The molecular biological studies on roles of *Drosophila* Mcm10, RecQ4 and heterochromatin proteins in DNA replication, genome maintenance and photoreceptor cell differentiation

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Thesis Abstract

Mini chromosome maintenance 10 (Mcm10) is an essential protein and is required for the initiation of DNA replication. Knockdown of *Drosophila* Mcm10 (dMcm10) in the eye imaginal discs caused a delay in the S and M phases, and induced genome damage and apoptosis. Surprisingly, the involvement of dMcm10 in R7 cell differentiation was also discovered by knockdown of dMcm10. Heterochromatin protein 1a (HP1a) has a diverse role in the nucleus, including the regulation of euchromatic genes. It has been reported that both Mcm10 and HP1a are required for DNA replication. However, underlying mechanism is not yet clarified especially for HP1a. As expected, knockdown of both HP1a and dMcm10 showed the disrupted progression of S phase in eye imaginal discs. The close proximity between HP1a with several DNA replication proteins such as dMcm10, RFC140 and DNA polymerase ε 255 kDa subunit was demonstrated in S phase by Proximity Ligation Assay (PLA). The PLA signals between dMcm10 and HP1a are specifically observed in the mitotic cycling cells, but not in the endocycling cells. Ectopic DNA synthesis and DNA damage without much of apoptosis were induced in the posterior regions of eye discs carrying double knockdown of dMcm10 and HP1a. Therefore, G1-S phase checkpoint defect was suggested by knockdown of both proteins. In addition, it is demonstrated that both dMcm10 and HP1a are required for differentiation of photoreceptor cells R1, R6 and R7. RecQ4 is classified as part of the RecQ family of helicases. Mutations in this gene have been reported to relate to three human recessive genetic disorders such as Rothmund-Thomson syndrome, Baller-Gerold syndrome and RAPADILINO syndrome. In *Drosophila* S2 cells, the replication role of RecQ4 was confirmed, especially the SLD2 domain of the protein is essential for this

function. The role of RecQ4 in loading of other replication proteins such as ORC2, PCNA, and DNA polymerase alpha on to chromatin was also demonstrated. In addition, the direct role of RecQ4 in Nucleotide Excision Repair (NER) pathway in the response to UV damage was proved.