PSF1 Is Essential for Immature Cells Proliferation

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Eukaryotic chromosomal replication is tightly regulated to maintain the integrity of genomic information. In yeast, Orc (origin recognition complex) is bound to replication origins throughout the cell cycle. From late M to G1 phase, MCM (minichromosome maintenance) protein is loaded onto the origin, marked by Orc, by Cdc6 and Cdt1, and forms the pre-replication complex (pre-RC). On activation and recruitment of additional factors, such as CDC45, the pre-RC is converted to the pre-initiation complex (pre-IC), which is the complex essential for the transition to DNA replication. In yeast, CDC45 is essential for the initiation and elongation of DNA replication.

Recently, a novel multi-protein complex "GINS" was identified. This GINS complex contains, Psf1 (partner of sld five 1), Psf2, Psf3, and Sld5 and forms a ring-like structure. During the S-phase, the GINS complex is loaded onto chromatin after the formation of pre-RCs, and then tightly associates with the replication origin. This binding is suppressed by p21 and geminin by inhibiting the loading of CDC45 onto chromatin and the pre-RC formation by binding to Cdt1. Moreover, the chromatin binding of GINS complex and of CDC45 are mutually dependent processes, but they do not associate with each other. The association of PSF1 and Dpb11/Cut5 with the origins is also mutually dependent. All genes encoding GINS components are evolutionarily conserved and are essential for cell growth. However, the functions of GINS complex in mammalian cells have not been reported.

We originally cloned the mouse ortholog of *PSF1* from a hematopoietic stem cell cDNA library and found that *PSF1* is expressed in blastocysts, adult bone marrow, and testis, in which the stem cell system is active. We used the gene-targeting technique to determine the physiological function of PSF1 *in vivo*. Mice homozygous for a non-functional mutant of *PSF1* died *in utero* around the time of implantation. *PSF1*$^{-/-}$ blastocysts failed to outgrowth in culture and exhibited a cell proliferation defect. Our data clearly indicate that *PSF1* is required for early embryogenesis.

Ref:

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