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Dilip Shah
Center for Translational Medicine, Thomas Jefferson University

Swapan K. Nath
Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation

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GLUTATHIONE: A POSSIBLE LINK TO AUTOPHAGY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Dilip Shah and Swapan K. Nath

Center for Translational Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA
Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA

Increased free radical formation and altered redox state are of fundamental importance in the pathogenesis of autoimmune diseases including Systemic Lupus Erythematosus (SLE). Free radicals are mainly derived from oxygen (Reactive Oxygen Species/ROS) and nitrogen (Reactive Nitrogen Species/RNS) at mitochondria, cellular membranes and the endoplasmic reticulum membrane as physiological responses to a variety of internal and external stress. At low levels, they act as signalling molecules and at high levels, they damage organelles, particularly the mitochondria and causes irreversible damage to lipids, DNA and proteins, thus provoking cell death through several modes, including apoptosis and necrosis. In the last 2 decades, there has been substantial progress in understanding the mechanism of oxidative stress in pathogenesis of SLE and level of intracellular glutathione has been regarded as a checkpoint of oxidative stress. Decreased intracellular glutathione levels in the various blood components, including total lymphocytes and its subsets (CD4, CD8 T cell) are strongly associated with disease severity and linked to increase Th1/Th2 cytokine imbalance and lymphocyte apoptosis in SLE patients. We have shown that changes in the intracellular redox environment of cells, through oxygen-derived free radical production known as oxidative stress, have been reported to be critical for cellular immune dysfunction, activation of apoptotic enzymes and apoptosis. Decreased intracellular glutathione levels in the various blood components, including total lymphocytes and its subsets (CD4, CD8 T cell) are strongly associated with disease severity and linked to increase Th1/Th2 cytokine imbalance and lymphocyte apoptosis in SLE patients. 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inhibition of autophagy by blocking mTOR signalling has been suggested as a novel treatment target in this disease.

Importantly, Lai et al. (2012) has shown that blockade of mTOR with supplementation of NAC reversing glutathione depletion and improving disease activity and fatigue in patients with SLE. NAC treatment promotes expansion of CD4+CD25+FOXP3+ T-cell subsets, inhibit anti-DNA antibody production. Indeed, NAC reversed the expansion of CD4+CD8+ T cells, which exhibited the most prominent mTOR activation before treatment with NAC and had been deemed responsible for promoting anti-DNA autoantibody production by B cells. They showed that NAC acts as a sensor of ΔΨm, mTOR governs T-cell signalling events implicated in the pathogenesis (Lai et al., 2012). Since, activation of autophagy has been considered to be principally regulated by mTOR pathway and supplementation of NAC block mTOR signalling in SLE patients. It will be intriguing to study the effect of therapeutic supplement of NAC on autophagy in animal models of Lupus and in SLE patients. Such kind of studies encourage to explore more therapeutic potential of NAC which might prove to provide an inexpensive and significant alternative therapy in SLE.

Conflict of Interest: Authors declare no conflict of interest.

REFERENCES


