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9-3-2014

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Recommended Citation

Shah, Dilip and Nath, Swapan K., "Glutathione: A possible link to autophagy in systemic lupus erythematosus" (2014). *Center for Translational Medicine Faculty Papers*. Paper 31.

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GLUTATHIONE: A POSSIBLE LINK TO AUTOPHAGY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Increased free radical formation and altered redox state are of fundamental importance in the pathogenesis of autoimmune diseases including Systemic Lupus Erythematos (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 (Shah *et al.*, 2011b). 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 (Shah *et al.*, 2013). 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 (Shah *et al.*, 2014). Altered signal transduction; mTOR is activated by relative depletion of glutathione and supplementation of N-Acetyl Cysteine (NAC), a precursor of glutathione, replenishes intracellular glutathione and inhibits mTOR signaling and diminished oxidative stress mediated damage in SLE (Fernandez and Perl, 2010). Management of disease through supplement of NAC and rapamycin has been showing promising therapy in SLE patients. Recently, several lines of evidence from genetic, cell biology and lupus animal model studies suggests a pivotal role of autophagy in mediating the occurrence and development of SLE (Alessandri *et al.*, 2012). Interestingly, autophagy is regulated by mTOR pathway and mTOR is activated by relative depletion of glutathione. Thus, redox signaling may provide a link between altered autophagy and depletion of glutathione and autophagy regulation by replenishment of intracellular glutathione may have a therapeutic intervention for the management of disease.

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 (Shah *et al.*, 2010), activation of apoptotic enzymes and apoptosis (Shah *et al.*, 2013). 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 (Shah *et al.*, 2011a). Similarly, Tewthanom *et al.* (2009) reported that administration of NAC may be beneficial in mild SLE patients in terms of decreasing lipid peroxidation.

Lai *et al.* (2012) demonstrates that GSH regulates the elevation of mitochondrial transmembrane potential ($\Delta\Psi_m$) or Mitochondrial Hyperpolarization (MHP), which in turn activates the mammalian Target Of Rapamycin (mTOR) in lupus T cells. mTOR skews cell death signal processing, modulates T-cell differentiation and, in particular, inhibits the development of CD4⁺/CD25⁺/Foxp3⁺ regulatory T cells which are deficient in patients with active SLE. Nevertheless, studies of Fernandez and Perl (2010; Lai *et al.*, 2012) are certainly important as they suggest the blockade of mTOR with rapamycin and NAC improves lupus disease activity.

Over recent years, perturbation in autophagy has been implicated in a number of diseases, including systemic lupus erythematosus (Alessandri *et al.*, 2012). Towns *et al.* (2005) found that serum factors, likely autoantibodies, purified from patients with SLE were able to induce autophagy in neuroblastoma cell lines, providing a further link between autophagy and SLE. Accordingly, several other groups have reported the activated autophagy pathway in T and B lymphocytes as a mechanism for survival of autoreactive T and B lymphocytes. The

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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 $\Delta\Psi_m$, 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.

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