Genetic studies of signal transduction pathway, responding to ageing stress and regulating telomere function.

N. Hayashi, S. Murakami

Cellular senescence is irreversible arrest of cell cycle. The probability to be into the senescence increases with the passage of cell division. Accumulation of many kinds of stress, such as ROS (reactive oxygen species), DNA lesion, shortened telomere, loss of heterochromatin structure and so on, would cause senescence. So, many signal pathways may work for the maintenance of its cellular life span. Budding yeast, *Saccharomyces cerevisiae*, has 32 protein phosphatases (PPase), and 30 in them are nonessential. We screened yeast knock-out series of PPases to investigate the regulatory pathway of cellular senescence. We examined telomere length of them by Southern blot analysis, and isolated the *sit4* cell that had slightly short telomere. *SIT4* gene encodes one of type 2A PPases (PP2A), and involved in cell cycle control. Silencing ability at telomere region in the *sit4* cells was also deficient, and phosphorylated Sir3 protein was accumulated. Life span in the *sit4* cells was as short as in the *sgs1* cells. Furthermore, we found altered structure of nucleoli and frequent recombination at rDNA region in them. These suggest that PP2A regulates phosphorylation of the Sir3 protein to maintain heterochromatin structure at telomere, and also these may suggest that formation of heterochromatin structure affects cellular life span.

Reference: Hayashi et al. The *SIT4* gene, which encodes protein phosphatase 2A, is required for telomere function in *Saccharomyces cerevisiae*. Curr Genet 47:359-367. 2005.

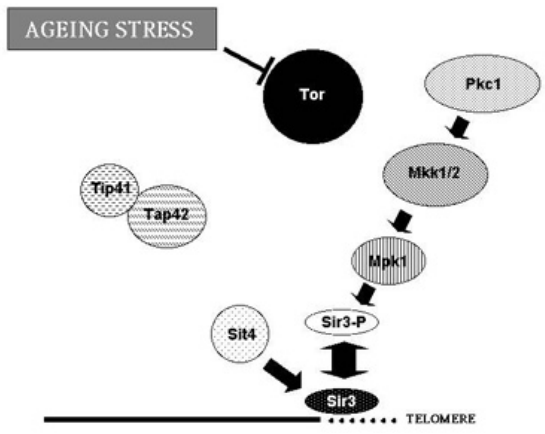

Figure. Model of regulatory system of heterochromatin status via Sir3 phosphorylation by PPase and MAP kinase.