Mouse Model of Advanced Stage Colorectal Cancer Is Created By Clurman Lab

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Colorectal cancer (CRC) is among the most common human cancers and is a leading cause of cancer deaths in developed countries. While colonoscopy screenings readily detect early-stage and curable CRC, patients who present with advanced stage CRC are much more difficult to treat and often die of their disease. Furthermore, few animal models of CRC have been able to recapitulate the characteristics of advanced-stage CRC, such as invasiveness and genomic instability. Existing mouse models, including those with defects in Wnt signaling or DNA repair pathways, develop a high frequency of tumors that localize to the small intestine rather than the colon or rectum, and tumors in these models rarely display metastatic spread or genomic instability. This failure to recapitulate human disease has hampered the use of mouse models in translational efforts. Now, Drs. Jonathan Grim and Bruce Clurman and their colleagues in the Clinical Research Division have developed and characterized a new mouse model that recapitulates the key aspects of advanced stage disease.

Grim *et al.* specifically deleted two known human CRC tumor suppressor genes within the large and small intestine: *Fbw7* and *TP53*. Fbw7 is an ubiquitin ligase that is responsible for degrading many proteins, including oncogenic proteins such as cyclin E, Myc, Notch, and Jun. Fbw7 mutation occurs in 8-10% of human CRC cases and can lead to DNA damage, which activates p53 pathways to trigger apoptosis in these cells. However, in late-stage CRC, loss of p53 is a frequent mutation. Therefore, the authors combined Fbw7 and p53 deletions in the gut. While mice with conditional loss of Fbw7 alone did not get tumors, they did have altered differentiation and proliferation of the intestinal epithelium, including increased numbers of Paneth cells, which make up the gut stem cell niche, and mucin-secreting Goblet cells. Furthermore, elevated levels of p53 and other Fbw7 oncogenic targets were observed. In contrast, the combined loss of Fbw7 and p53 caused highly penetrant, aggressive, adenocarcinomas that metastasized to the regional lymph nodes and the liver. Importantly, these tumors also exhibited chromosomal instability, which is characteristic of the most common and aggressive form of human CRC, but is rarely seen in mouse models. Together, these data reveal the synergistic role of Fbw7 and p53 in maintaining cellular integrity and suppressing advanced CRC.

This new mouse model of CRC is likely to provide a useful and accurate tool with which to study events leading to advanced CRC that are relevant to human disease. It will thus hopefully lead to novel treatments for invasive and genomically unstable CRC.

Grim JE, Knoblaugh SE, Guthrie KA, Hagar A, Swanger J, Hespelt J, Delrow JJ, Small T, Grady WM, Nakayama KI, Clurman BE. 2012. Fbw7 and p53 cooperatively suppress advanced and chromosomally unstable intestinal cancer. *Molecular and Cellular Biology* 32:2160-7.

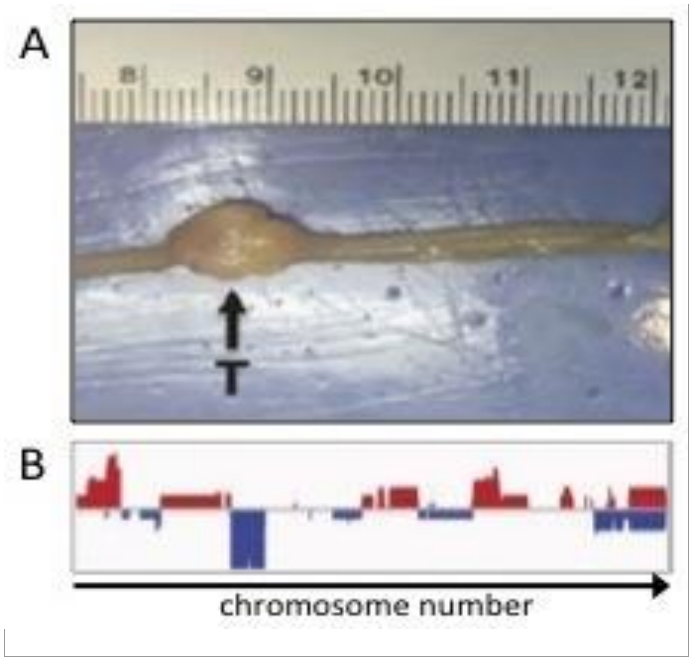

Image courtesy of the authors

A. An intestinal tumor (T) in mice lacking p53 and Fbw7. B. Genomic copy number profiling demonstrated a large number of genomic losses (blue) and gains (red) in cell lines and tumors lacking p53 and Fbw7.