【Grant-in-Aid for Specially Promoted Research】

Understanding of clonal evolution in cancer and normal tissues

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Purpose and Background of the Research

●Outline of the Research

Recent research has revealed widespread mutations in cancer-related genes across various organs, often linked to aging and inflammation, challenging conventional models of carcinogenesis. This study aims to explore somatic mosaicism (Fig.1), shedding light on its evolution to cancer and the impact of mutated clones on tissue function and disease development. It promises insights into cancer mechanisms and tissue health throughout life.

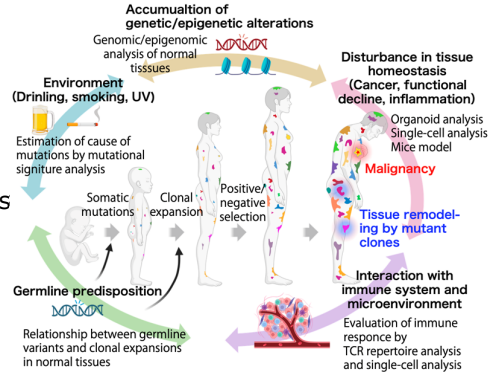

Fig.1 Research concept

●Background

The "multi-step carcinogenesis" model (Fig.2) proposes that cancer develops through acquiring advantageous mutations known as "driver mutations." Recent cancer genomics studies have identified major driver mutations across most cancer types. However, more recently, it has also been revealed that seemingly normal tissues contain clones with these driver mutations (“somatic mosaicism”), challenging conventional views of multi-step carcinogenesis.

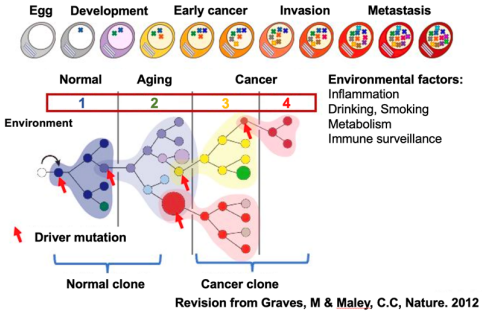

Fig.2 Multi-step carcinogenesis

Mutated clones causing "somatic mosaicism" have been found in various tissues, such as blood, esophagus, skin, bronchi, liver, bladder, and endometrium (Fig.3). This indicates that tissue reconstruction by mutated clones associated with aging is a common phenomena in our bodies. Traditionally, it was believed that the genomes of normal cells remain stable throughout life. However, accumulating evidence suggests that somatic mutations occur in all cells over time, and tissues are gradually replaced by clones acquiring advantageous mutations. The biological and pathological significance of somatic mosaicism is still being explored, with much remaining unknown.

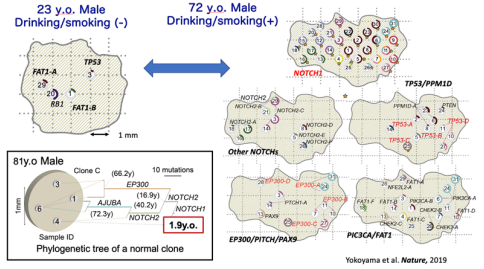

Fig.3 Somatic mosaicism in esophagus

●Questions and Purposes

In this study, we address the following questions regarding somatic mosaicism:

(1) What distinguishes a few clones leading to cancer development over a lifetime from the vast majority of clones that do not? (Fig.4)

(2) When and how do these minority clones acquire mutations and expand to develop cancer?

(3) Can tissues reconstructed by mutated clones maintain normal function? Is there a potential involvement in organ dysfunction, immune abnormalities, and disease onset associated with aging and chronic inflammation?

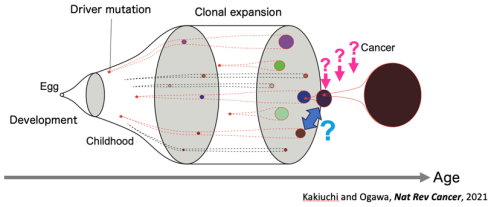

Fig.4 Clonal evolution leading to cancer

Expected Research Achievements

To answer the questions, we'll (1) reveal clonal evolution in normal tissues across various organs, (2) use phylogenetic analysis to understand the evolution from normal to cancerous clones, and (3) assess functional changes in tissues reconstructed by mutated clones.

(1) Landscape of clonal evolution (somatic mosaicism) in normal tissue

Plan 1 involves analyzing single-cell-derived organoids to study mutation accumulation with age and environmental influence. We'll also examine minute samples (Fig.5) to uncover somatic mutations and gain insights into mutated genes and clone expansion within normal tissues.

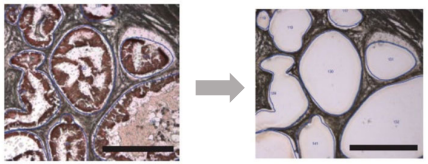

Fig.5 Microscopic collection of samples

(2) Elucidation of evolution from normal clones to carcinogenesis

In Plan 2, we'll study mutations in normal and cancer clones, using phylogenetic trees (Fig.6) to explore cancer development and differentiate between cancerous and non-cancerous clones. By incorporating epigenome and immune analyses, we aim to uncover deeper insights into cancer evolution and its underlying mechanisms.

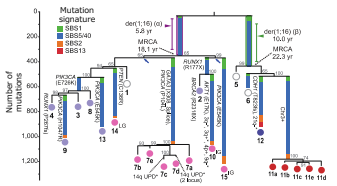

Fig.6 Phylogenetic tree of breast cancer and related clones

(3) Tissue function decline, aging, and disease caused by mutated clones

In Plan 3, we'll explore how mutated clones impact tissue function, aging, and chronic diseases, employing single-cell analysis (Fig.7) and spatial genomics to study mutations and gene expression. Our goal is to understand mutated cells' properties and their interactions with their microenvironments, including immune cells.

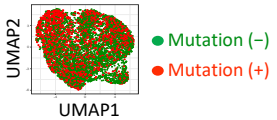

Fig.7 Combined analysis of gene mutation and expression of single cells

This study aims to broaden our grasp of human somatic mosaicism and our knowledge on aging, environmental responses, and diseases beyond cancer research. promising new insights into the human lifecycle and homeostasis. From the perspective of clinical medicine, it’s expected to establish a foundation for early cancer detection, risk prediction, prevention, and intervention techniques.

Homepage Address, etc.	https://plaza.umin.ac.jp/kyoto_tumorpatho/index.html