Title

P450 Oxidoreductase Dysregulation: A Negative Prognostic Marker and Somatic Target in High-Mortality Cancers

Co-Authors and affiliations

Isabel S. Barata a,b,c; Amit V. Pandey a,b

a Translational Hormone Research Program, Department of Biomedical Research, University of Bern, Bern, Switzerland.

b Pediatric Endocrinology, Diabetology and Metabolism, University Children's Hospital, Bern, Switzerland.

c Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland.

Background: Cytochrome P450 oxidoreductase (POR) is the master regulator for activities of microsomal P450 enzymes, governing critical pathways in steroidogenesis and drug metabolism. However, the specific role of POR dysregulation and somatic variation in cancer progression and patient outcome remains poorly defined. This study aimed to identify which cancers are vulnerable to POR dysregulation and to pinpoint the specific somatic mutations that may act as oncogenic drivers.

Methods: We conducted a comprehensive *in silico* investigation by first analyzing POR expression across cancer types using TCGA and GTEx data and correlating expression with patient outcomes. Secondly, we analysed all *POR* variants reported in the Catalogue of Somatic Mutations in Cancer (COSMIC), filtering them against gnomAD and predicting *in silico* pathogenicity using general and cancer-specific predictors (CRAVAT, CScape).

Results: Our expression analysis revealed that POR is highly overexpressed in glioblastoma (GBM) and pancreatic adenocarcinoma, two of the most treatment-resistant cancers. Critically, high POR expression levels in GBM patients correlate with significantly lower overall survival.

We identified 174 POR missense variants in COSMIC database, including 63 variants absent from population databases (gnomAD) and 17 located in critical cofactor-binding domains. Our pathogenicity pipeline ultimately prioritized a "hit list" of 23 distinct variants, plus three recurrent mutations, as high-confidence oncogenic and disease-driver mutations.

Impact & Conclusion: This work elevates POR from a general metabolic enzyme to a clinically relevant, negative prognostic factor in high-mortality cancers like GBM. We provide the first comprehensive "hit list" of 23 somatic *POR* driver mutations.