

ABSTRACT

The mevalonate pathway is an important metabolic pathway implicated in multiple aspects of tumorigenesis. In this study, I provided evidences about genetic and pharmacologic perturbation of p53, which directly influenced expression of mevalonate pathway enzymes, including 3'-Hydroxy-3'-Methylglutaryl - CoenzymeA Reductase, Mevalonate Kinase, Farnesyl Diphosphate Synthase, Farnesyl Diphosphate Farnesyl Transferase 1. Three different cell lines have been considered, U343 MG (U343) and U251 MG (U251) glioma cells, both classified as IV grade glioblastoma cell lines, with two different malignancy grade, and Normal Human Astrocytes (NHA), their normal counterpart.

In particular, NHA and U343 cells have wild type p53 (wtp53) while U251 bearing mutation (R273H)p53. This mutation affects p53 DNA binding site, preventing transcriptional function of the protein.

Different basal expression level of the mevalonate pathway's genes have found among the different cell lines considered and I hypothesized that this could be ascribable to p53 mutation status and function. Indeed, I observed that functional and active p53 recognized specific p53 Responsive Elements (p53REs) present in MVA enzymes gene-sequences. p53 bound to these regions correlated with increased transcription levels of mentioned genes and such effect has abolished in cells bearing mut(R273H)p53 or by site-directed mutagenesis of p53REs.

These new findings expose another facet of p53 functions, unrelated to tumor suppression, and render it a novel regulator of mevalonate pathway providing insight into the role of this pathway in cancer progression.