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Research Subjects
(1) Universality and Diversity of DNA replication systems and their evolution
(2) Regulation of Spatio-temporal regulation of replication program through chromatin architecture and its spatial arrangement
(3) Dynamic formation and resolution of cellular G-quadruplex structures and their biological functions
(4) Cellular responses to replication stress and maintenance of genomic integrity: crosstalks with biological stress responses and relevance to cancer development
(5) Novel strategies for anti-cancer treatment targeting replication factors
(6) Roles of replication factors in development and functions of various organs and tissues

Current Research Activities
Our goal is to understand the molecular mechanisms underlying the faithful inheritance of genetic materials and stable maintenance of the genome. Toward this goal, we are studying various aspects of chromosome dynamics, with particular focus on regulation during S phase, using *E. coli*, fission yeast, and mammalian cells. We try to elucidate how chromosomes replicate and how the inheritance of the replicated chromosomes is regulated to enable stable maintenance of the genome through generations. Answers to these questions will shed light on how defects in these processes may contribute to the development of diseases, including cancers, and to senescence. It will also help to identify novel target proteins for cancer therapies.

There are three major issues associated with genome DNA replication.
① Once and only once replication of a genome during a cell cycle and its strict coordination with mitosis.
② DNA replication during S phase is under sptiao-temporal regulation and the process is intimately related to epigenome maintenance and alterations.
③ DNA replication encounters various threats along the course of the process. Cells need to cope with these “replication stress” to ensure completion of the entire genome duplication without major errors.

The failures in ① and ③ are directly linked to increased genome instability and generation of cell populations of abnormal growth.
In order to elucidate mechanisms associated with these issues, we are working on the following four major subjects.

1) How are the timing and nuclear localization of DNA replication determined, and how is it related to the processes of other chromosome transactions.

We discovered crucial roles of Rif1, an evolutionally conserved nuclear factor, in genome-wide regulation of replication timing **(Figure 1**). We are particularly interested in how association of Rif1 with nuclear membrane contributes to regulation of not only replication timing but also other events such as DSB repair and transcription.

2) Biological functions of G-quadruplex, especially in regulation of DNA replication.

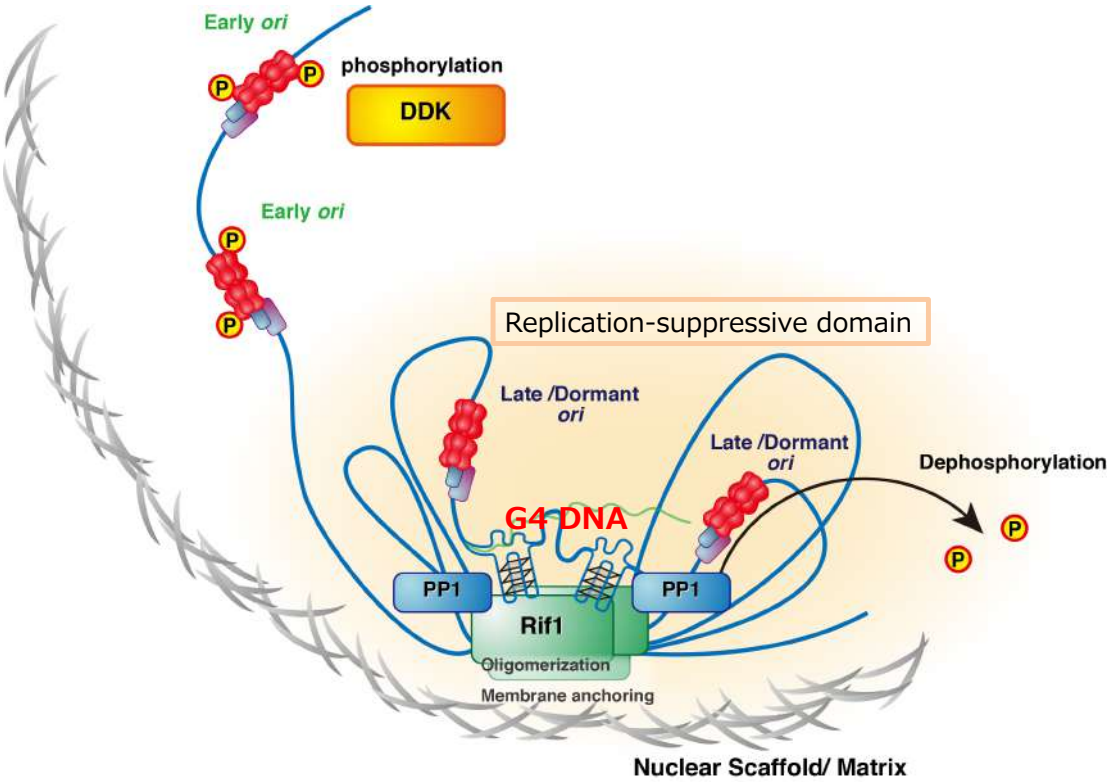
Based on our findings, we have come to realize the crucial and ubiquitous roles of non-B DNA, more specifically, G-quadruple structures. Recent numerous reports indicate the essential roles of various G4 structures in transcription, recombination, genome rearrangement, epigenome regulation and others (**Figure 2**). Through analyzing the roles of G4 structures in replication initiation and chromatin regulation, we would like to disclose more general biological functions of G4 structures.

3)Mechanisms of cellular responses to replication stress and how are they connected other diverse cellular stress responses.

DNA replication needs to continue until the entire genome is replicated, once it is initiated. The block to ongoing DNA replication is a threat to the genomic integrity, and needs to be removed swiftly. Claspin/Mrc1 is a key protein that transmits the replication stress signal to the downstream effectors. We have discovered a novel function of Mrc1/Claspin in regulation of initiation through interaction with Cdc7 kinase. We also discovered a crucial role of Cdc7 in activating replication checkpoint through phosphorylation of Claspin (**Figure 3**). Furthermore, we have shown that Claspin is required also for cells to resume growth after serum starvation and for their responses to other forms of stresses including osmotic shock and high temperature (**Figure 4**).

4)Roles of replication factors in development of individual organs and tissues and potential mechanistic diversification of replication systems.

We are interested in the in vivo roles of cell cycle/ checkpoint factors, and are making mutant mice in which these genes are conditionally knocked out in specific tissues/ organs by using the Cre-loxP system (**Figure 5**). We are also developing novel anti-cancer strategies utilizing cell cycle regulators as a target.



Kanoh, Y. *et al.* (2015) ***Nat. Struct. Mol. Biol.*** 22: 889-897
Toteva, T. *et al.* (2017) ***Proc. Natl. Acad. Sci. USA.*** 114: 1093-1098.

Figure 1 Regulation of chromatin architecture for establishing replication timing domains.
Rif1 faciliccctates chromatin loop formation through its binding to G4 structures present in the intergenic segments and its multimerization activitiy. This will generate chromatin architecture that may be related to the replication timing domain structures.

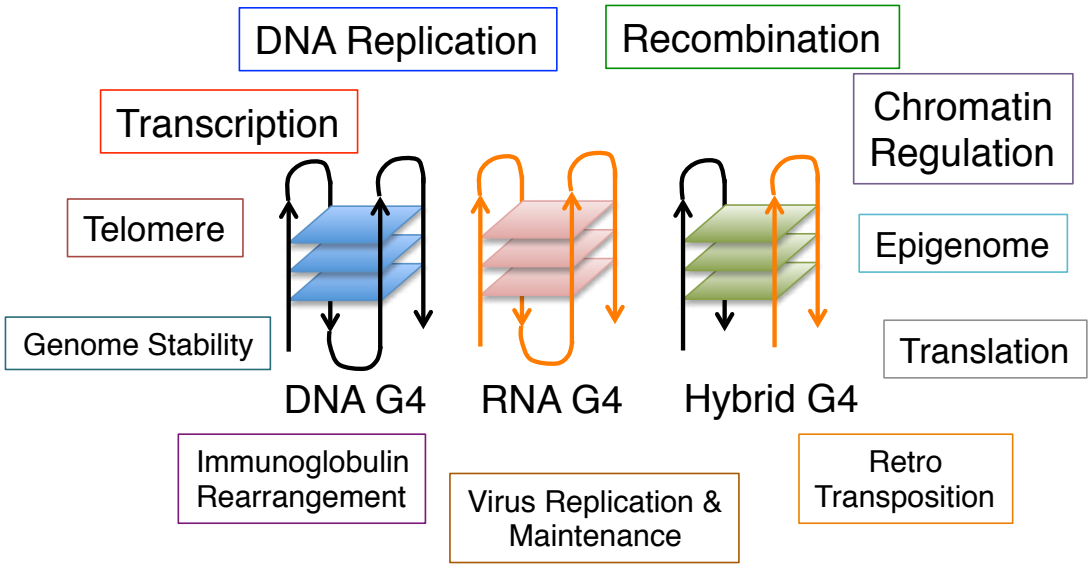


Figure 2 Potential biological roles of G4.

Increasing numbers of reports indicate the crucial roles of G4, formed on DNA, RNA and RNA-DNA hybrids, in various chromosome transactions.</caption>

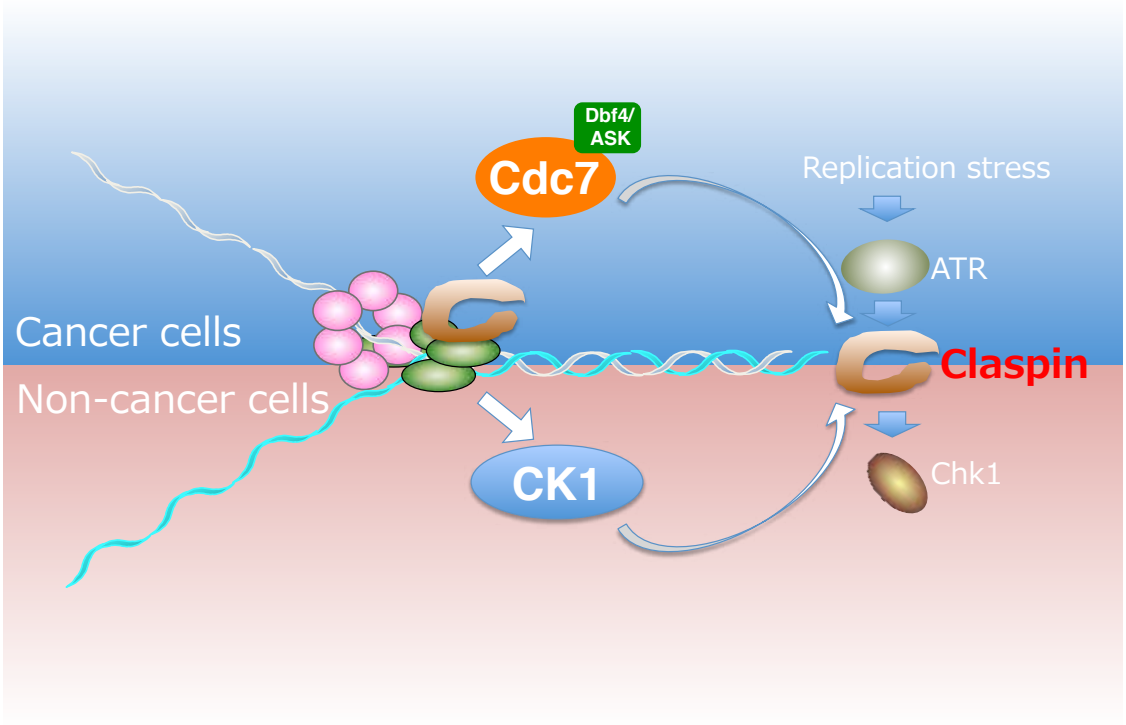


Figure 3 Differential mechanism of replication stress responses in cancer and non-cancer cells.
A conserved pathway induced by replication stress is drawn to the right corner of the figure. In this pathway, Claspin needs to be phosphorylated at a conserved CKBD motif to facilitate the binding of Chk1 kinase to Claspin. In cancer cells, Cdc7 is mainly responsible for this phosphorylation, whereas in non-cancer cells, CK1 (casein kinase 1γ1) plays a predominant role. This differential mechanism can be exploited to develop a strategy for cancer cell-specific cell killing by targeting Cdc7 kinase. </caption>

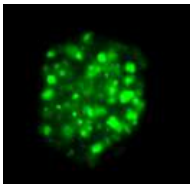
Generation of cancer cells

Various biological stresses
(Nutrition, temperature, Oxidation,
Hypoxia, Bacterial infection etc.)

↓

Replication stress
(DNA damage signals)

DNA damage foci
in nuclei



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Failure of DNA damage responses

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Tumors: Malignant transformation

Figure 4 Formation of cancer cells.
Various cellular stresses could induce replication stress, thus activating Claspin-dependent checkpoint pathway. DNA damages are transiently induced by replication stress, but eventually removed by cellular DNA repair system. Once this cellular defense system is compromised, genome integrity is lost and cells are transformed into cancer state.

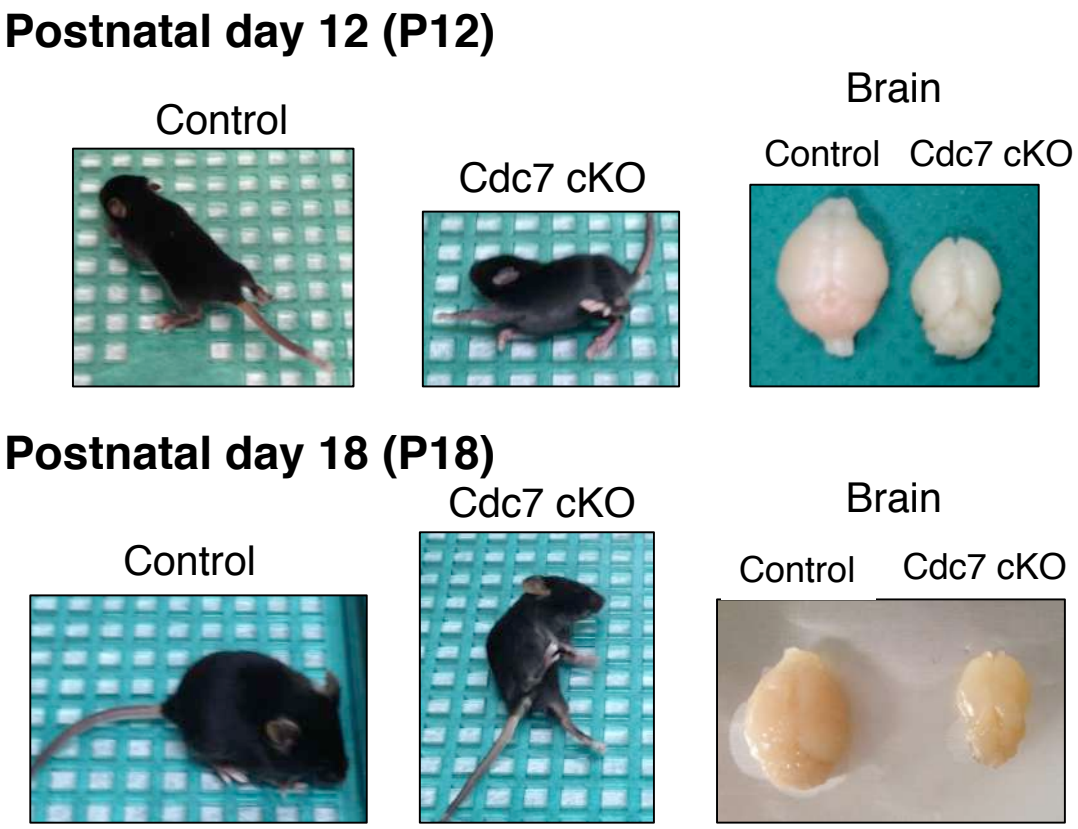

Figure 5 Cdc7 knockout in neural stem cells causes defect in brain formation and growth retardation after birth.

Cdc7 (f/+) *Nestin*^{Cre} mice are born, but exhibit abnormal walking and limb-clasping reflexes, growth retardation and die by 20 days after birth.

Future Plan

In each cell cycle, three billion base pairs of the human genome are replicated within 6–8 hrs with amazing accuracy, while initiation takes place at tens of thousands of so called "replication origins". Selection of replication origins for initiation is regulated by a number of factors, while a large fraction of origin selection may be determined stochastically. Yet, the initiation does take place at sequences that may be associated with some features. Our studies as well those from other groups suggest that G-quadruplex (G4) may be a candidate structure that may be associated with replication initiation. G4 plays crucial roles in regulation of transcription. The dynamic nature of G4 (formation and disassembly) needs to be examined in detail, since it may be the core of its biological functions.

Plan #1: Roles of G4 in plastic and stochastic regulation of biological reactions

G4 has been implicated in initiation of DNA replication as well as transcription (**Figure 2**). We have already indicated the importance of G4 in establishment of replication timing domain structures by showing that Rif1, a factor crucial for replication timing regulation, binds specifically to G4 DNA (**Figure 1**). Rif1-G4 interaction may

contribute to dynamic regulation of chromatin architecture due to the intrinsic nature of instability of G4. We would like to clarify the modes and nature of interaction between G4 and its binding partners, elucidate the mode of actions of these proteins and ultimately obtain global views on biological functions of G4, and on potential roles of G4 in stochastic regulation of biological reactions. It would be necessary to develop methods and tools to identify the cellular G4 with high sensitivity and specificity, and also to detect G4 in live cells. Another goal is to reconstitute "human-like" replication system in *E.coli* with purified proteins on G4 sequences.

Plan #2: Biological stresses and induction of genome instability

"Oncogenic stress" are known to induce replication stress, which inhibits the progression of replication forks. Thus, replication stress triggers the tumorigenesis process. The maintenance of replication fork integrity is central to the stable inheritance of genetic information through generations and to its preservation during the lifespan of an individual. Our recent results indicate the crosstalk between various biological stresses and replication stress (**Figure 4**). We would like to examine the possibility that general biological stresses may induce genomic instability responsible for cancer formation.

Plan #3: Roles of replication factors in organ/ tissue development

Replication factors are involved not only in the process of DNA replication but also in other aspects of chromosome functions. In order to clarify the organismal roles of replication factors, we target Cdc7, Claspin and other replication factors and generate genetically modified mice. Tissue/ organ-specific knock-out will reveal their novel functions (**Figure 5**), and will lead to understanding the pathology of human genetic disorders caused by mutations in these factors.

Plan #4: Novel anti-cancer strategies targeting replication factors

We have found a cancer cell specific mechanism of coping with replication stress (**Figure 4**). We will try to dissect various pathways in cancer cells and non-cancer cells, and the obtained information will be exploited to develop novel strategies that would specifically target cancer cells for growth inhibition and cell killing.

Messages to Students

Science can unite the world through its own universal language. The journey to new discovery is long and hard, but is rewarding. With your new findings, you can communicate with the entire world. We would like to provide international and stimulating environment in which you can devote yourself to science.
We are recruiting highly motivated and interested individuals who are communicative and can share excitement with us in the laboratory. We have had students from many foreign countries including Korea, Malaysia, Taiwan, China, Vietnam, Hong Kong, Canada, Italy, France and Germany and have been excited to have many different cultures in our laboratory.
We welcome "diversity", since I strongly believe that "diversity" is the most powerful driving force for making totally novel findings.
You are welcome to visit our laboratory or contact me by e-mail at any time to find out more about our current activities. We have monthly progress report meetings (first Monday of the month) and weekly journal clubs (every Monday morning), which you are welcome to attend.
I can answer your questions by Skype or Zoom on line interview. Contact me through e-mail (masai-hs@igakuken.or.jp) at any time.

Original papers (after 2006)

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