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. Multiancestry comprehensive molecular analysis of gastric cancer

Gastric cancer is among the most common malignancies worldwide, characterized by geographical, epidemiological and histological heterogeneity. Here, we report an extensive, multiancestral landscape of driver events in gastric cancer, involving 1,335 cases. Seventy-seven significantly mutated genes (SMGs) were identified, including *ARHGAP5* and *TRIM49C*. We also identified subtype-specific drivers, including *PIGR* and *SOX9*, which were enriched in the diffuse subtype of the disease. SMGs also varied according to Epstein-Barr virus infection status and ancestry. Non-protein-truncating *CDH1* mutations, which are characterized by in-frame splicing alterations, targeted localized extracellular domains and uniquely occurred in sporadic diffuse-type cases. In patients with gastric cancer with East Asian ancestry, our data suggested a link between alcohol consumption or metabolism and the development of *RHOA* mutations. Moreover, mutations with potential roles in immune evasion were identified. Overall, these data provide comprehensive insights into the molecular landscape of gastric cancer across various subtypes and ancestries.

2. Genomic analysis and evolutionary simulation of MSI-H colorectal cancer

Intratumor heterogeneity (ITH) in microsatellite instability-high (MSI-H) colorectal cancer (CRC) has been poorly studied. We aimed to clarify how the ITH of MSI-H CRCs is generated in cancer evolution and how immune selective pressure affects ITH. We reanalyzed public whole-exome sequencing data on 246 MSI-H CRCs. In addition, we performed a multi-region analysis from 6 MSI-H CRCs. To verify the process of subclonal immune escape accumulation, a novel computational model of cancer evolution under immune pressure was developed. Our analysis presented the enrichment of functional genomic alterations in antigen-presentation machinery (APM). Associative analysis of neoantigens indicated the generation of immune escape mechanisms via HLA alterations. Multiregion analysis revealed the clonal acquisition of driver mutations and subclonal accumulation of APM defects in MSI-H CRCs. Examination of variant allele frequencies demonstrated that subclonal mutations tend to be subjected to selective sweep. Computational simulations of tumour progression with the interaction of immune cells successfully verified the subclonal accumulation of immune escape mutations and suggested the efficacy of early

initiation of an immune checkpoint inhibitor (ICI) -based treatment. Our results demonstrate the heterogeneous acquisition of immune escape mechanisms in MSI-H CRCs by Darwinian selection, providing novel insights into ICI-based treatment strategies.

3. Evaluating selection working on intra-tumor heterogeneity.

A tumor is defined as a population of cells that rapidly expands from a single original cell. It is now widely acknowledged that a tumor is composed of genetically diverse subclones, leading to intra-tumor heterogeneity (ITH). Ongoing discussions center on the impact of selection on the quality and quantity of ITH, as it directly affects the medical response of tumors, resistance to therapy, and the likelihood of recurrence and/or metastasis. The central question revolves around the significance of Darwinian selection within the tumor cell population. Various studies have suggested that the observed ITH patterns could be explained by non-Darwinian or neutral models, while others propose a role for Darwinian selection.We are currently developing a novel and straightforward statistical test to assess the influence of Darwinian selection (or positive selection) on intratumor heterogeneity. Through this approach, we plan to analyze ITH data across different cancer types and investigate the contribution of Darwinian selection, examining its relationship with factors such as cancer type, age, clinical stage, and genomic background. These findings underscore the importance of understanding Darwinian selection in shaping ITH and emphasize its potential implications for improving cancer diagnosis and treatment strategies.

Publications

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