

2007 Ohio Student Research Forum

Wright State University
Dayton, OH**TITLE:** An extra copy of the E2F1 allele causes hepatocellular carcinoma**AUTHOR:** Enrique Feria-Arias, Shih Yin Tsai, and Gustavo Leone**MENTOR(S):** Gustavo Leone**INSTITUTION:** Ohio State University (Human Cancer Genetics Department)

E2F family has 8 members identified in mammalian so far, unlike drosophila who have only one activator and one repressor. Previously in our lab, we have already shown that inactivation of E2F activators, including E2F1, 2, and 3, in mouse embryonic fibroblasts (MEFs) eliminates cell proliferation (Wu, *et al.* 2001). This leads us to believe that the activators compensate each other. In our laboratory, we had formerly generated E2F1 and E2F3a double knockout mice ($E2f3a^{-/-} E2f1^{-/-}$) that showed severe mouse postnatal development retardation. This suggests that E2F1 and E2F3a have functional redundancy during mouse development. To further investigate the specificity and redundancy of these two activators, we generated mice with insertion of E2F1 cDNA into E2F3a exon 1 locus, creating E2F1 knockin mice ($E2f3a^{E2f1/E2f1}$). The $E2f3a^{E2f1/E2f1}$ construct can express E2F1 under E2f3a promoter regulation, but disrupts E2F3a protein expression. This $E2f3a^{E2f1/E2f1}$ allele rescued all the development defects that we had observed in $E2F1^{-/-}$ background. However, we discovered that the $E2f3a^{E2f1/E2f1}$ mice developed hepatocellular carcinoma (HCC) around 12 months of age. The extra copies of E2F1 allele seemed to have an oncogenetic function in HCC tumorigenesis. In previous studies, over-expression of E2F1 had been linked with hepatocellular carcinoma (HCC) (Lee, *et al.* 2004). In fact, amplification of chromosome 20q, where the E2F1 gene is located, has been observed in human HCC (Wong, *et al.* 2000). In order to further understand the molecular pathway by which E2F1 causes HCC, we did micro array analysis of the E2F1 knockin mice at 3 months of age, a pre-tumor stage, in order to see which genes were being abnormally expressed early on. We obtained a list of over one hundred genes that were differentially expressed, so to confirm the expression specificity in liver we ran real time PCR (RT-PCR) for some of these overexpressed genes. In conclusion, we have seen that an extra copy of E2F1 allele causes HCC. Furthermore, this extra copy is associated with the abnormal expression pattern of an abundance of genes at an early stage of tumorigenesis.

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