Hindawi
BioMed Research International
Volume 2019, Article ID 8086257, 11 pages
https://doi.org/10.1155/2019/8086257

Review Article

The Immunomodulatory Effect of Alpha-Lipoic Acid in Autoimmune Diseases

Wei Liu,[1] **Lian-jie Shi**,[2] **and Sheng-guang Li**[2]

[1]*Department of Respiratory and Critical Care Medicine, The 900th Hospital of the Joint Logistic Support Force, PLA, Fujian Medical University, Fuzhou 350025, China*
[2]*Department of Rheumatology and immunology, Peking University International Hospital, Beijing 102206, China*

Correspondence should be addressed to Sheng-guang Li; lishengguang@vip.sina.com

Received 10 September 2018; Revised 11 February 2019; Accepted 21 February 2019; Published 20 March 2019

Academic Editor: Hai-Feng Pan

Alpha-lipoic acid is a naturally occurring antioxidant in human body and has been widely used as an antioxidant clinically. Accumulating evidences suggested that α-lipoic acid might have immunomodulatory effects on both adaptive and innate immune systems. This review focuses on the evidences and potential targets involved in the immunomodulatory effects of α-lipoic acid. It highlights the fact that α-lipoic acid may have beneficial effects in autoimmune diseases once the immunomodulatory effects can be confirmed by further investigation.

1. Background

Alpha-lipoic acid (ALA) is a naturally occurring dithiol compound that is wildly synthesized in the mitochondrion by plants and animals. Physiologically, ALA is a cofactor for α-ketoglutarate dehydrogenase complex to protect mitochondria from oxidative attack.

ALA and dihydrolipoic acid (DHLA) are the oxidized form and reduced form of LA, respectively. They are a pair of powerful redox couple which can directly scavenge reactive oxygen species (ROS), chelate metals, and regenerate other antioxidants to show antioxidant biochemical properties. With both liposoluble and water-soluble dual properties, ALA and DHLA can fully function intracellularly and extracellularly [1, 2].

Based on its cogent antioxidant properties and proven safety, ALA has been widely used to treat oxidative stress associated diseases, such as diabetes, neurological diseases, and cardiovascular diseases. More and more studies on LA had been performed; better understanding had been achieved towards the mechanisms of molecules, including the fact that ALA stimulated glucose uptake in insulin-sensitive cells and enhanced both the antioxidant defenses and the function of endothelial vascular cells [3]. Several lines of evidence suggested that ALA might have immunomodulatory effect.

With the progress of investigation of basic and clinical immunology, the role of oxidative stress on the pathogenesis of some autoimmune diseases has been generally recognized and interaction of ROS with the immune system well proven. On one hand, ROS may have a physiological role in signal transduction of all kinds of immune cells. For example, macrophage produced ROS to kill bacteria and regulatory T cells (Treg) released ROS to suppress activation of other T cells [4]. On the other hand, in pathological status, immune cells produce excessive ROS which exacerbated inflammation and broke balance in the immune system. For example, oxidative stress was one of the contributors to immune system dysregulation and dysfunction [5], which in turn led to deteriorate oxidative stress in systemic lupus erythematosus (SLE) [6, 7]. Both oxidative stress and immune dysfunction participated in the development and progression of SLE. Recently, redox-controlled activation of the mechanistic target of rapamycin (mTOR) has been recognized to play a critical regulatory role in the immune system [8], which highly implies that mTOR is a key bridge of metabolic stress and autoimmunity. It can be speculated that the antioxidant may be used for the treatment of certain autoimmune diseases based on evidence that ROS clearance played a role in immune regulation. Here in, we summarize the evidence

of the immunomodulatory effects of ALA and possible mechanisms involved by literature review.

1.1. The Involved Signaling Pathways of ALA

1.1.1. IKKβ, Ras/Erk1/2, and PI3K/Akt/mTOR Signaling Pathways. The mTOR, which could drive expansion of plasmablast [9] and T follicular helper (Tfh) cells [10], induce the differentiation of Th1 and Th17 [11], and restrict the differentiation of Treg [12] and CD8 memory T cells [13], is an essential mediator of immunity.

ALA had been shown to regulate upstream kinases of mTOR in multiple pathological conditions [1].

ALA blocked TNF-α induced IKK/NF-κB signaling cascades in RA-FLS and human umbilical vein endothelial cells (HUVECs) [14, 15]. TNF-α activated mTORC1 pathway via IKKβ activation in tumor angiogenesis and insulin resistance [16, 17]. Therefore, it can be speculated that ALA may suppress IKKβ-mediated activation of mTORC1.

ALA inhibited Erk signaling to improve atherosclerotic lesions and inhibit vascular smooth muscle cells proliferation [18]. ALA also inhibited activation of Erk mediated by 5-hydroxytryptamine (5-HT) [19] and epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) [20]. The activation of Akt/S6K1 and Erk suppressed by ALA attenuated hepatic stellate cell activation and ROS generation stimulated by TGF-β/PDGF [21].

However, Erk signaling activated by ALA has been reported to protect cardiovascular system and nervous system. ALA increased heme oxygenase-1 (HO-1) to protect vascular smooth muscle cells [22], ameliorated glucose/glucose oxidase- (G/GO-) induced injury of rat cardiomyoblast [23], inhibited adipocyte differentiation [24], protected cortical neurons from 4-hydroxy-2-nonenal- (HNE-) mediated oxidative damage and neurotoxicity [25], and promoted neurite outgrowth via activation of Erk [26].

The effect of bidirectional regulation of Erk1/2 kinases on mouse fibroblasts mediated by ALA was dependent on the cell culture medium containing serum or not [27, 28], which, to some extent, can interpret the fact that ALA regulated the same kinase in different directions in different pathological states.

ALA activated Akt kinase to protect pancreatic beta cells from hydrogen peroxide-mediated oxidative stress [29]. In rat L6 muscle cells, ALA mitigated insulin resistance via Akt activation and Erk inhibition [30].

ALA enhanced apoptosis and suppressed cell proliferation of human breast cancer cell line [31]. ALA also induced hepatoma cells apoptosis [32] to exert antitumor effects by suppression of PI3K/Akt pathway. ALA also inhibited leptin production of adipocytes and ameliorated insulin resistance of Goto-Kakizaki (GK) rat to improve disorders of glucose and lipid metabolism [33, 34].

Cytoprotective effect of ALA also could be mediated through phosphorylation of Akt kinase to ameliorate endoplasmic reticulum stress-induced FRTL5 thyroid cell death [35], protect neurons from injury induced by bupivacaine, amyloid and hydrogen peroxide [36, 37], reduce ischemia-reperfusion injury [38, 39] and oxidative stress injury of rat L6 muscle cells induced by TNFα and palmitate [30], decrease hydrogen peroxide-induced apoptosis of pancreatic beta cells [29], attenuate LPS-induced cardiac dysfunction [40], monocyte activation, and acute inflammatory responses [41], and ameliorate vascular endothelial dysfunction [42, 43].

1.1.2. AMPK Signaling Pathway. ALA has been reported to activate AMPK to upregulate adipose triglyceride lipase (ATGL) to reduce body weight and visceral fat content of diabetic mice [44].

Through AMPK/mTORC1/S6K1 signaling pathway, leucine and glucose induced insulin resistance which could be attenuated by ALA via TSC2-mTOR inhibitors-phosphorylation [45, 46] and AMPK activation [47] in skeletal muscle. ALA also activated AMPK to downregulate expression of S6K1 [48] leading to inhibition of insulin secretion in pancreatic beta cells, which implies involvement of mTOR.

However, ALA was also reported to inhibit the phosphorylation of AMPK, which suppressed appetite and prevented obesity in the hypothalamus [49–51] consistent with the effect of ALA on peripheral tissue to improve insulin resistance and decrease lipid accumulation and lipogenesis.

Overall, ALA regulated some upstream kinase of mTOR in inconsistent directions in diverse cell types of different diseases. It has been proven that mTOR can modulate T cell differentiation and inhibit Treg cells which are deficient in SLE patients [52, 53]. N-acetylcysteine (NAC), a well-known antioxidant, has been reported to inhibit mTOR in vitro [54] and improve the outcome of murine lupus [55] and even SLE patients [56]. It has also been observed that disease activity could be reduced and Treg populations could be reversed by mTOR blockade in treating SLE patients [57]. Although these existing indirect evidence was tempting to conclude that ALA had effect on regulation of mTOR signaling, regulation of the mTOR pathway by ALA in immune cells is worthy of further investigation for patients with autoimmune diseases of high relapse rate and poor responsiveness to traditional treatment.

2. Effects of ALA on Immune System

The proven effects of ALA on adaptive immune cells, including T and B cells, are briefly summarized in Table 1 and Figure 1, and the proven effects on innate immune cells including NK cells, macrophages, and monocytes are summarized in Table 1, all of which will be discussed in detail below.

2.1. Effects on Adaptive Immune Cells

2.1.1. Effects on T Cells. Multiple sclerosis (MS) is an autoimmune disease in central nervous system, which is characterized by the migration and the long-term survival of myelin-specific T lymphocytes into the central nervous system (CNS). A common model of MS is experimental autoimmune encephalomyelitis (EAE). Studies demonstrated the beneficial effects of ALA on treating EAE by suppressing

Table 1: Evidence of ALA on adaptive immune cells.

		T cell	B cell
Animal model	EAE	Decrease the number of Th17 and Th1 in CNS; Increase Treg numbers in spleen; Reduce migration.	
	High fat diet mice	Recover transcriptional levels of the differentiation-related genes of jejunal T cells.	Restore transcriptional levels of BCR signaling pathway relating genes; Decrease the apoptotic percentage of splenic B lymphocytes.
	Atopic dermatitis	Suppress production of IFN-γ and IL-4 by CD4+T.	Reduce total serum IgE levels.
	Models of established atherosclerosis	Reduce T cell migration in response to chemokines.	
	Endotoxemia mice		Increase the number of splenic B cells.
Patients	AIDS	Increase the number of Th cells; Improve the lymphocyte proliferation response; Ameliorate the impaired mitochondrial function of $CD4^+$T cells.	
	Advanced cancer	Induce lymphocyte progression from G0/G1 to S phase.	
	Jurkat T cells	Inhibit NF-κB activation induced by TNF Reduce migration.	
Normal human		Increase cAMP which affects proliferation and activation of T cells; Down-regulate the expression of CD4 molecules; Reduce migration.	

ALA: α-lipoic acid.
EAE: experimental autoimmune encephalomyelitis.
Th17: T helper cell 17.
Th1: T helper cell 1.
CNS: central nervous system.
Treg: regulatory T cells.
BCR: B-cell receptor.
IFN-γ: interferon-γ.
AIDS: acquired immunodeficiency syndrome.
NF-κB: nuclear factor kappa B.
TNF: tumor necrosis factor.
cAMP: cyclic adenosine monophosphate.

the infiltration of inflammatory cells [58–61]. Recently, Wang and colleagues [60] reported that ALA reduced the number of Th17 and Th1 cells in CNS and increased the number of splenic Treg cells in EAE mice. It highly implied that ALA showed immunomodulatory effects on differentiation and proliferation of T cells. ALA has also been reported to increase cAMP synthesis through activation of prostaglandin receptors (EP2 and EP4) in peripheral blood T cells [62] (Figure 1, ①). The elevated levels of intracellular cAMP decreased the expression of IL-2 and IL-2Rα (CD25) [63] (Figure 1, ②), which in turn affected proliferation and activation of T cells [64].

More studies indicated that ALA could regulate function of T cells in many ways. ALA could ameliorate the impaired mitochondrial function of $CD4^+$T cells of acquired immunodeficiency syndrome (AIDS) patients [65], downregulate the expression of CD4 molecules of human peripheral blood T cells [66], inhibit nuclear factor kappa B (NF-κB) activation induced by tumor necrosis factor-alpha (TNF) in Jurkat T cells [67] (Figure 1, ③), suppress production of interferon-γ (IFN-γ) and interleukin-4 (IL-4) (Figure 1, ④) by $CD4^+$T cells to reduce the severity of atopic dermatitis lesions in mice model [68], and induce lymphocyte progression from G0/G1 to S phase (Figure 1, ⑤), which might be related to restore the function of immune system in advanced cancer patients [69].

Besides effects on T cell proliferation, differentiation, and the cytokines produced by them, ALA could also inhibit migration of T cells. Ying and colleagues found that ALA could directly reduce T cell migration in response to chemokines to reduce T cell numbers in atherosclerotic plaque in models of established atherosclerosis [70]. ALA was also reported to reduce migration of T cell [58, 71], lymphocyte and monocyte of models of MS [61], and Jurkat T cells [72], which were associated with downregulated

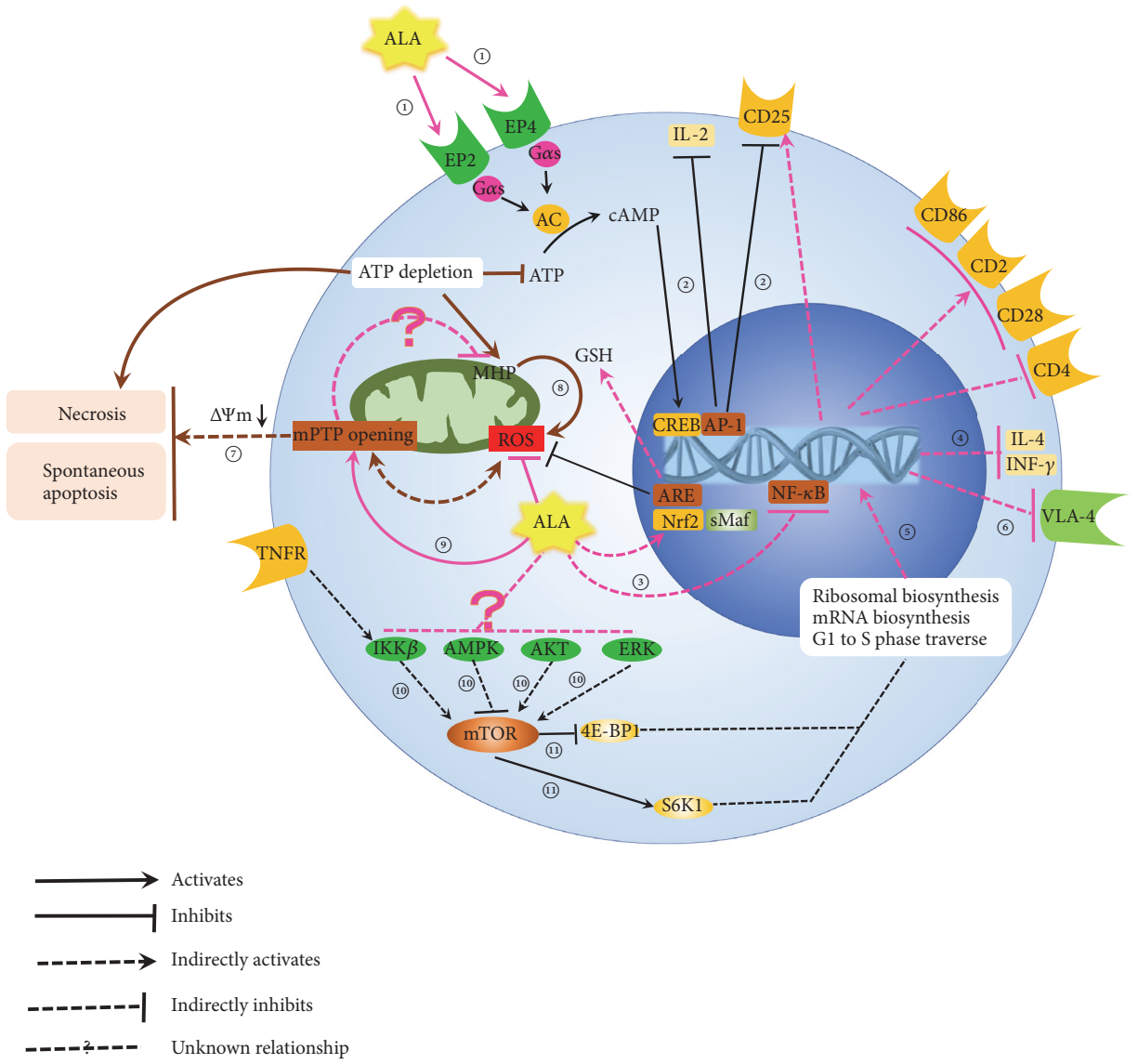

Figure 1: *Effect of ALA on T cell.* ① ALA increase cAMP synthesis through activation of prostaglandin receptors (EP2 and EP4) in peripheral blood T cells. ② The expression of IL-2 and IL-2Rα (CD25) could be inhibited when the level of cAMP was increased by ALA. ③ ALA could inhibit NF-κB activation induced by TNF in Jurkat T cells. ④ ALA could suppress production of interferon-γ (IFN-γ) and interleukin -4 (IL-4). ⑤ ALA could induce lymphocyte progression from G0/G1 to S phase. ⑥ ALA was also reported to reduce migration of T cell, lymphocyte and monocyte of models of MS, and Jurkat T cells, which were associated with down-regulated expression of very late activation-4 antigen (VLA-4). ⑦ Uncontrolled mPTP opening leads to decrease $\Delta\Psi$m irreversibly until dissipation which results in apoptosis and necrosis of cells. ⑧ Persistent MHP in SLE T cells could enhance ROS production. ⑨ Studies showed that ALA and DHLA promoted mPTP opening in mitochondria of rat liver. ⑩ mTORC1 was a central common regulator of a complex signaling network In cytoplasm, in which Ras/Erk, PI3K/Akt, and IKKβ activated mTORC1 while Dsh/GSK3 and LKBl/AMPK inactivated mTORC1. ⑪ Activated mTORC promoted protein synthesis by phosphorylating the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and p70 ribosomal S6 kinase 1 (S6K1).

expression of very late activation-4 antigen (VLA-4) (Figure 1, ⑥) and inhibition of MMP-9 activity by ALA [72].

2.1.2. Effects on B Cells. The studies showed that ALA supplement might play a role in high fat diet mice to prevent the development of oxidative stress and to attenuate B-cell injury by increasing the gene expression of the B-cell receptor (BCR) signaling pathway and decrease the apoptotic percentage of splenic B lymphocytes [73], which was also relevant to the improvement of gene expression level of BCR [74]. It has been proven that ALA increased the number of splenic B cells in endotoxemia mice [75] and reduced total serum IgE levels of atopic dermatitis mice model [68]. These experiments suggest that ALA plays a regulating role on proliferation, apoptosis and function of B cells (Table 1).

Table 2: Evidence of ALA on innate immune cells.

		NK cell	Macrophage	Monocyte
Animal model	EAE		Inhibit the phagocytosis of myelin.	Decrease monocytes infiltration into the CNS.
	High fat diet mice		Suppress infiltration and activation of macrophage to attenuate visceral adipose inflammation.	
	BMDM or RAW 264.7		Decrease the production of MCP-1 and TNF-α induced by LPS.	
Normal human		Increase cAMP production to suppress cytotoxicity and IFN-γ production.		Induce the expression of HO-1 by Nrf2.

ALA: α-lipoic acid.
NK cell: natural killer cell.
EAE: experimental autoimmune encephalomyelitis.
CNS: central nervous system.
BMDM: bone marrow-derived macrophages.
MCP-1: monocyte chemotactic protein 1.
TNF-α: tumor necrosis factor-alpha.
LPS: lipopolysaccharide.
cAMP: cyclic adenosine monophosphate.
IFN-γ: interferon-γ.
HO-1: heme oxygenase-1.
Nrf2: nuclear factor-erythroid 2-related factor.

2.1.3. Effects on Innate Immune Cells

Natural Killer Cell (NK Cell), Macrophage, and Monocyte (See Table 2). Cytotoxicity and cytokines secretion are two main functions of NK cells. The former is associated with the release of granzymes (perforin and proteases) from their cytoplasm. INF-γ secretion is a representative of the latter. INF-γ is a potent macrophage activator for both phagocytosis and lysis. IFN-γ secretion induced by IL-12/IL-18 and cellular cytotoxicity in NK cells could be inhibited by ALA, which increased cAMP production via G protein-coupled receptors- (GPCRs-) dependent and GPCRs-independent mechanisms [62, 76, 77]. In addition, it has also been demonstrated that both cAMP and cAMP-inducing agents (PGE1, theophylline, and histamine) suppressed cytolytic function of NK cells [78]. PGE2, another cAMP elevating agent, also suppressed cytotoxicity and IFN-γ production induced by IL-15 [79]. Therefore, ALA could suppress NK function in a few ways.

It has also been found that ALA regulated activation, phagocytosis, and migration of macrophage by either direct or indirect means. ALA inhibited the phagocytosis of myelin by macrophages [80], which was the main autoantigen in EAE mice, and decreased the production of monocyte chemotactic protein 1 (MCP-1) and TNFα induced by lipopolysaccharide (LPS) of macrophages [81, 82]. Also, ALA decreased monocytes infiltration into the CNS and stabilized brain endothelial cells in EAE rat [61], which might be associated with the downregulated intracellular adhesion molecule-1 (ICAM-1) expression of monocytes [83] and the upregulated vascular cell adhesion molecule-1 (VCAM-1) expression of endothelial cells [84]. In addition, ALA could induce the expression of heme oxygenase-1(HO-1) by nuclear factor-erythroid 2-related factor 2 (Nrf2) in human monocytic cells [85].

3. Other Potential Targets of ALA Immunomodulatory Effects

ALA has been widely used for decades in clinic and studied in various experimental models. Therefore, we found the potential targets for immunomodulatory effects of ALA in these researches.

3.1. Mitochondrial Membrane Potential ($\Delta\Psi m$). Mitochondria provide place for the citric acid cycle and oxidative phosphorylation, which is the energy station of cells and is involved in cell differentiation, cell cycle regulation, and cell death. The stability of $\Delta\Psi$m is essential for the maintenance of normal physiological function of cells. The electron transport chain and the F_0F_1-ATPase complex maintain an electrochemical gradient namely "$\Delta\Psi$m", and vice versa, $\Delta\Psi$m tightly regulates the production of ROS and ATP synthesis [86]. Mitochondrial permeability transition pore (mPTP) is a series of protein channels which are located in the inner and outer mitochondrial membrane. mPTP closes completely to stabilize $\Delta\Psi$m whereas mPTP opens transiently to a low conductance state to result in lowering $\Delta\Psi$m. Uncontrollable mPTP opening leads to decrease $\Delta\Psi$m

irreversibly until dissipation which results in apoptosis and necrosis of cells [87, 88] (Figure 1, ⑦). In the process of both activation and apoptosis of T lymphocytes, ΔΨm was transiently reversibly elevated, that is what mitochondrial hyperpolarization (MHP) in physiological status should be [89]. However, persistent MHP in T cells of SLE patients would enhance ROS production (Figure 1 ⑧), which resulted in activation of macrophages [90] and dendritic cells [91] to exacerbate inflammation [92, 93] and resulted in ATP depletion which increased IL-10 production and spontaneous apoptosis of T cells [94]. T cell apoptosis not only provided a source of nuclear antigens but also was correlated with SLE disease activity [95, 96]. Increased production of IL-10 could promote T cell apoptosis [97] and contribute to the production of autoantibodies by hyperactive SLE B lymphocytes [98, 99]. There were proofs showing that ALA and DHLA promoted mPTP opening of mitochondria in rat liver [3, 93, 100] (Figure 1, ⑨). Thus, the authors speculate that ALA may attenuate mitochondrial dysfunction in SLE from several aspects. ALA opens mPTP to reduce ΔΨm, which improves pathological MHP of SLE T cells and directly quenches ROS to correct dysfunction of T cells and B cells.

3.2. Neutrophil Extracellular Traps (NETs). Neutrophils play a very important role in innate immune system and are the first leukocytes to be recruited to the site of infection to eliminate pathogens by multiple mechanisms which include phagocytosis, inflammatory mediators secretion, and NETs release which is also known as NETosis. NETs are composed of nucleic acids, histone proteins, and granule proteins with or without death of neutrophils [101]. NETs only fight against pathogens but also have been implicated in pathogenesis of the autoimmune diseases (e.g., SLE [102, 103], RA [104, 105], psoriasis [106], and autoimmune small-vessel vasculitis [107]) and thrombosis [108]. Nuclear material of NETs components became autoantigens after it was extruded from the cell to induce autoantibodies production [109]. NETs formation was dependent on autophagy and ROS generation [110, 111] and regulated by mTOR signaling pathway [112, 113]. It has been speculated that ALA may be capable of quenching ROS and regulating mTOR signaling, which suggests that it may have beneficial effects on NETs formation to reduce the autoantibodies production and protect vascular endothelium.

3.3. Nrf2 Signaling Pathway. ALA is well recognized to be an activator of Nrf2 signaling [1, 114]. The nuclear factor-erythroid 2-related factor 2 (Nrf2), a central regulator of cellular resistance to oxidant stress, binds antioxidant response element (ARE) to regulate expression of a lot of ARE-containing genes to play a pivotal role in control of oxidant homeostasis [115]. There is a little evidence to show association between Nrf2 signaling and pathogenesis of autoimmune disease. It has been demonstrated that Nrf2-deficient female mice developed severe nephritis similar to lupus [116] and Nrf2 gene variant was relevant with nephritis in childhood-onset SLE patients [117]. Nrf2 (-/-) mice developed regenerative immune-mediated hemolytic anemia [118] and disruption of Nrf2 aggravated [119] while activation of Nrf2 attenuated [120] neuroinflammatory disorders in EAE. Hence, ALA may have regulatory effects in immune system via Nrf2 pathway.

4. Safety of ALA

ALA, a naturally occurring antioxidant in human body and available from common dietary sources, has been used to treat diabetic neuropathy and retinopathy for over 50 years in Germany. A number of clinical trials have reported that oral LA supplementation up to 2400 mg/d and intravenous LA supplementation up to 600 mg/d for three weeks showing no adverse effects versus placebo [1, 2]. Moreover, flexible regulatory effects of ALA have been shown by Sen and colleagues that ALA promoted apoptosis induced by Fas in Jurkat cells but not healthy peripheral blood lymphocytes [121]. The data of these studies supports the safety of ALA.

5. Summary

In conclusion, ALA, a natural ingredient of human body, not only acts as a powerful antioxidant but also is able to regulate the immune system in either direct or indirect ways. Studies reviewed above might suggest that ALA is used to treat autoimmune diseases including SLE, RA, and primary vasculitis as well as MS. The current therapies for systemic rheumatic diseases are effective. However, there was still a high percent of patients with not enough or no response to the therapies. Therefore, if the immunomodulatory effects of ALA could be confirmed by further investigation, it might have beneficial effects in conjunction with the current treatment of rheumatic diseases.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Wei Liu and Lian-jie Shi contributed equally to the paper.

Acknowledgments

The authors acknowledge Guo-xiang Lai, M.D., from the 900th Hospital of the Joint Logistic Support Force, PLA, for his contribution to the figure drawing and medical writing assistance while drafting this manuscript. This work is supported by grants from Fuzhou General Hospital (2018 J05) and Clinical Key Specialty Construction Project in Fujian Province (Min Wei Medical Letter [2015] no. 593).

References

[1] K. P. Shay, R. F. Moreau, E. J. Smith, A. R. Smith, and T. M. Hagen, "Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential," *Biochimica et Biophysica Acta*, vol. 1790, no. 10, pp. 1149–1160, 2009.

[2] A. Gorąca, H. Huk-Kolega, A. Piechota, P. Kleniewska, E. Ciejka, and B. Skibska, "Lipoic acid—biological activity and therapeutic potential," *Pharmacological Reports*, vol. 63, no. 4, pp. 849–858, 2011.

[3] L. Rochette, S. Ghibu, C. Richard, M. Zeller, Y. Cottin, and C. Vergely, "Direct and indirect antioxidant properties of α-lipoic acid and therapeutic potential," *Molecular Nutrition & Food Research*, vol. 57, no. 1, pp. 114–125, 2013.

[4] C. Nathan and A. Cunningham-Bussel, "Beyond oxidative stress: an immunologist's guide to reactive oxygen species," *Nature Reviews Immunology*, vol. 13, no. 5, pp. 349–361, 2013.

[5] A. Perl, "Oxidative stress in the pathology and treatment of systemic lupus erythematosus," *Nature Reviews Rheumatology*, vol. 9, no. 11, pp. 674–686, 2013.

[6] Y. L. Lightfoot, L. P. Blanco, and M. J. Kaplan, "Metabolic abnormalities and oxidative stress in lupus," *Current Opinion in Rheumatology*, vol. 29, no. 5, pp. 442–449, 2017.

[7] X. Huang, J. Li, S. Dorta-Estremera et al., "Neutrophils regulate humoral autoimmunity by restricting interferon-γ production via the generation of reactive oxygen species," *Cell Reports*, vol. 12, no. 7, pp. 1120–1132, 2015.

[8] N. Huang and A. Perl, "Metabolism as a target for modulation in autoimmune diseases," *Trends in Immunology*, vol. 39, no. 7, pp. 562–576, 2018.

[9] M. Torigoe, S. Iwata, S. Nakayamada et al., "Metabolic reprogramming commits differentiation of human CD27(+)IgD(+) B cells to plasmablasts or CD27(-)IgD(-) cells," *The Journal of Immunology*, vol. 199, no. 2, pp. 425–434, 2017.

[10] W. Yi, S. Gupta, E. Ricker et al., "The mTORC1-4E-BP-eIF4E axis controls de novo Bcl6 protein synthesis in T cells and systemic autoimmunity," *Nature Communications*, vol. 8, no. 1, 2017.

[11] G. M. Delgoffe, K. N. Pollizzi, A. T. Waickman et al., "The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2," *Nature Immunology*, vol. 12, no. 4, pp. 295–304, 2011.

[12] J. Wei, L. Long, K. Yang et al., "Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis," *Nature Immunology*, vol. 17, no. 3, pp. 277–285, 2016.

[13] X. Xu, K. Araki, S. Li et al., "Autophagy is essential for effector CD8(+) T cell survival and memory formation," *Nature Immunology*, vol. 15, no. 12, pp. 1152–1161, 2014.

[14] C.-K. Lee, E. Y. Lee, Y. G. Kim, S. H. Mun, H.-B. Moon, and B. Yoo, "Alpha-lipoic acid inhibits TNF-α induced NF-κB activation through blocking of MEKK1-MKK4-IKK signaling cascades," *International Immunopharmacology*, vol. 8, no. 2, pp. 362–370, 2008.

[15] Z. Ying, T. Kampfrath, Q. Sun, S. Parthasarathy, and S. Rajagopalan, "Evidence that α-lipoic acid inhibits NF-κB activation independent of its antioxidant function," *Inflammation Research*, vol. 60, no. 3, pp. 219–225, 2011.

[16] D. F. Lee, H. P. Kuo, C. T. Chen et al., "IKKbeta suppression of TSC1 function links the mTOR pathway with insulin resistance," *International Journal of Molecular Medicine*, vol. 22, no. 5, pp. 633–638, 2008.

[17] D. F. Lee, H. P. Kuo, C. T. Chen et al., "IKK beta suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway," *Cell*, vol. 130, no. 3, pp. 440–455, 2007.

[18] W.-R. Lee, A. Kim, K.-S. Kim et al., "Alpha-lipoic acid attenuates atherosclerotic lesions and inhibits proliferation of vascular smooth muscle cells through targeting of the Ras/MEK/ERK signaling pathway," *Molecular Biology Reports*, vol. 39, no. 6, pp. 6857–6866, 2012.

[19] J. S. Grewal, Y. V. Mukhin, M. N. Garnovskaya, J. R. Raymond, and E. L. Greene, "Serotonin 5-HT(2A) receptor induces TGF-β1 expression in mesangial cells via ERK: Proliferative and fibrotic signals," *American Journal of Physiology-Renal Physiology*, vol. 276, no. 6, pp. F922–F930, 1999.

[20] M. N. Budisavljevic, L. Hodge, K. Barber et al., "Oxidative stress in the pathogenesis of experimental mesangial proliferative glomerulonephritis," *American Journal of Physiology-Renal Physiology*, vol. 285, no. 6, pp. F1138–F1148, 2003.

[21] N.-P. Foo, S.-H. Lin, Y.-H. Lee, M.-J. Wu, and Y.-J. Wang, "α-Lipoic acid inhibits liver fibrosis through the attenuation of ROS-triggered signaling in hepatic stellate cells activated by PDGF and TGF-β," *Toxicology*, vol. 282, no. 1-2, pp. 39–46, 2011.

[22] P.-Y. Cheng, Y.-M. Lee, N.-L. Shih, Y.-C. Chen, and M.-H. Yen, "Heme oxygenase-1 contributes to the cytoprotection of alpha-lipoic acid via activation of p44/42 mitogen-activated protein kinase in vascular smooth muscle cells," *Free Radical Biology & Medicine*, vol. 40, no. 8, pp. 1313–1322, 2006.

[23] Y. Yao, R. Li, Y. Ma et al., "α-Lipoic acid increases tolerance of cardiomyoblasts to glucose/glucose oxidase-induced injury via ROS-dependent ERK1/2 activation," *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, vol. 1823, no. 4, pp. 920–929, 2012.

[24] K. Cho, H. Moon, H. Moini, L. Packer, D. Yoon, and A. Chung, "α-Lipoic acid inhibits adipocyte differentiation by regulating pro-adipogenic transcription factors via mitogen-activated protein kinase pathways," *The Journal of Biological Chemistry*, vol. 278, no. 37, pp. 34823–34833, 2003.

[25] H. Mohmmad Abdul and D. A. Butterfield, "Involvement of PI3K/PKG/ERK1/2 signaling pathways in cortical neurons to trigger protection by cotreatment of acetyl-L-carnitine and α-lipoic acid against HNE-mediated oxidative stress and neurotoxicity: Implications for Alzheimer's disease," *Free Radical Biology & Medicine*, vol. 42, no. 3, pp. 371–384, 2007.

[26] X. Wang, Z. Wang, Y. Yao et al., "Essential role of ERK activation in neurite outgrowth induced by alpha-lipoic acid," *Biochimica et Biophysica Acta*, vol. 1813, no. 5, pp. 827–838, 2011.

[27] S. S. Shi, R. M. Day, A. D. Halpner, J. B. Blumberg, and Y. J. Suzuki, "Homocysteine and α-lipoic acid regulate p44/42 MAP kinase phosphorylation in NIH/3T3 cells," *Antioxidants & Redox Signaling*, vol. 1, no. 1, pp. 123–128, 1999.

[28] Y. J. Suzuki, S. S. Shi, R. M. Day, and J. B. Blumberg, "Differential regulation of MAP kinase signaling by pro- and antioxidant biothiols," *Annals of the New York Academy of Sciences*, vol. 899, pp. 159–167, 2000.

[29] B. W. Lee, S. J. Kwon, H. Y. Chae et al., "Dose-related cytoprotective effect of alpha-lipoic acid on hydrogen peroxide-induced oxidative stress to pancreatic beta cells," *Free Radical Research*, vol. 43, no. 1, pp. 68–77, 2009.

[30] M. Ishiki, Y. Nishida, H. Ishibashi et al., "Impact of divergent effects of astaxanthin on insulin signaling in L6 cells," *Endocrinology*, vol. 154, no. 8, pp. 2600–2612, 2013.

[31] E. Dozio, M. Ruscica, L. Passafaro et al., "The natural antioxidant alpha-lipoic acid induces p27Kip1-dependent cell cycle

arrest and apoptosis in MCF-7 human breast cancer cells," *European Journal of Pharmacology*, vol. 641, no. 1, pp. 29–34, 2010.

[32] D.-Y. Shi, H.-L. Liu, J. S. Stern, P.-Z. Yu, and S.-L. Liu, "Alpha-lipoic acid induces apoptosis in hepatoma cells via the PTEN/Akt pathway," *FEBS Letters*, vol. 582, no. 12, pp. 1667–1671, 2008.

[33] P. L. Prieto-Hontoria, P. Pérez-Matute, M. Fernández-Galilea, J. A. Martínez, and M. J. Moreno-Aliaga, "Lipoic acid inhibits leptin secretion and Sp1 activity in adipocytes," *Molecular Nutrition & Food Research*, vol. 55, no. 7, pp. 1059–1069, 2011.

[34] M. S. Bitar, S. Wahid, C. W. Pilcher, E. Al-Saleh, and F. Al-Mulla, "α-lipoic Acid Mitigates Insulin Resistance in Goto-Kakizaki Rats," *Hormone and Metabolic Research*, vol. 36, no. 8, pp. 542–549, 2004.

[35] S. J. Lee, S. H. Kim, J. G. Kang et al., "Alpha-lipoic acid inhibits endoplasmic reticulum stress-induced cell death through PI3K/Akt signaling pathway in FRTL5 thyroid cells," *Hormone and Metabolic Research*, vol. 43, no. 7, pp. 445–451, 2011.

[36] X. Wang, X. Zhang, Y. Cheng et al., "α-Lipoic acid prevents bupivacaine-induced neuron injury in vitro through a PI3K/Akt-dependent mechanism," *NeuroToxicology*, vol. 31, no. 1, pp. 101–112, 2010.

[37] L. Zhang, G. q. Xing, J. L. Barker et al., "α-lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signalling pathway," *Neuroscience Letters*, vol. 312, no. 3, pp. 125–128, 2001.

[38] C. Deng, Z. Sun, G. Tong et al., "Alpha-lipoic acid reduces infarct size and preserves cardiac function in rat myocardial ischemia/reperfusion injury through activation of pi3k/akt/nrf2 pathway," *PLoS ONE*, vol. 8, no. 3, Article ID e58371, 2013.

[39] C. Müller, F. Dünschede, E. Koch, A. M. Vollmar, and A. K. Kiemer, "α-Lipoic acid preconditioning reduces ischemia-reperfusion injury of the rat liver via the PI3-kinase/Akt pathway," *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 285, no. 4, pp. G769–G778, 2003.

[40] S. Jiang, W. Zhu, C. Li et al., "α-Lipoic acid attenuates LPS-induced cardiac dysfunction through a PI3K/Akt-dependent mechanism," *International Immunopharmacology*, vol. 16, no. 1, pp. 100–107, 2013.

[41] W. J. Zhang, H. Wei, T. Hagen, and B. Frei, "α-Lipoic acid attenuates LPS-induced inflammatory responses by activating the phosphoinositide 3-kinase/Akt signaling pathway," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 104, no. 10, pp. 4077–4082, 2007.

[42] M. S. Bitar, A. K. Ayed, S. M. Abdel-Halim, E. R. Isenovic, and F. Al-Mulla, "Inflammation and apoptosis in aortic tissues of aged type II diabetes: amelioration with α-lipoic acid through phosphatidylinositol 3-kinase/Akt- dependent mechanism," *Life Sciences*, vol. 86, no. 23-24, pp. 844–853, 2010.

[43] A. R. Smith and T. M. Hagen, "Vascular endothelial dysfunction in aging: Loss of Akt-dependent endothelial nitric oxide synthase phosphorylation and partial restoration by (R)-α-lipoic acid," *Biochemical Society Transactions*, vol. 31, no. 6, pp. 1447–1449, 2003.

[44] W. Chen, C. Kang, S. Wang et al., "Alpha-Lipoic acid regulates lipid metabolism through induction of sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase," *Diabetologia*, vol. 55, no. 6, pp. 1824–1835, 2012.

[45] A. K. Saha, X. J. Xu, E. Lawson et al., "Downregulation of AMPK accompanies leucine- and glucose-induced increases in protein synthesis and insulin resistance in rat skeletal muscle," *Diabetes*, vol. 59, no. 10, pp. 2426–2434, 2010.

[46] A. K. Saha, X. J. Xu, T. W. Balon, A. Brandon, E. W. Kraegen, and N. B. Ruderman, "Insulin resistance due to nutrient excess: is it a consequence of AMPK downregulation?" *Cell Cycle*, vol. 10, no. 20, pp. 3447–3451, 2011.

[47] W. J. Lee, K. H. Song, and E. H. Koh, "Alpha-lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle," *Biochemical and Biophysical Research Communications*, vol. 332, no. 3, pp. 885–891, 2005.

[48] E. D. Targonsky, F. Dai, V. Koshkin et al., "alpha-lipoic acid regulates AMP-activated protein kinase and inhibits insulin secretion from beta cells," *Diabetologia*, vol. 49, no. 7, pp. 1587–1598, 2006.

[49] M.-S. Kim, J.-Y. Park, C. Namkoong et al., "Anti-obesity effects of α-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase," *Nature Medicine*, vol. 10, no. 7, pp. 727–733, 2004.

[50] W. J. Lee, H. K. Eun, C. W. Jong, M.-S. Kim, J.-Y. Park, and K.-U. Lee, "Obesity: The role of hypothalamic AMP-activated protein kinase in body weight regulation," *The International Journal of Biochemistry & Cell Biology*, vol. 37, no. 11, pp. 2254–2259, 2005.

[51] M. S. Kim and K. U. Lee, "Role of hypothalamic 5′-AMP-activated protein kinase in the regulation of food intake and energy homeostasis," *Journal of Molecular Medicine*, vol. 83, no. 7, pp. 514–520, 2005.

[52] D. Fernandez and A. Perl, "mTOR signaling: a central pathway to pathogenesis in systemic lupus erythematosus?" *Discovery Medicine*, vol. 9, no. 46, pp. 173–178, 2010.

[53] D. Fernandez and A. Perl, "Metabolic control of T cell activation and death in SLE," *Autoimmunity Reviews*, vol. 8, no. 3, pp. 184–189, 2009.

[54] A. O'Loghlen, M. I. Pérez-Morgado, M. Salinas, and M. E. Martín, "N-acetyl-cysteine abolishes hydrogen peroxide-induced modification of eukaryotic initiation factor 4F activity via distinct signalling pathways," *Cellular Signalling*, vol. 18, no. 1, pp. 21–31, 2006.

[55] S. Suwannaroj, A. Lagoo, D. Keisler, and R. W. McMurray, "Antioxidants suppress mortality in the female NZB × NZW F1 mouse model of systemic lupus erythematosus (SLE)," *Lupus*, vol. 10, no. 4, pp. 258–265, 2001.

[56] Z.-W. Lai, R. Hanczko, E. Bonilla et al., "*N*-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial," *Arthritis & Rheumatism*, vol. 64, no. 9, pp. 2937–2946, 2012.

[57] Z.-W. Lai, R. Kelly, T. Winans et al., "Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial," *The Lancet*, vol. 391, no. 10126, pp. 1186–1196, 2018.

[58] G. H. Marracci, R. E. Jones, G. P. McKeon, and D. N. Bourdette, "Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis," *Journal of Neuroimmunology*, vol. 131, no. 1-2, pp. 104–114, 2002.

[59] M. Morini, L. Roccatagliata, R. Dell'Eva et al., "Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis," *Journal of Neuroimmunology*, vol. 148, no. 1-2, pp. 146–153, 2004.

[60] K.-C. Wang, C.-P. Tsai, C.-L. Lee et al., "α-lipoic acid enhances endogenous peroxisome-proliferator-activated receptor-γ to

ameliorate experimental autoimmune encephalomyelitis in mice," *Clinical Science*, vol. 125, no. 7, pp. 329–340, 2013.

[61] G. Schreibelt, R. J. P. Musters, A. Reijerkerk et al., "Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity," *The Journal of Immunology*, vol. 177, no. 4, pp. 2630–2637, 2006.

[62] R. V. Schillace, N. Pisenti, N. Pattamanuch et al., "Lipoic acid stimulates cAMP production in T lymphocytes and NK cells," *Biochemical and Biophysical Research Communications*, vol. 354, no. 1, pp. 259–264, 2007.

[63] K. A. Anderson, T. J. Ribar, M. Illario, and A. R. Means, "Defective survival and activation of thymocytes in transgenic mice expressing a catalytically inactive form of Ca2+/calmodulin-dependent protein kinase IV," *Molecular Endocrinology*, vol. 11, no. 6, pp. 725–737, 1997.

[64] E. M. Kuklina and S. V. Shirshev, "Role of cAMP-dependent signal transduction in the control of T lymphocyte activation," *Biochemistry (Moscow)*, vol. 65, no. 6, pp. 629–639, 2000.

[65] L. Milazzo, B. Menzaghi, I. Caramma et al., "Effect of antioxidants on mitochondrial function in HIV-1-related lipoatrophy: A pilot study," *AIDS Research and Human Retroviruses*, vol. 26, no. 11, pp. 1207–1214, 2010.

[66] G. H. Marracci, W. E. Marquardt, A. Strehlow et al., "Lipoic acid downmodulates CD4 from human T lymphocytes by dissociation of p56Lck," *Biochemical and Biophysical Research Communications*, vol. 344, no. 3, pp. 963–971, 2006.

[67] Y. J. Suzuki, B. Aggarwal, and L. Packer, "Alpha-lipoic acid is a potent inhibitor of NF-kappa B activation in human T cells," *Biochemical and Biophysical Research Communications*, vol. 189, no. 3, pp. 1709–1715, 1992.

[68] G. Kim, T. Kim, A. Jang, H. Ahn, Y. S. Park, and C. Park, "α-Lipoic acid suppresses the development of DNFB-induced atopic dermatitis-like symptoms in NC/Nga mice," *Experimental Dermatology*, vol. 20, no. 2, pp. 97–101, 2011.

[69] G. Mantovani, A. Macciò, C. Madeddu et al., "Antioxidant agents are effective in inducing lymphocyte progression through cell cycle in advanced cancer patients: assessment of the most important laboratory indexes of cachexia and oxidative stress," *Journal of Molecular Medicine*, vol. 81, no. 10, pp. 664–673, 2003.

[70] Z. Ying, N. Kherada, B. Farrar et al., "Lipoic acid effects on established atherosclerosis," *Life Sciences*, vol. 86, no. 3-4, pp. 95–102, 2010.

[71] P. Chaudhary, G. H. Marracci, and D. N. Bourdette, "Lipoic acid inhibits expression of ICAM-1 and VCAM-1 by CNS endothelial cells and T cell migration into the spinal cord in experimental autoimmune encephalomyelitis," *Journal of Neuroimmunology*, vol. 175, no. 1-2, pp. 87–96, 2006.

[72] G. H. Marracci, G. P. McKeon, W. E. Marquardt, R. W. Winter, M. K. Riscoe, and D. N. Bourdette, "α lipoic acid inhibits human T-cell migration: Implications for multiple sclerosis," *Journal of Neuroscience Research*, vol. 78, no. 3, pp. 362–370, 2004.

[73] J. Cui, Y. Xiao, Y. Shi, G. Le, and X. Miao, "Comparative proteome analysis of splenic lymphocytes in long-term high-fat diet and dietary supplement with lipoic acid mice," *Cellular Immunology*, vol. 264, no. 2, pp. 156–162, 2010.

[74] J. Cui, Y. Xiao, Y.-H. Shi, B. Wang, and G.-W. Le, "Lipoic acid attenuates high-fat-diet-induced oxidative stress and B-cell-related immune depression," *Nutrition Journal* , vol. 28, no. 3, pp. 275–280, 2012.

[75] B. Wessner, E.-M. Strasser, N. Manhart, and E. Roth, "Supply of R-α-lipoic acid and glutamine to casein-fed mice influences the number of B lymphocytes and tissue glutathione levels during endotoxemia," *Wiener Klinische Wochenschrift*, vol. 118, no. 3-4, pp. 100–107, 2006.

[76] S. Salinthone, R. V. Schillace, G. H. Marracci, D. N. Bourdette, and D. W. Carr, "Lipoic acid stimulates cAMP production via the EP2 and EP4 prostanoid receptors and inhibits IFN gamma synthesis and cellular cytotoxicity in NK cells," *Journal of Neuroimmunology*, vol. 199, no. 1-2, pp. 46–55, 2008.

[77] S. Salinthone, R. V. Schillace, C. Tsang, J. W. Regan, D. N. Bourdette, and D. W. Carr, "Lipoic acid stimulates cAMP production via G protein-coupled receptor-dependent and -independent mechanisms," *The Journal of Nutritional Biochemistry*, vol. 22, no. 7, pp. 681–690, 2011.

[78] J. C. Roder and M. Klein, "Target-effector interaction in the natural killer cell system. IV. Modulation by cyclic nucleotides," *The Journal of Immunology*, vol. 123, no. 6, pp. 2785–2790, 1979.

[79] P. C. Joshi, X. Zhou, M. Cuchens, and Q. Jones, "Prostaglandin E2 suppressed IL-15-mediated human NK cell function through down-regulation of common γ-chain," *The Journal of Immunology*, vol. 166, no. 2, pp. 885–891, 2001.

[80] A. Van Der Goes, J. Brouwer, K. Hoekstra, D. Roos, T. K. Van Den Berg, and C. D. Dijkstra, "Reactive oxygen species are required for the phagocytosis of myelin by macrophages," *Journal of Neuroimmunology*, vol. 92, no. 1-2, pp. 67–75, 1998.

[81] J. A. Deiuliis, T. Kampfrath, Z. Ying, A. Maiseyeu, and S. Rajagopalan, "Lipoic acid attenuates innate immune infiltration and activation in the visceral adipose tissue of obese insulin resistant mice," *Lipids*, vol. 46, no. 11, pp. 1021–1032, 2011.

[82] A. K. Kiemer, C. Müller, and A. M. Vollmar, "Inhibition of LPS-induced nitric oxide and TNF-α production by α-lipoic acid in rat Kupffer cells and in RAW 264.7 murine macrophages," *Immunology & Cell Biology*, vol. 80, no. 6, pp. 550–557, 2002.

[83] H. A. Lee and D. A. Hughes, "Alpha-lipoic acid modulates NF-κB activity in human monocytic cells by direct interaction with DNA," *Experimental Gerontology*, vol. 37, no. 2-3, pp. 401–410, 2002.

[84] T. Kunt, T. Forst, A. Wilhelm et al., "α-Lipoic acid reduces expression of vascular cell adhesion molecule-1 and endothelial adhesion of human monocytes after stimulation with advanced glycation end products," *Clinical Science*, vol. 96, no. 1, pp. 75–82, 1999.

[85] R. M. Ogborne, S. A. Rushworth, and M. A. O'Connell, "α-lipoic acid-induced heme oxygenase-1 expression is mediated by nuclear factor erythroid 2-related factor 2 and p38 mitogen-activated protein kinase in human monocytic cells," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 25, no. 10, pp. 2100–2105, 2005.

[86] A. Perl, P. Gergely Jr., G. Nagy, A. Koncz, and K. Banki, "Mitochondrial hyperpolarization: A checkpoint of T-cell life, death and autoimmunity," *Trends in Immunology*, vol. 25, no. 7, pp. 360–367, 2004.

[87] A. P. Halestrap, "What is the mitochondrial permeability transition pore?" *Journal of Molecular and Cellular Cardiology*, vol. 46, no. 6, pp. 821–831, 2009.

[88] D. Siemen and M. Ziemer, "What is the nature of the mitochondrial permeability transition pore and What is it Not?" *IUBMB Life*, vol. 65, no. 3, pp. 255–262, 2013.

[89] G. Nagy, A. Koncz, D. Fernandez, and A. Perl, "Nitric oxide, mitochondrial hyperpolarization, and T cell activation," *Free Radical Biology & Medicine*, vol. 42, no. 11, pp. 1625–1631, 2007.

[90] J. J. Cohen, R. C. Duke, V. A. Fadok, and K. S. Sellins, "Apoptosis and programmed cell death in immunity," *Annual Review of Immunology*, vol. 10, pp. 267–293, 1992.

[91] B. Sauter, M. L. Albert, L. Francisco, M. Larsson, S. Somersan, and N. Bhardwaj, "Consequences of cell death: exposure to necrotic tumor cells, but not primary tissue cells or apoptotic cells, induces the maturation of immunostimulatory dendritic cells," *The Journal of Experimental Medicine*, vol. 191, no. 3, pp. 423–433, 2000.

[92] P. Gergely Jr., C. Grossman, B. Niland et al., "Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus," *Arthritis & Rheumatism*, vol. 46, no. 1, pp. 175–190, 2002.

[93] N. Saris, A. Karjalainen, V. Teplova, and K. Lindros, "The stimulation of the mitochondrial permeability transition by dihydrolipoate and α-lipoate," *Biochemistry and Molecular Biology International*, vol. 44, no. 1, pp. 127–134, 1998.

[94] P. Gergely Jr., B. Niland, N. Gonchoroff, R. Pullmann Jr., P. E. Phillips, and A. Perl, "Persistent mitochondrial hyperpolarization, increased reactive oxygen intermediate production, and cytoplasmic alkalinization characterize altered IL-10 signaling in patients with systemic lupus erythematosus," *The Journal of Immunology*, vol. 169, no. 2, pp. 1092–1101, 2002.

[95] W. Emlen, J. Niebur, and R. Kadera, "Accelerated *in vitro* apoptosis of lymphocytes from patients with systemic lupus erythematosus," *The Journal of Immunology*, vol. 152, no. 7, pp. 3685–3692, 1994.

[96] L. A. Casciola-Rosen, G. Anhalt, and A. Rosen, "Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes," *The Journal of Experimental Medicine*, vol. 179, no. 4, pp. 1317–1330, 1994.

[97] L. Georgescu, R. K. Vakkalanka, K. B. Elkon, and M. K. Crow, "Interleukin-10 promotes activation-induced cell death of SLE lymphocytes mediated by Fas ligand," *The Journal of Clinical Investigation*, vol. 100, no. 10, pp. 2622–2633, 1997.

[98] L. Llorente, W. Zou, Y. Levy et al., "Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus," *The Journal of Experimental Medicine*, vol. 181, no. 3, pp. 839–844, 1995.

[99] H. Peng, W. Wang, M. Zhou, R. Li, H.-F. Pan, and D.-Q. Ye, "Role of interleukin-10 and interleukin-10 receptor in systemic lupus erythematosus," *Clinical Rheumatology*, vol. 32, no. 9, pp. 1255–1266, 2013.

[100] H. Moini, L. Packer, and N.-E. L. Saris, "Antioxidant and prooxidant activities of α-lipoic acid and dihydrolipoic acid," *Toxicology and Applied Pharmacology*, vol. 182, no. 1, pp. 84–90, 2002.

[101] B. G. Yipp and P. Kubes, "NETosis: how vital is it?" *Blood*, vol. 122, no. 16, pp. 2784–2794, 2013.

[102] E. Villanueva, S. Yalavarthi, C. C. Berthier et al., "Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus," *The Journal of Immunology*, vol. 187, no. 1, pp. 538–552, 2011.

[103] A. Hakkim, B. G. Fürnrohr, K. Amann et al., "Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 107, no. 21, pp. 9813–9818, 2010.

[104] N. Dwivedi and M. Radic, "Citrullination of autoantigens implicates NETosis in the induction of autoimmunity," *Annals of the Rheumatic Diseases*, vol. 73, no. 3, pp. 483–491, 2014.

[105] R. Khandpur, C. Carmona-Rivera, A. Vivekanandan-Giri et al., "NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis," *Science Translational Medicine*, vol. 5, no. 178, Article ID 178ra40, 2013.

[106] A. M. Lin, C. J. Rubin, R. Khandpur et al., "Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis," *The Journal of Immunology*, vol. 187, no. 1, pp. 490–500, 2011.

[107] K. Kessenbrock, M. Krumbholz, U. Schönermarck et al., "Netting neutrophils in autoimmune small-vessel vasculitis," *Nature Medicine*, vol. 15, no. 6, pp. 623–625, 2009.

[108] T. A. Fuchs, A. Brill, D. Duerschmied et al., "Extracellular DNA traps promote thrombosis," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 107, no. 36, pp. 15880–15885, 2010.

[109] E. Darrah and F. Andrade, "NETs: the missing link between cell death and systemic autoimmune diseases?" *Frontiers in Immunology*, vol. 3, p. 428, 2013.

[110] S. Hahn, S. Giaglis, C. S. Chowdury, I. Hösli, and P. Hasler, "Modulation of neutrophil NETosis: interplay between infectious agents and underlying host physiology," *Seminars in Immunopathology*, vol. 35, no. 4, pp. 439–453, 2013.

[111] Q. Remijsen, T. V. Berghe, E. Wirawan et al., "Neutrophil extracellular trap cell death requires both autophagy and superoxide generation," *Cell Research*, vol. 21, no. 2, pp. 290–304, 2011.

[112] A. Itakura and O. J. T. McCarty, "Pivotal role for the mTOR pathway in the formation of neutrophil extracellular traps via regulation of autophagy," *American Journal of Physiology-Cell Physiology*, vol. 305, no. 3, pp. C348–C354, 2013.

[113] A. M. McInturff, M. J. Cody, E. A. Elliott et al., "Mammalian target of rapamycin regulates neutrophil extracellular trap formation via induction of hypoxia-inducible factor 1 ," *Blood*, vol. 120, no. 15, pp. 3118–3125, 2012.

[114] D. Fratantonio, A. Speciale, M. S. Molonia et al., "Alpha-lipoic acid, but not di-hydrolipoic acid, activates Nrf2 response in primary human umbilical-vein endothelial cells and protects against TNF-α induced endothelium dysfunction," *Archives of Biochemistry and Biophysics*, vol. 655, pp. 18–25, 2018.

[115] Q. Ma, "Role of Nrf2 in oxidative stress and toxicity," *Annual Review of Pharmacology and Toxicology*, vol. 53, pp. 401–426, 2013.

[116] K. Yoh, K. Itoh, A. Enomoto et al., "Nrf2-deficient female mice develop lupus-like autoimmune nephritis," *Kidney International*, vol. 60, no. 4, pp. 1343–1353, 2001.

[117] E. J. Córdova, R. Velázquez-Cruz, F. Centeno, V. Baca, and L. Orozco, "The NRF2 gene variant, -653G/A, is associated with nephritis in childhood-onset systemic lupus erythematosus," *Lupus*, vol. 19, no. 10, pp. 1237–1242, 2010.

[118] J.-M. Lee, K. Chan, Y. W. Kan, and J. A. Johnson, "Targeted disruption of Nrf2 causes regenerative immune-mediated hemolytic anemia," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 101, no. 26, pp. 9751–9756, 2004.

[119] D. A. Johnson, S. Amirahmadi, C. Ward, Z. Fabry, and J. A. Johnson, "The absence of the pro-antioxidant transcription factor Nrf2 exacerbates experimental autoimmune encephalomyelitis," *Toxicological Sciences*, vol. 114, no. 2, pp. 237–246, 2009.

[120] T. K. Pareek, A. Belkadi, S. Kesavapany et al., "Triterpenoid modulation of IL-17 and Nrf-2 expression ameliorates neuroinflammation and promotes remyelination in autoimmune encephalomyelitis," *Scientific Reports*, vol. 1, no. 1, 2011.

[121] C. K. Sen, S. Roy, and L. Packer, "Fas mediated apoptosis of human Jurkat T-cells: Intracellular events and potentiation by redox-active α-lipoic acid," *Cell Death & Differentiation*, vol. 6, no. 5, pp. 481–491, 1999.