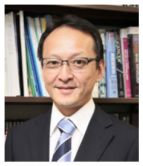
【Grant-in-Aid for Scientific Research (S)】

Regulation of genome by hydrogel: Spatial analysis of reprogramming of cancer stem cells towards development of therapeutic drugs



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Project Information	Project Number : 24H00037　　Project Period (FY) : 2024-2028 Keywords : hydrogel, biomaterial, cancer stem cell, reprogramming, molecular target therapy

Purpose and Background of the Research

●Outline of the Research

Cancer is the leading cause of death in Japan, and although initial treatment is advanced, recurrence is a problem. Cancer contains a small number of cancer stem cells that are ineffective in treatment and cause recurrence, but the problem is that there are no diagnostic or therapeutic methods. Therefore, there is a great need in society to develop a method to rapidly find and treat cancer stem cells. We have conducted interdisciplinary research using hydrogels and found that hydrogels rapidly create cancer stem cells in 24 hours by reprogramming on the hydrogel, designated as "**HARP phenomenon**". This is a highly original and groundbreaking discovery.

The cornerstone of this research is "changing the fate of cells using hydrogels." We will develop highly functional gels, clarify the properties of cancer cells, and establish diagnostic and therapeutic methods for cancer stem cells based on the information obtained through integrated analysis. The series of research will be the result of the fusion of different fields of materials science, biology, and medicine, and is expected to establish a new academic field, "**Materials Genomics**".

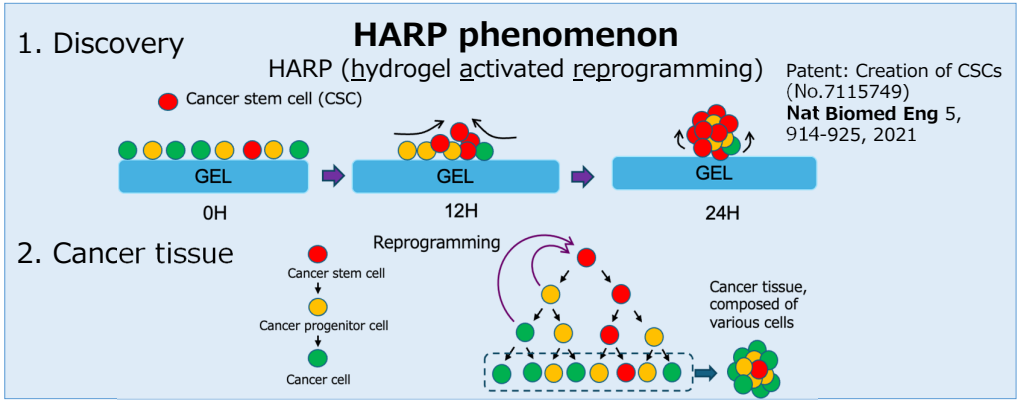

Figure 1. 1. Discovery: yellow and green cancer cells are ancestral to red cancer stem cells; 2. Cancer tissue: cancer consists of a hierarchical structure of red cancer stem cells, yellow cancer precursor cells, and green cancer cells.

●Background

Starting point of this study is a discovery of a breakthrough method (HARP phenomenon) on DN gel produced by Dr. Gong in Hokkaido Univ (Gong, **Science** 344, 2014). We have been collaborating with Dr. Gong for more than 10 years (Mu, **Nat Commun** 13, 2022), and the HARP phenomenon using the original hydrogel is highly creative (Tanaka, **Grant-in-Aid for Scientific Research(A)** 19H01171). Spatial transcriptome analysis requires an eye for pathology and advanced techniques, and the laboratory is equipped with high-quality histopathological analysis techniques (Saito, **Nature** 602, 2022; Suzuki, **Nature** 603, 2022; Yamasoba, **Cell** 185 2022; Kimura, **Cell** 185, 2022).

●Purpose

In this research, we will develop highly functional gels that induce the HARP phenomenon with high efficiency by changing the charge and elastic modulus of various monomers. We will use spatial information technology to create gels that mimic cancer stem cell niches to rapidly detect and diagnose recurrent cancer cells in patients. Screening of chemical libraries will be conducted with the aim of developing cancer stem cell therapeutics.

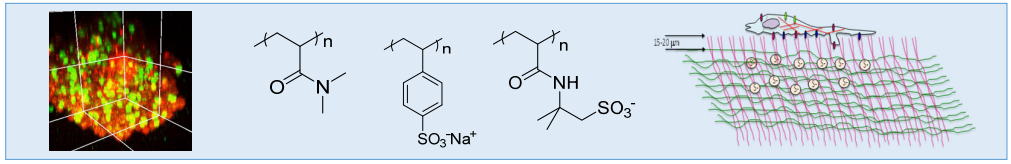

Figure 2. Photograph of SOX2-expressing cells (green color) by HARP phenomenon (left). Chemical formula of the monomers that can induce HARP phenomenon (middle). Schematic diagram of cells stimulated by double network gel (right).

Expected Research Achievements

● Develop gels that mimic cancer stem cell niches.

We will develop gels that mimic cancer stem cell niches. Specific methods will be established through integrated information analysis using single cell analysis, Raman microscopy, and spatial transcriptome analysis using cell lines and patient-derived pathological tissues.

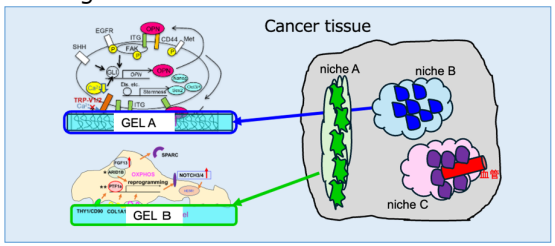

Figure 3. Development of gels that mimic cancer stem cell niches. Hypothesis is that Gel A mimics Niche A and Gel B mimics Niche B. In addition, develop a new gel that corresponds to Niche C.

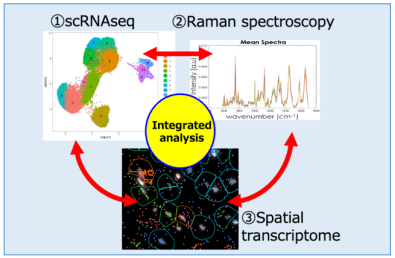

Figure 4. Spatial Integration Analysis Model. Integrate single cell analysis, Raman spectra, and spatial transcriptome analysis data to analyze cancer stem cell clusters.

● Diagnosis and treatment of cancer stem cells with gels (social return)

We will focus on lung cancer stem cells for establishing therapeutic methods. For personalized medicine, we will explore the possibility of predicting recurrence and treatment using biopsy and surgical specimens. In the development of cancer stem cell therapeutics, FDA-approved drug library will be used in order to obtain effective seeds in a short period of time.

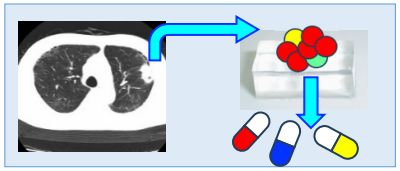

Figure 5. Diagnose cancer stem cells from lung cancer tissue and obtain therapeutic agents.

●Establishment of a new academic field "Materials Genomics" (social return)

The goal of this research is to cure cancer by hydrogel. This research will challenge to change the fate of cells using biomaterials, and will be the result of interdisciplinary research among materials science, biology, and medicine, expecting to create a new academic field as "Materials Genomics".

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