【Grant-in-Aid for Transformative Research Areas（B）】

Molecule- and cell-scale bridging approach to epigenome inheritance（Epigenobridge）

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Purpose and Background of the Research

●Overview

Approximately 70 years of research since the elucidation of the DNA structure has unveiled the mechanism of DNA replication, segregation, and inheritance. Additionally, the Human Genome Project has decoded the entire human genome sequence. Furthermore, with the establishment of genome editing toolkits, it has become possible to manipulate genome. However, DNA sequences are not the only inherited information. Eukaryotic genomic DNA wraps around histone proteins to form an array of nucleosomes, each carrying a distinct chemical modifications. The pattern and its location along DNA (epigenomes) determine the three-dimensional structure of genomic DNA, which regulates gene expression. The epigenomic information must be appropriately inherited upon cell division for proper maintenance of cellular functions.

●Histone recycling and strand bias

Previous research has shown that the epigenome (chemical modification of histones) is inherited by histone recycling (Figure 1), in which histone proteins are recycled to replicated DNA when DNA replication protein complexes and nucleosomes collide. It has also been revealed that histones are recycled equally to the two replicated strands during symmetric stem cell division but unevenly during asymmetric division (differentiation). Revealing the molecular mechanisms of the strand bias is a challenge that leads to a fundamental understanding of epigenetic inheritance.

●Histone recycling and strand bias

The current field has a large gap between molecular and cellular scale research. Therefore, we aim to revolutionize the field. To accomplish this, we will establish the molecular and cellular scale bridge approach and will repeat (1) elucidation of the molecular mechanisms of histone recycling, (2) reconstitution of artificial chromosomes based on the mechanisms, and (3) measurement and comparison of recycling efficiency and strand bias in cells and the artificial chromosomes. The final goal will be to unveil the unified basic principle of histone recycling that transcends scale and can explain intracellular phenomena.

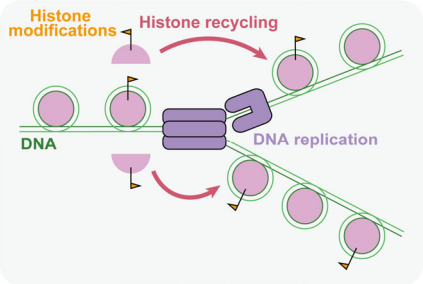

Figure 1 Histone recycling

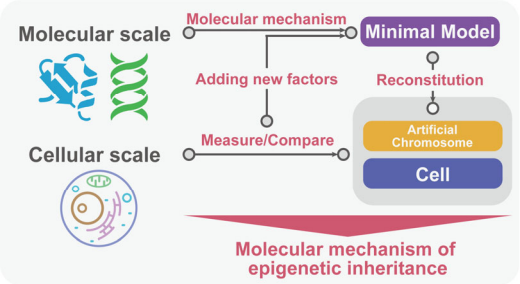

Figure 2 Research map

●Researches of the planning groups

A01: Strand bias mechanism in histone recycling explored using nanopore analysis and molecular simulations. We will explore the effects and molecular mechanisms of histone chaperones on recycling efficiency and strand bias.

A02: Histone chaperone cooperation mechanism in histone recycling explored using optical tweezers. We will explore the molecular mechanism of histone recycling by a combination of chaperones.

A03: Role of chromosome conformation in histone recycling explored using artificial chromosomes. We will explore the control of histone recycling by 3D genome-like chromosome structures.

A04: Histone recycling dynamics in cells and artificial environments explored using omics measurement. We will explore the differences in histone recycling dynamics between cells and artificial chromosomes.

Expected Research Achievements

●Epigenomic inheritance across scales

I have developed the idea of “actively regulated epigenetic inheritance,” which differs from “passive inheritance.” Based on this idea, we aim to transform the field and ultimately realize epigenome editing through the collaboration of experts in molecular mechanism, chromosome reconstitution, and chromosome measurement.

In this study, we will establish a technology for reconstituting artificial chromosomes that behave like cells and whose recycling efficiency and strand bias can be predicted based on molecular mechanisms.

In addition, we will clarify the molecular mechanism by which histone chaperones regulate histone recycling, reveal to what extent intracellular histone recycling can be explained by their effects alone, and identify factors responsible for the unexpected phenomena.

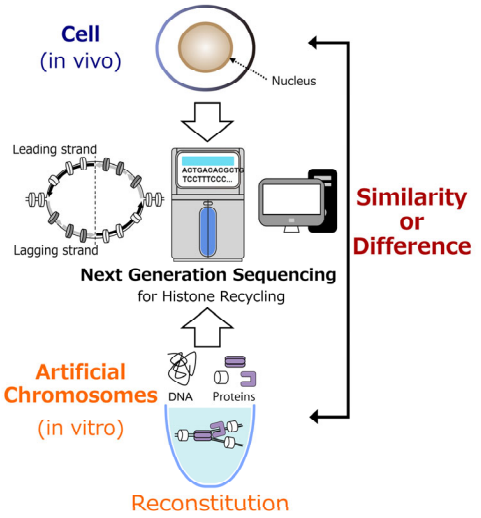

Figure 3 How to proceed

●Understanding epigenomic inheritance across scales

We will expand this research area to (1) the “basic research direction,” where we will deeply understand the mechanism of epigenomic inheritance; (2) the “technology development direction,” where we will clarify the mechanism of epigenomic inheritance during cell differentiation and manipulate it; and (3) the “medical research direction” to identify the causes of diseases related to the epigenomic inheritance defects. Through these expansions, this research area will significantly impact society.

Homepage Address, etc.	https://epigenobridge.notion.site