex from cytoskeletal sequestration by dyneins [17] More specifically, ULK1 phosphorylates Beclin 1 on Ser14, increasing PI3KCIII activity. The extension of the autophagosome is facilitated by two ubiquitin-like conjugation systems, the Atg5-Atg12 conjugation system and the Atg8 conjugation system. Mammals possess the microtubule-associated protein-1 light chain 3B (LC3B), which connects to Atg8 [18].

There are three primary forms of autophagy that have been identified based on the various routes by which intracellular components are carried to lysosomes: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA).

The process of macroautophagy (as shown in fig 1) known as autophagy, involves enclosing cytoplasmic proteins, organelles, or other things in a membrane of isolation called a "phagophore," which then expands and contracts to generate autophagosomes. After combining with lysosomes to generate autolysosomes, local hydrolases degrade the cytoplasmic cargo. Autophagosomes can also fusion with endosomes, multivesicular bodies, and MHC class II-loading compartments [19].

The lysosome, on the other hand, directly absorbs cytosolic components during microautophagy through invagination of the lysosomal membrane. Both macroautophagy and microautophagy are capable of swallowing large structures via both selective and nonselective processes [20].

Targeted proteins undergo CMA when they are translocated across the lysosomal membrane in a complex with chaperone proteins, such as heat shock chaperone70, which are recognised by lysosomalassociated membrane protein (LAMP)2A, causing their unfolding and death [21]. It has been demonstrated that macroautophagy and CMA interact directly with one another. In reality, macroautophagy in cultured cells is inhibited, CMA is activated, and macroautophagy is induced when CMA is blocked [22].

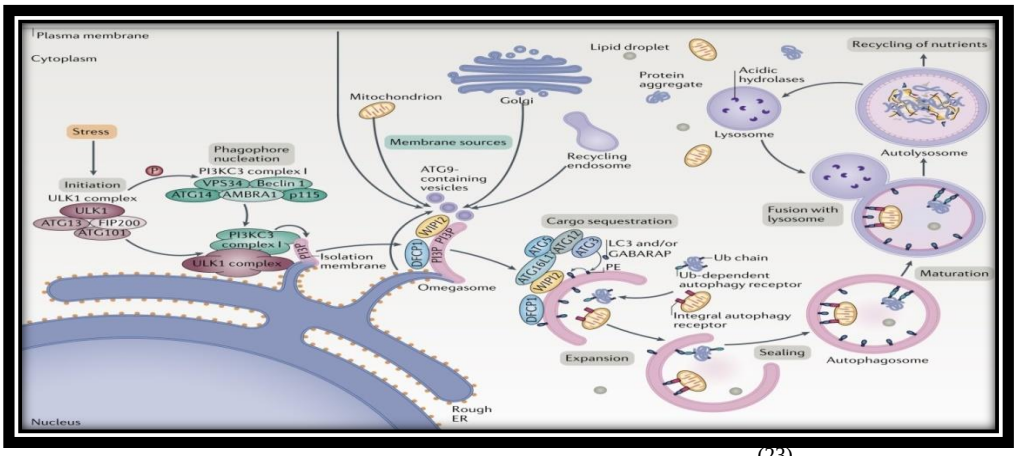

Fig. 1: Overview of the autophagy process. [23]

The therapeutic and pathogenic role of autophagy in autoimmune diseases:

Based on its immune system functions, autophagy may have a destructive or therapeutic role in autoimmune illnesses depending on the pathophysiology of the disease and the key players in disease progression (as shown in fig 2).

Several variations found in other autophagy-related genes, including ATG7, IRGM (immunity related GTPase M), LRRK2 (leucine rich repeat kinase 2), MAP1(microtubule associated protein),LC3B (light chain B3), MTMR3 ((Myotubularin Related Protein 3), and APOL1(Apolipoprotein L1), have been reported to be linked to SLE susceptibility [24]. A member of the Atg12-Atg5-Atg16 complex, which functions in part as an E3 ligase for the conjugation of Atg8/LC3-PE, Atg5 is a protein with ubiquitin folds. ATG5 mutations that are both frequent and unusual have been linked to SLE susceptibility [25].

Approaches to treating SLE are increasingly focusing on autophagy as a therapeutic target. Kanamycin is an FDA-approved immunosuppressive drug for

organ transplantation. It supports the necessity of mTORC1 inhibition for autophagy and explains why it suppresses T cells [26] By lowering autoantibodies, preventing proteinuria, and extending survival in both mice and patients, rapamycin has been found to be helpful in treating lupus in both animals and humans. In a clinical study, rapamycin was used to treat patients with resistant SLE. In comparison to standard therapy, the rapamycin-treated group showed less disease activity and prednisone need. To produce this suppressive effect, the Rab4 (connected to Ras in the Brain), HRES 1, and Rab5A (associated with Ras in the Brain 5A) pathways may also be blocked by decreasing the production of type I IFN by DCs.[27].

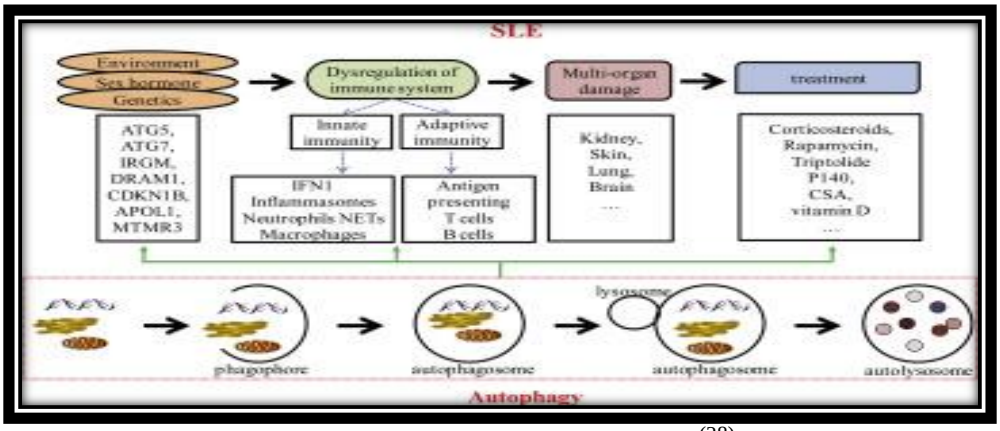

Fig 2: The role of autophagy in SLE [28]

Conclusion:

There is growing evidence that autoimmune diseases like SLE are caused in part by autophagy. The initial support for the notion came from advanced genetic research that identified many susceptibility-associated variations in genes related to autophagy. This idea has been validated by numerous studies showing how anomalies in autophagy, particularly in adaptive immune cells, contribute to the onset and progression of SLE in cell cultures, animal models, and clinical settings. Despite the dearth of knowledge on the subject, recent research has also shown that enhanced podocyte autophagy may be a useful therapeutic target in lupus nephritis. Understanding the role of autophagy in the disease will provide significant new insights into the pathophysiology of SLE

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