【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project: **Comprehensive studies on the molecular basis of early development and clonal evolution in cancer using advanced genomics.**

OGAWA, Seishi

(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number：19H05656　Researcher Number：60292900

Keywords: Genome biology, Oncology

【Purpose and Background of the Research】

Whole spectrum of genetic mutations has been clarified in most of the common cancers. However, it remains unclear how heterogeneity in cancer is acquired during initial development and clonal selection in the clinical course. To address these issues, combinations of multiple mutations, cryptic noncoding genomic lesions, and their functional implication should be elucidated. By single-cell sequencing, micro-scale sampling, whole genome sequencing, long-read sequencing, we will elucidate the molecular basis of early development and clonal evolution in cancer. We will also analyze large cohort of cancer patients to establish novel disease classification, to stratify patients according to prognosis, and to identify therapeutic molecular targets, which will be validated for functional implication in mouse models.

【Research Methods (Figure 1)】

1) Sequencing of high-density micro-scale samples, organoid, and laser microdissection tissues will demonstrate the process of clonal expansion in pre-cancer lesions of pancreatic, colon, and breast cancers. Serial sampling of multiple lesions will allow for clonal evolution from primary to aggressive, metastatic, and recurrent cancers.

2) The in-house single-cell sequencing method will simultaneously provide both information of genetic mutations and gene expression levels from a single cell, which will make it possible to display expression profile in each mutated cell from heterogenous fractions.

3) Whole genome and long-read sequencing will identify structural variants in noncoding regions whose significance will be validated by mouse model.

4) Large scale study of cancer patients will reveal

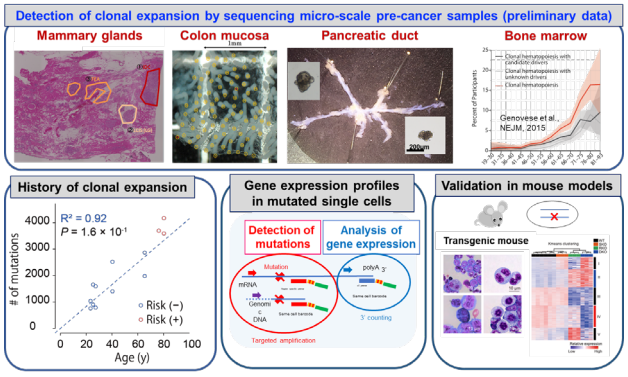

Figure 1. Analysis of origins of cancers by multiple technologies of advanced genomics

association of genetic lesions with disease phenotype, therapeutic response, and prognosis. Coincidence and mutual exclusiveness of genetic mutations will be investigated to elucidate mechanism of stepwise acquisition of heterogeneity in cancer.

【Expected Research Achievements and Scientific Significance】

We will comprehensively demonstrate the process of age-related clonal expansion and remodeling in pre-cancer tissues using single-cell sequencing and micro-scale sampling and clarify their adaptive response to environmental stress and association with initial process in cancer development. We will also identify implication of noncoding lesions by whole genome / long-read sequencing (Figure 2). Moreover, we will conduct such studies in large cohort of patients for achievement of precision medicine on the basis of 'personality of each case' which will be defined by establishment of novel disease classification, prognostic stratification of patients, and identification of therapeutic molecular targets.

【Publication Relevant to the Project】

・Yokoyama A, Ogawa S, *et al*., Age-related remodelling of oesophageal epithelia by mutated cancer drivers. ***Nature.*** 565:312-317, 2019

・Yoshizato T, Ogawa S, *et al*., Somatic mutations and clonal hematopoiesis in aplastic anemia. ***N Engl J Med.*** 373:35-47, 2015

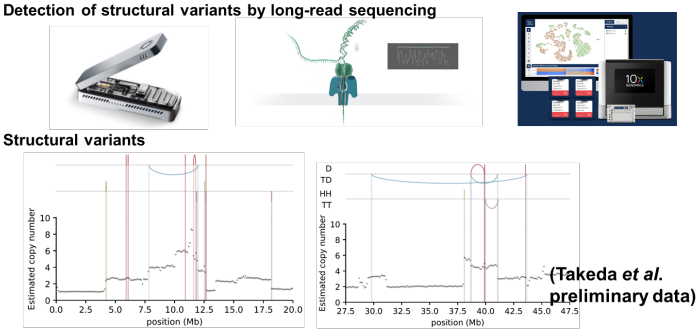

Figure 2. Identification of non-coding lesions and structural variations

【Term of Project】

FY2019-2023

【Budget Allocation】

153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://plaza.umin.ac.jp/kyoto_tumorpatho/

sogawa-tky@umin.ac.jp