DEPARTMENT OF CHEMISTRY & CHEMICAL BIOLOGY

Targeting NRF2 for disease prevention and intervention

A LECTURE BY:

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The cellular defense response regulated by Nrf2 is crucial in maintaining cellular homeostasis and human health. Dysregulation of the Nrf2 pathway has been found in many human diseases including cancer. Through detailed mechanistic investigations, Keap1 has been revealed as the primary regulator of Nrf2 by functioning as a substrate adaptor of the Keap1-Cul3-Rbx1 E3 ubiquitin ligase. Subsequent to Keap1-Cul3-Rbx1, other E3 ubiquitin ligases have been identified. To illustrate this point, recently we identified Hrd1, an endoplasmic reticulum integral membrane protein, as another E3 ubiquitin ligase for Nrf2. In the first part of my talk, the molecular mechanisms of Nrf2 regulation will be discussed.

The physiological role of Nrf2 has been well studied. In normal cells, activation of Nrf2 by chemopreventive compounds confers protection. Therefore, many efforts have been geared to identify small synthetic molecules or natural products that inactivate Keap1-mediated ubiquitylation of Nrf2, thus activating the Nrf2 pathway. These Nrf2 activators have proven to be useful in protecting against many diseases in rodent models and in human clinical trials. However, the “dark-side” of Nrf2 has also been realized since 2008, that is, cancer cells have high constitutive expression of Nrf2 largely due to somatic mutations in Keap1, indicating that Nrf2 inhibitors can be developed into chemotherapy drugs to overcome chemoresistance and to slow down tumor progression. In this part of the talk, therapeutic development of Nrf2 modulators for disease prevention and intervention will be discussed.