Paraspeckle Protein p54^{nrb} Links Sox9-mediated Transcription with RNA Processing during Chondrogenesis in Mice

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Chondrogenesis is an important biological event in endochondral bone development, skeletogenesis and tissue patterning. Genetic and biological studies indicate that a transcription factor, Sox9, plays an essential role in chondrogenesis. However, it is unclear how Sox9 conducts chondrogenesis. To address this, we have attempted to identify transcriptional partners of Sox9 by screening full-length cDNA library of a chondrogenic cell lien, ATDC5. We have identified approximately 50 positive clones. One of clones encodes p54^{nrb} cDNA. We found that p54^{nrb} localizes with Sox9 in mouse chondrocytes (Figure1). In addition, p54^{nrb} physically and functionally interacts with Sox9, and couples Sox9-dependnet transcriptional activity with mRNA maturation of the target genes during chondrocyte differentiation. Importantly, transgenic mice overexpressing a mutant of p54^{nrb}, which blocks mRNA maturation of a chondrogenic gene, collagen 2a1, manifest severe dwarfisms (Figure2). Histological analyses revealed that chondrogenesis was severely impaired in the transgenic mice. Collectively, these results indicate that p54^{nrb} functions as an important transcriptional partner for Sox9 during chondrogenesis. Our study provides a novel insight into the molecular basis of Sox9 regulation and chondrogenesis and would contribute to establish therapeutic approaches for cartilage diseases such as osteoarthritis.

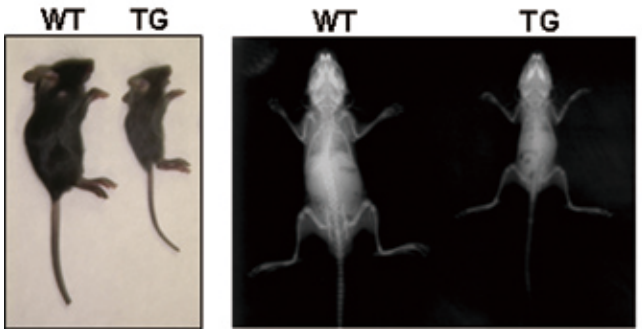

Fig. 2

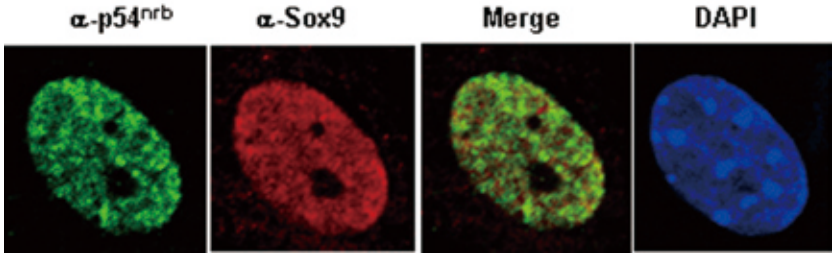

Fig. 1

The Heterochromatin Protein Swi6/HP1 Activates Replication Origins at Pericentromere and Silent Mating-type Locus

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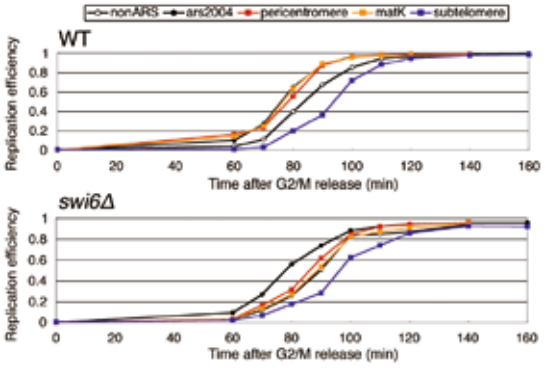

Fig. 1 Early replication at the pericentromere and *mat* locus depends on Swi6.

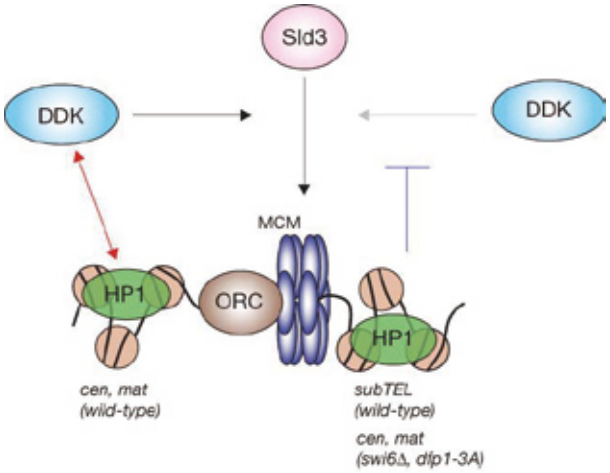

Fig. 2 A model for regulation of replication in heterochromatic loci. Swi6 recruits DDK to the pericentromere and *mat* through physical interaction, which promotes loading of Sld3 onto pre-RCs and early replication of the loci.

Heterochromatin is a structurally compacted region of chromosomes in which transcription and recombination are inactivated. DNA replication is temporally regulated in heterochromatin, but the molecular mechanism for regulation has not been elucidated. Among heterochromatin loci in *Schizosaccharomyces pombe*, the pericentromere and the silent mating-type (*mat*) locus replicate in early S phase, whereas the sub-telomeric region does not, suggesting complex mechanisms for regulation of replication in heterochromatin regions. We show that Swi6, an *S. pombe* counterpart of heterochromatin protein 1 (HP1), is required for early replication of the pericentromere and the *mat* locus. Origin-loading of Sld3, which depends on Dfp1/Dbf4-dependent kinase Cdc7 (DDK), is stimulated by Swi6. An HP1-binding motif in Dfp1 is required for interaction with Swi6 in vitro and for early replication of the pericentromere and *mat* locus. Tethering of Dfp1 to the pericentromere and *mat* locus in *swi6*-deficient cells restores early replication of these loci. Our results show that a heterochromatic protein positively regulates initiation of replication in silenced chromatin by interacting with an essential kinase.