A Multidisciplinary Approach to Understanding How DPP3 Catalytic Activity Influences Its Interaction with Keap1 and Vice Versa

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The Keap1–Nrf2 (Kelch-like ECH-associated protein 1 – Nuclear factor erythroid 2-related factor 2) signaling pathway is the main regulator of the oxidative and electrophilic stress response in the cell [1]. More than a decade ago, dipeptidyl peptidase 3 (DPP3), a ubiquitously expressed zinc-dependent exopeptidase, was identified as a component of the Keap1 protein interaction network, suggesting its involvement in cellular responses to oxidative stress [2]. By binding to the Kelch domain of Keap1, DPP3 disrupts the Keap1–Nrf2 regulatory pathway, thereby preventing Keap1-mediated ubiquitination and degradation of Nrf2 and promoting Nrf2-dependent transcription of cytoprotective genes. While Nrf2 activation is protective in normal cells, its constitutive upregulation in cancer cells promotes evasion of oxidative stress, resistance to apoptosis, and increased proliferation, a phenomenon often referred to as the "dark side" of Nrf2 signaling.

Although DPP3 catalytic activity is not required for its interaction with Keap1, the potential impact of peptidase inhibition on this interaction has not yet been investigated. The aim of this study was to examine how enzymatic inactivation of DPP3 influences its interaction with the Kelch domain of Keap1, and vice versa, using a combination of experimental approaches (isothermal titration calorimetry and kinetic analyses) and computational methods (standard and adaptive steered molecular dynamic simulations).

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References:

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