KEAP1

“Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex”.

Keap1 has been shown to interact with Nrf2, a master regulator of the antioxidant response, which is important for the amelioration of oxidative stress.

Under quiescent conditions, Nrf2 is anchored in the cytoplasm through binding to Keap1, which, in turn, facilitates the ubiquitination and subsequent proteolysis of Nrf2. Such sequestration and further degradation of Nrf2 in the cytoplasm are mechanisms for the repressive effects of Keap1 on Nrf2. Keap1 is not only a tumor suppressor gene, but also a metastasis suppressor gene.

Oxidative stress is a major contributor to macrovascular diabetes mellitus complications (MCD). Nuclear factor (erythroid-derived 2)-like 2 (NRF2) governs cellular antioxidant defence system by activating the transcription of various antioxidant genes, combating diabetes-induced oxidative stress. Accumulating experimental evidence has demonstrated that NRF2 activation protects against MCD.

Structural inhibition of Kelch-like ECH-associated protein 1 (KEAP1) is a canonical way to activate NRF2. More recently, novel approaches, such as activation of the Nfe2l2 gene transcription, decreasing KEAP1 protein level by microRNA-induced degradation of Keap1 mRNA, prevention of proteasomal degradation of NRF2 protein and modulation of other upstream regulators of NRF2, have emerged in the prevention of MCD.

A review of Wu et al. provided a brief introduction of the pathophysiology of MCD and the role of oxidative stress in the pathogenesis of MCD. By reviewing previous work on the activation of NRF2 in MCD, we summarize strategies to activate NRF2, providing clues for the future intervention of MCD. Controversies over NRF2 activation and future perspectives are also provided in this review [1].

1)
Wu J, Sun X, Jiang Z, et al. Protective role of NRF2 in macrovascular complications of diabetes [published online ahead of print, 2020 Jul 6]. J Cell Mol Med. 2020;10.1111/jcmm.15583. doi:10.1111/jcmm.15583