Compounds that Facilitate the Reactivation of Mutant P53 into Wildtype

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The tumor suppressor protein p53, also known as the “guardian of the genome,” is known for its various protective functions in the cell ranging from cell cycle regulation to apoptosis. The protein is inactivated in almost all human cancers, and in more than 50 percent of cancers, TP53 is mutated(with 90 percent of the mutations encoding for missense mutant proteins). These mutations, which occur in the p53 DNA binding domain (DBD), cause the protein to be less thermodynamically stable at physiological temperature and incapable of binding effectively to DNA to transcribe genes essential for tumor suppressor activity. Therefore, the reactivation of mutant p53 into wildtype remains a promising solution for many cancer patients due to renewed p53-dependent tumor suppressor activity. A previous study indicates that substituted quinolines have anti-cancer effects on human breast cancer cells as they stimulate gap junction activity and decrease alpha survivin expression. In order to investigate whether these quinolines have the potential to reactivate mutant p53, I used two genetically engineered tumor cell lines, SF-295 GFP (glioblastoma) and DLD-1 GFP (colon cancer), harboring mutant p53 for a drug screen. The cell lines were initially made by transfection with pGF-p53-mCMV-EF1a-Puro Lenti virus vector so that the screen could be performed using a GFP (green fluorescent protein) assay, whereby the degree of reactivation directly correlates to the amount of fluorescence. One compound in particular demonstrated an ability to significantly reactivate mutant p53 into wildtype in glioblastoma cells. Hence, this compound is a promising solution for glioblastoma cancer therapy and could potentially serve as a candidate for drug development.