INVESTIGATING THE ROLE OF P53 IN CASPASE-2-MEDIATED CELL CYCLE REGULATION AND APOPTOSIS IN THE PREVENTION OF GENOMIC INSTABILITY.

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Background: The protease caspase-2 and the transcription factor p53 are involved in the induction of apoptosis and cell cycle arrest and both are classified as tumor suppressors. Although less well known than p53, the role of caspase-2 as a tumor suppressor has been confirmed in mouse models, and in human cancers. However, unlike p53, the mechanisms underlying caspase-2 activation and function are poorly understood. In vitro studies suggest an interaction between these proteins. To investigate the connection between these two proteins, we treated cell lines with different p53 status with G1 or S phase inducers. After treatment, we used a fluorescent reporter developed in our lab to show that caspase-2 was activated only following G1 phase arrest in the cells without p53 and only following S phase arrest in the cells with p53. Thus, activation of caspase-2 is regulated by p53 according to the stage of the cell cycle. However, the functions of caspase-2 that respond to arrest at different phases of the cell cycle in the presence and absence of p53 are unknown. We hypothesize that caspase-2 activation is determined by p53 in response to cell cycle arrest resulting in apoptosis or cell cycle regulation to protect against the accumulation of DNA damage

Materials/Methods: To determine the functional outcomes of this interaction, we treated HCT116, HCT116 Casp2-/-, HCT116 TP53-/-, and HCT116 Casp2-/-/TP53-/- with a G1 inducer, and determined cell cycle arrest and recovery under these conditions. In addition, we treated the aforementioned cell lines with the DNA damage inducer camptothecin (CPT), and assessed DNA damage by measuring pH2ax and activation of caspase-2, and p53 by western blot

Results: We found that the absence of both proteins resulted in a bypass of a cell cycle checkpoint shown by the increase number of cells in G2 in the double knockout. In addition, the absence of both proteins resulted in a decrease of pH2AX after treatment with CPT suggesting an impairment in the DNA damage response. Lastly, we observed an increase in the activation of caspase-2 in the absence of p53, and vice versa

Conclusions: These result suggest that caspase-2, and p53 might be working in independent pathways, which are activated to compensate for the absence of each other. Overall, understanding the functional relationship between p53 and caspase-2 will be important for identifying new therapeutic targets

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