Human Genome Center

Laboratory of Molecular Medicine
ゲノム医科学分野

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The Laboratory of Molecular Medicine focuses on comprehensive characterization of currently-untreatable diseases including cancer on the basis of molecular genomics and aims to make "breakthroughs for human health" by identifying novel disease-related genes/pathways, including potential therapeutic or preventive targets and biomarkers, and to understand human diseases as heterogeneous but intervention-able "biological systems". This group has also organized the facility for the analysis of next-generation high-performance sequencers.

1. Geographic and age variations in mutational processes in colorectal cancer

Incidence rates of colorectal cancer vary geographically and have changed over time. Notably, in the past two decades, the incidence of early-onset colorectal cancer, which affects individuals below 50 years of age, has doubled in many countries. The reasons for this increase are unknown. We investigate whether mutational processes contribute to geographic and age-related differences by examining 981 colorectal cancer genomes from 11 countries. No major differences were found in microsatellite-unstable cancers, but variations in mutation burden and signatures were observed in the 802 microsatellite-stable cases. Multiple signatures, most with unknown aetiologies, exhibited varying prevalence in Argentina, Brazil, Colombia, Russia and Thailand, indicating geographically diverse levels of mutagenic exposure. Signatures SBS88 and ID18, caused by the bacteria-produced mutagen colibactin, had higher mutation loads in countries with higher colorectal cancer incidence rates. SBS88 and ID18 were also enriched in early-onset colorectal cancers, being 3.3 times more common in individuals who were diagnosed before 40 years of age than in those over 70 years of age, and were imprinted early during colorectal cancer development. Colibactin exposure was further linked to APC driver mutations, with ID18 being responsible for about 25% of APC driver indels in colibactin-positive cases. This study reveals geographic and age-related variations in colorectal cancer mutational processes, and suggests that mutagenic exposure to colibactin-producing bacteria in early life may contribute to the increasing incidence of early-onset colorectal cancer.

2. Genomic and transcriptomic landscape of carcinogenesis in patients with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a rare inherited condition that causes many small growths called polyps to form in the upper part of the stomach and carries a high risk of developing stomach cancer. In this study, researchers examined tissue samples from multiple sites in the stomach—from normal lining to polyps and full cancer—from seven people with GAPPS. They used advanced genetic techniques to read all the DNA and RNA in these samples to understand how normal tissue transforms into cancer. Their analysis showed that mutations in a gene called APC are present early, in both polyps and cancers, but an addition-

al mutation in another gene called KRAS appears only in the cancer tissue. This combination of APC and KRAS changes was seen repeatedly across different patients and even within different parts of the same tumor, suggesting these two changes together play a key role in driving cancer development in GAPPS. Because KRAS changes were linked closely with cancer, they might help doctors detect cancer earlier or decide the best time to treat the disease if tools like circulating tumor DNA testing can be developed.

3. Orchestration of Skin Pathology in Cutaneous Lupus Erythematosus by HLA Class I Down-Regulated Senescent Epidermal Basal Cells

We investigated the role of senescent epidermal basal cells in the pathogenesis of cutaneous lupus erythematosus (CLE) using skin samples from patients with CLE and a systemic lupus erythematosus (SLE) mouse model. We performed comprehensive senescence profiling using publicly available gene expression and single-cell RNA sequencing datasets, complemented by in vitro experiments and in vivo pharmacological intervention. We found that p21WAF1/CIP1-high senescent epidermal basal cells in CLE exhibited elevated type I interferon (IFN) expression. These senescent cells amplified IFN signaling in neighboring normal epidermal basal cells, leading to increased HLA class I (HLA-I) expression. In contrast, senescent epidermal cells themselves upregulated epidermal growth factor receptor (EGFR) signaling, which suppressed HLA-I expression and enabled evasion from immune surveillance. This heterogeneity in HLA-I expression promoted preferential CD8-positive T cell–mediated cytotoxicity toward normal epidermal basal cells, resulting in their apoptosis. Furthermore, we demonstrated that pharmacological clearance of senescent epidermal basal cells with the senolytic agent fisetin ameliorated SLE-like skin lesions in the mouse model. These findings indicate that senescent cells create a pathogenic microenvironment that redirects cytotoxic T cell responses against normal epidermis in CLE, thereby contributing to skin disease. Targeting senescent cells and their associated signaling pathways may represent a novel therapeutic approach for cutaneous manifestations of CLE and SLE.

Publications

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