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Redox sensor NPGPx restrains ZAP70 recruitment to lipid rafts for modulating TCR responses and autoimmunity

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Excessive T cell activation can provoke inflammation and autoimmunity in mammalians. Therefore, precise elucidation of the T cell regulatory mechanism is necessitated for therapeutic treatment in autoimmune diseases. Emerging evidences demonstrated that the functional redox machineries are imperative for maintaining the intact T cell responses. The tyrosine kinase, ζ-chain-associated protein of 70 kDa (ZAP70), is essential for T cell development and activation. However, it remains elusive whether a direct redox regulation affects ZAP70 activity upon TCR stimulation. Here, we report that deficiency of non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase (NPGPx), a redox sensor, resulted in T cell hyperactivation and elevated autoimmune development in mice. Through unbiased proteomic approaches, ZAP70 is identified as the key interacting protein of NPGPx through disulfide bonding. NPGPx is activated by TCR-induced ROS and subsequently binds to a specific cysteine residue of ZAP70 to restrain its recruitment to membrane lipid rafts. The retention of ZAP70 in cytosol by NPGPx diminishes its kinase activity and subdues TCR responses. These results elucidate a delicate redox mechanism that NPGPx acts as a modulator to curb ZAP70 functions in maintaining T cell homeostasis and preventing autoimmunity. Moreover, we also observed that NPGPx expression was downregulated in the T cells as well as in the PBMC of SLE patients compared with healthy controls. Therefore, this novel redox modulation of ZAP70 by NPGPx casts new light on the intimate link between redox regulation and TCR responses, providing a potential therapeutic window for treating autoimmune diseases.

