Laboratory of Hisao Masai

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

Summary of our current research activities

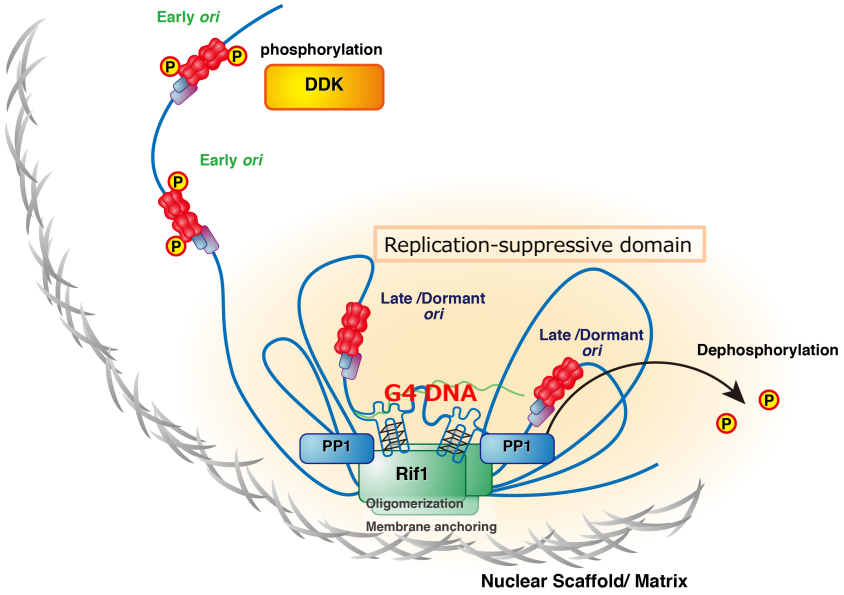
Our goal is to understand the molecular mechanisms underlying the faithful inheritance of genetic materials and stable maintenance of the genome. Toward this goal, we are studying various aspects of chromosome dynamics, with particular focus on regulation during S phase, using *E. coli*, fission yeast, 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 the genome during a cell cycle and its strict coordination with mitosis.
② DNA replication during S phase is under spatio-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.



Kanoh, Y. *et al.* (2015) ***Nat. Struct. Mol. Biol.*** 22: 889-897
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Figure 1 Regulation of chromatin architecture for establishing replication timing domains. Rif1 facilitates chromatin loop formation near nuclear membrane 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.

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.

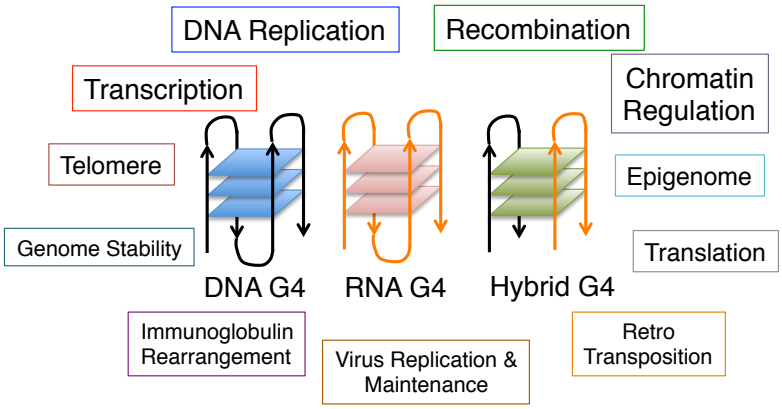

Figure 2 Potential biological roles of G4. Increasing numbers of reports indicate the crucial roles of G4, formed on DNA, RNA and RNA-DNA hybrids, in various chromosome transactions.

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 in cancer cells (**Figure 3**). Interestingly, in non-cancer cells, casein kinase plays a predominant role in phosphorylation of Claspin. On the basis of this finding, we are targeting Cdc7 for novel cancer therapy. 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**).

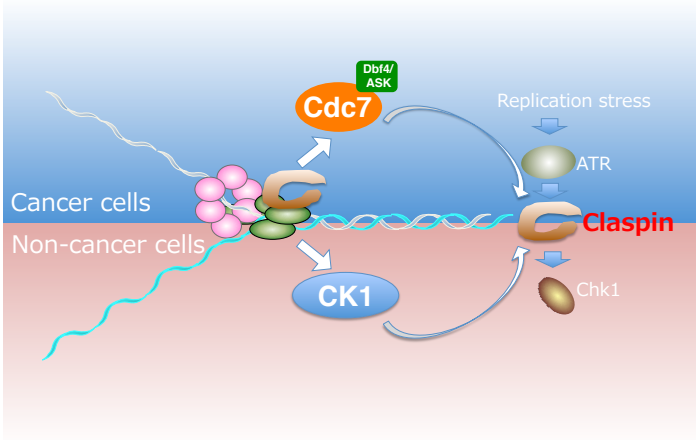

Figure 3 Differential mechanisms of replication stress responses in cancer and non-cancer cells. A conserved pathway induced by replication stress is drawn to the right corner of the figure. In this pathway, Claspin needs to be phosphorylated at a conserved CKBD motif to facilitate the binding of Chk1 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.

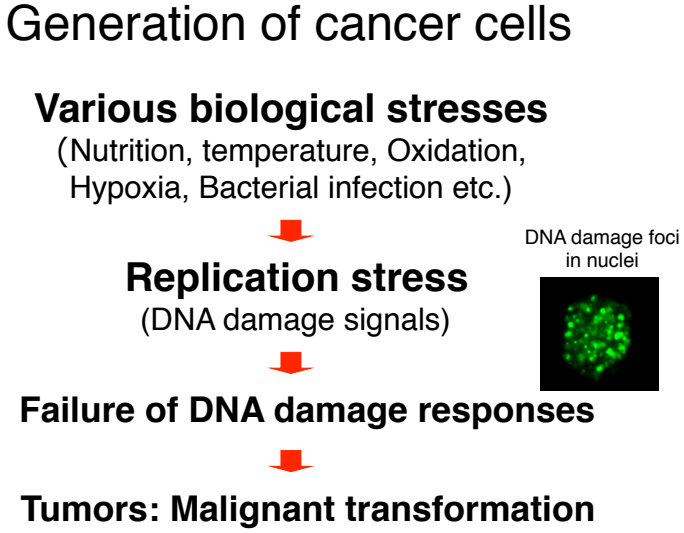

Figure 4 Formation of cancer cells. Various cellular stresses could induce replication stress, thus activating Claspin-dependent checkpoint pathway. DNA damages are transiently induced by replication stress, but eventually removed by cellular DNA repair system. Once this cellular defense system is compromised,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

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). Cdc7 and its activation subunit, ASK, are required for brain development in mice, while they are differentially required for development of hematopoietic cells.

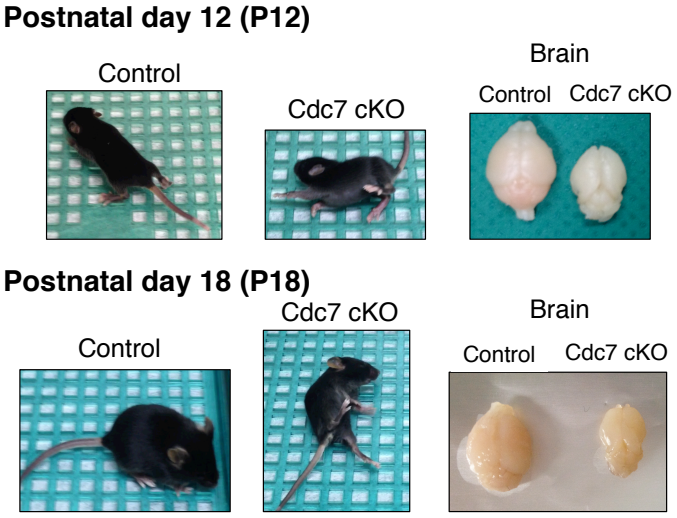

Figure 5 Cdc7 knockout in neural stem cells causes defect in brain formation and growth retardation after birth. Cdc7 (f/+) *Nestin*^{Cre} mice are born, but exhibit abnormal walking and limb-clasping reflexes, growth retardation and die by 20 days after birth. ASK (f/+) *Nestin*^{Cre} also exhibits similar phenotypes.

Original papers (after 2006)

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