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IDENTIFICATION AND VALIDATION OF THE RESPONSE ELEMENTS FOR THE P53 FAMILY MEMBERS IN THE GENE ENCODING THE MITOCHONDRIAL TUMOR SUPPRESSOR PROLINE DEHYDROGENASE

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p53 regulates cell cycle arrest, apoptosis, autophagy and other processes in response to various stresses. A recent work has discovered additional functions for this tumor suppressor gene, i.e. the control of cellular metabolism and energy production. p53 was previously shown to markedly upregulate the metabolic enzyme Proline dehydrogenase (PRODH), which catalyzes the first step in proline degradation and contributes to p53 function inducing ROS mediated apoptosis in response to genotoxic stress. Characterization of the p53-REs in PRODH, as well as determination of the inducibility by the other p53 family members is critical to understanding its regulation in normal or pathological conditions.

Induction of endogenous PRODH in response to genotoxic damage or p53 family members overexpression was observed in mammalian cell lines. Bioinformatic analysis identified eight putative p53 consensus sequences in the *PRODH* gene, located both in the promoter and intronic regions. We selected five REs whose sequences showed higher affinity for p53 and correspondent yeast reporter strains were created using the "*delitto perfetto*" approach. A well established yeast transactivation assay was applied to analyze the induction of the reporter gene luciferase through the specific PRODH p53RE upon modulated expression of p53, p63 and p73 proteins. Furthermore, chromatin immunoprecipitation (ChIP) assays were carried out in human tumor cell lines.

Three of the p53-REs responded to p53 and to the other members of the family, although at different extent. These results will help to elucidate fine regulation of PRODH, a protein involved in many metabolic pathways often deregulated in cancer.