Increased vulnerability of human NQO1 towards cancer-associated inactivation through divergent evolution

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Abstract

Human NAD(P)H:quinone oxidoreductase 1 (NQO1) is a FAD-dependent enzyme involved in the antioxidant defense, activation of cancer pro-drugs and stabilization of oncosuppressors such as p53 and p73 [1]. A single nucleotide and cancer-associated polymorphism in NQO1 (P187S) causes its loss-of-function due to inactivation and destabilization of the enzyme by altering the dynamics of the FAD binding site and the C-terminal domain [2, 3, 4]. NQO1 is also a paradigm of the relationship between human flavoproteome stability and the bioavailability of flavin precursors [5].

Our experimental and structural analyses support that cancer-associated vulnerability of NQO1 towards inactivation is linked to divergence of several stabilizing amino acids along primate evolution. Accordingly, we identify and characterize reverse mutations that protect the P187S polymorphism towards inactivation in vitro and inside cells. The protective role of these mutations is futher discussed in the context of a structural and thermodynamic mechanism of rescue involving a population-shift in the conformational ensemble of apo-P187S.

References

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