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Understanding of inflammation-induced somatic gene alterations in intestinal epithelium using organoids.

Recently, genomic analyses of non-tumor tissues such as skin, esophagus, and endometriosis have been performed, and it has been reported that cancer-related gene mutations were accumulated even in normal tissues. It is known that in the patients with ulcerative colitis (UC) has chronic inflammation in their colon, and in long-term cases, they have worse risk to develop colorectal cancer. However, it is not clear that which genetic mutations are accumulating in colonic epithelium during inflammation. We established
non-tumor colonic organoids derived from patients with ulcerative colitis and healthy subjects. And generated 76-lines of clonal organoids and performed whole-exome sequencing analysis. Then, we identify a unique pattern of somatic mutagenesis in the inflamed epithelium of patients with UC. Targeted sequencing validates the pervasive spread of mutations that are related to IL-17 signaling. Furthermore, genome editing using CRISPR/Cas9 reveals that the IL17 signaling gene mutations confer resistance to the proapoptotic response induced by IL-17A. Some of these genetic mutations are known to exacerbate experimental colitis in mice. Our findings indicate its potential contribution to the pathogenesis of ulcerative colitis.