Investigation of HCC Development Following Senescence in UHRF1 Overexpressing Zebrafish Livers

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide. UHRF1, a gene essential for DNA methylation, is highly expressed in HCC patients. Transgenic zebrafish that overexpress human UHRF1 have been utilized to confirm that UHRF1 overexpression drives HCC. In the current zebrafish model of the cancer, the level of UHRF1 overexpression is highest at 5 days post fertilization (dpf) and decreases thereafter, which correlates with the onset of senescence at 5 dpf and tumor development by 15 dpf. The purpose of this study was to investigate the transition from senescence to tumorigenesis. The goal of first part of the study was to determine the length of the senescence stage. Zebrafish were treated with BrdU, a synthetic nucleoside used to tag cells that are dividing, at 3 dpf; livers of these treated zebrafish were analyzed by immunofluorescence at 3, 5, 8, 10 and 12 dpf. The senescence stage was found to last from 5 to 10 dpf. The second part of this study sought to investigate whether any senescent hepatocytes re-enter the cell cycle. Zebrafish were treated with BrdU at 3 dpf and then EdU, a second cell division marker, at 9, 10 or 12 dpf. Analysis of zebrafish livers at 9, 10 and 12 dpf revealed that some previously senescent hepatocytes were dividing, demonstrating, for the first time in an animal model, that senescence escape is possible. Providing unique insight on HCC development, this study will hopefully lead to the discovery of novel treatments for the cancer.

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