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The role of MYC-EGR1 Pathway in Colorectal Cancer Development and its Relationship to Wnt Signaling

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Colorectal tumors show high levels of Wnt pathway activity, most often due to an initiating mutation in critical Wnt pathway components. Wnt pathway activation leads to β-catenin-driven expression of genes that generally stimulate cell cycle progression. One such Wnt pathway target gene is MYC, a well described oncogene involved in many cancers, including colorectal. MYC is known to stimulate proliferation but in certain cellular contexts, can stimulate apoptosis by stimulating the expression of EGR1. This is termed a noncanonical MYC target gene because EGR1 lacks typical MYC binding elements in its promoter. This unique MYC-EGR1 pathway is activated in specific cellular contexts, lacking appropriate p53 activity, often associated with colorectal tumorigenesis. In these experiments, sister HCT116 human colorectal cancer cell lines were treated with shRNA to employ RNA interference targeting MYC or EGR1 to assess the roles these genes might play in colorectal cancer cell proliferation. β-catenin wildtype and mutant HCT116 cells were treated with a non-targeting (scramble, control) shRNA, MYC shRNA, and EGR1 shRNA to specifically and temporarily target the expression of these gene. After transduction, cultures were grown, and cells were counted to assess proliferation of these cell lines with the specific interruptions in gene expression. The goal of our experiment was to evaluate the proliferation of these cells after transduction with targeted shRNAs and assess any impact that MYC and EGR1 have on proliferation in this cellular context. As the MYC-EGR1 pathway has also been shown to stimulate apoptosis in cells lacking functional p53, we also performed an apoptosis analysis and evaluated the propensity of the cell lines to

apoptosis. These experiments give further insight into the role of the MYC-EGR1 pathway in colorectal cancer development and its relationship in to the Wnt signaling pathway in colorectal cancer cells.