

***In vivo* longitudinal imaging of colon tumorigenesis in conditional *Apc* knock-out mice**

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Summary of research project

Colorectal cancer is the second leading cause of cancer-related death in the United States. Despite our improved understanding of the genetic contributions of this disease, mortality due to colorectal cancer remains unaffected. Evidence has mounted to suggest that the host stromal components play key roles in the initiation and progression of a tumor and, therefore, may be an important factor in developing new therapeutic approaches. A variety of biological processes, such as vascular changes, matrix modulation, and infiltration of inflammatory cells, occur in and near the tumors before neoplastic transformation. However, our studies to understand the tumor-microenvironment interactions during tumorigenesis have been seriously hampered by the lack of methods to visualize these processes at the cellular and molecular level in experimental mouse models.

We have recently developed a miniature high-resolution fluorescence endomicroscope that is 1 mm in diameter and has a side view with single cell resolution. The goal of this proposed research is to utilize this novel technology to visualize tumor-microenvironment interactions longitudinally over the course of spontaneous colon tumorigenesis. To investigate the early stage tumorigenesis, we will use an orthotopic mouse model in which floxed APC genes can be inactivated by enema Adeno-cre administration in the colon. This model not only accurately mimics the sporadic somatic mutation seen in humans, but also allows us to control the timing and site of tumor formation facilitating our proposed image-based approach.

The effectiveness of our approach will be demonstrated by addressing questions, such as when the alterations of vasculature commence, how this vascular change progresses, and when and where specific stromal cell types are recruited and contribute to tumor growth. We will seek answers to these questions by direct longitudinal visualizations of tumors and their natural microenvironments through various stages from initial genetic mutation to aberrant crypt foci, and to adenoma. To this end, initial cellular behavior of *Apc* inactivated cells, structural changes in colonic crypt, morphological changes in vasculature, and recruitment of immune cells will be visualized, which can provide valuable insights into the mechanisms of the tumor progression. We expect to obtain an insight into whether and why certain initial aberrant foci fail to grow while others develop into malignant tumors.

The knowledge gained from this 1-year exploratory study will lead us to further questions, serve as a basis for future studies, and may provide insights into new strategies for early detection and treatment in the premalignant stages of colorectal cancer. The cellular-level mouse colonoscopy established in this project may be widely applied to other studies, for example, in colon pathophysiology, mucosal immunology, and inflammatory bowel disease.