KEAP1/NRF2 AS A DRUGGABLE TARGET

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Disrupted redox and protein homeostasis and chronic inflammation are characteristic features of most human pathologies. Transcription factor NF-E2 p45-related factor 2 (Nrf2) and its partner, Kelch-like ECH-associated protein 1 (Keap1), regulate the expression of large networks of genes encoding proteins that provide protection against damage by oxidants and pro-inflammatory agents, allowing adaptation and survival under various conditions of stress. Most pharmacological activators of Nrf2 (termed inducers) are electrophiles that target discreet highly reactive sensor cysteines within Keap1, impairing its repressor function, and allowing for Nrf2 accumulation and enhanced transcription of its target genes. The Keap1/Nrf2 regulatory network includes drug metabolizing, antioxidant, anti-inflammatory, metabolic enzymes, as well as proteasome subunits and autophagy-related proteins and thus Nrf2 has a critical role in the maintenance of the cellular redox and protein homeostasis, and in the resolution of inflammation. Pharmacological Nrf2 activation with electrophilic inducers has comprehensive and long-lasting protective effects in cell culture and animal models of numerous human pathologies – from liver disease to neurological conditions, and has shown benefits in clinical trials. Non-electrophilic inducers that disrupt the Keap1-Nrf2 protein-protein interactions are also emerging.