論文内容の要旨

論文題目　Regulation of replication origin selection and timing in fission yeast

（分裂酵母染色体 DNA 複製開始部位の選択とタイミングの制御機構の解析）

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Cdc7/Hsk1 is a conserved kinase required for initiation of DNA replication, and Mrc1 is known to be required for maintenance of replication fork integrity under replication stress. We show here that, in fission yeast, the timing and efficiency of initiation at early-firing origins is facilitated in *mrc1*Δ, but not in *mrc1-3A* mutant or *cds1*Δ in which DNA replication checkpoint is deficient. Timing of Cdc45 loading is also advanced specifically in *mrc1*Δ. Strikingly, *mrc1*Δ can bypass *hsk1*Δ lethality, suggesting that an essential role of Hsk1 may be to relieve the inhibition caused by Mrc1. Mrc1 binds selectively to early-firing origins in a manner independent of Hsk1 after Mcm4 loading but prior to Cdc45 loading. We speculate that this binding transiently inhibits Cdc45 loading and initiation and phosphorylation by Hsk1 triggers the initiation. Our results indicate novel checkpoint–independent functions of Mrc1 for timely and regulated initiation of fission yeast DNA replication.

Furthermore, with a hope that bypass mutants of *hsk1*Δ may represent novel regulators of origin regulation, we isolate four novel insertion mutants which can bypass *hsk1*Δ lethality. Among them, a null mutant of *rif1*, which is a telomere maintenance factor binding to telomere in a Taz1 dependent manner, exhibits more efficient bypass than *mrc1*Δ did. Rif1 binds to specific late origin in M phase and moves away in S phase, and late origin firing is observed over a wide range on chromosome, although Rif1 does not required for DNA replication checkpoint. As Hsk1 and its regulation factor of Him1/Dfp1 interact with Rif1, Rif1 might regulate replication program in S phase through Hsk1 function. Our results suggest that timely firing of replication origins in fission yeast may be regulated by Hsk1 in conjunction with multiple other factors including Mrc1 and Rif1.