

Abstract

Colorectal carcinoma is one of the most commonly diagnosed tumor diseases worldwide and is the cause of more than nine percent of deaths due to neoplasia. Colorectal cancer develops through different ways and one of them is the so-called serrated pathway, which is characterized by the presence of the *BRAF V600E* oncogenic mutation. Tumors arising through serrated pathway do not respond to classical therapy, and therefore are currently being studied at the molecular level. The oncogenic variant of the BRAF kinase activates MAPK signaling and is considered to be the main cause of serrated intestinal tumor formation. However, the mere presence of this oncogene is not sufficient for tumor development that requires further changes within the genome of the cell. In this thesis, we try to clarify what effect the *BRAF V600E* mutation has on the cells of the intestinal epithelium. In addition, we try to identify a possible cooperation between *BRAF* gene mutation and disruption of p53 and Wnt signaling, whose components are also frequently mutated in colorectal cancer. As a model for studying the processes associated with *BRAF V600E* activation, we use a mouse strain with conditional expression of a mutant variant of the *Braf* gene. We isolate intestinal organoids from these mice and subsequently perform *in vitro* analyses. To achieve the set goals, we mainly use biochemical and proliferation analyses and modify the genome of organoids using CRISPR/Cas9 technology. In the present work, we demonstrate that *Braf V600E* affects the behavior and proliferation of intestinal epithelial cells and point out that results from the small and large intestine may differ. Our observations also suggest that secondary mutations in the *Wip1*, *Apc*, or *Rnf43* genes have the potential to contribute to the onset or development of malignancies associated with *Braf V600E*.

Keywords

BRAF kinase, MAPK signaling pathway, colorectal carcinoma, epithelial cells transformation, intestinal organoids