EFFECT OF CANCER MUTATIONS ON DPP III – KEAP1 BINDING

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The NRF2-KEAP1 signaling pathway plays a critical role in regulating the antioxidative stress response in cells.[1] KEAP1 acts as the main cellular sensor of oxidative stress and as a repressor of the transcription factor NRF2, which is responsible for the transcription of antioxidant response element genes (ARE). Therefore, the release of NRF2 from KEAP1 and its translocation to the nucleus promote cell survival. However, this pathway is often deregulated in cancer cells, which may lead to chemotherapy resistance.[2] It has been reported that under oxidative stress conditions, dipeptidyl peptidase III (DPP III) can also bind competitively to KEAP1 and induce the release of NRF2.[3] This interaction occurs mainly between the ETGE binding motif in the flexible loop of DPP III and the Kelch domain of KEAP1. Mutations of DPP III found in cancer tissues and reported in the cBioPortal for Cancer Genomics were selected to investigate their potential to induce structural and functional changes in DPP III. We were particularly interested in identifying mutations that affect binding between DPP III and KEAP1 and potentially modulate oxidative stress response and chemotherapy resistance in cancer cells. In this study, we combined different experimental and computational approaches and identified several highly relevant mutations for DPP III – KEAP1 binding.[4]

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