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Title	Mps3 (Sun domain protein) phosphorylation dependent nuclear envelope remodeling facilitates rapid movements of chromosomes during meiosis
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Citation	大阪大学, 2011, 博士論文
Version Type	
URL	https://hdl.handle.net/11094/59448
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博士の専攻分野の名称	博　士（理学）
学 位 記 番 号	第　２４８８２　号
学位授与年月日	平成23年９月20日
学位授与の要件	学位規則第４条第１項該当 理学研究科生物科学専攻
学 位 論 文 名	Mps3 (Sun domain protein) phosphorylation dependent nuclear envelope remodeling facilitates rapid movements of chromosomes during meiosis. （SUN ドメインタンパク質 Mps3 のリン酸化に依存した減数分裂期の核膜リモデリングと染色体運動）
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論 文 内 容 の 要 旨

Abstract :
The dynamic behavior of chromosomes during meiosis prophase –I has been likened to a middle school dance, where partners find one another (homologous chromosomes), form couples (bivalents or synaptonema complex) that move about and trade information, and then separate to opposite sides of the dance hall (nucleus). Individuals can be attracted to more than one partner or find themselves trapped behind or between other couples and, failing to form a couple effectively, end up on the wrong side of the dance hall. As with meiotic prophase–I, chromosomes move rapidly to find its partner called rapid prophase movements, but it is not clear how these movements will be regulated to form couple effectively.

On entry of *S. cerevisiae* cells into meiosis, telomeres attach to the nuclear envelope (NE) and transiently cluster on a limited area near Spindle pole body (SPB; an equivalent to mammalian centrosome) to form a “chromosomal bouquet”. Telomere clustering is thought to promote recognition and stable pairing of homologous chromosomes. A component of the *S. cerevisiae* SPB, Mps3, which is an inner nuclear envelope protein with the conserved SUN domain, is involved in the telomere clustering/movement during meiosis. Mps3 protein changes the localization during meiosis; from SPB to NE. This relocalization of Mps3 is independent of Mps3 Sun domain, actin, Csm4, Ndj1, but depends on *S. cerevisiae* CDK (cyclin-dependent kinase; Cdc28-cyclin) and DDK (Dbf4 –Cdc7) activities. When cells with an inhibitor-sensitive allele, the *cdc28-as1* and *cdc7-as3*, are treated with the inhibitor (1NM-PP1 and PP1, respectively) upon meiotic entry, relocation of Mps3 is severely hampered. This suggests that CDK and DDK regulate dynamics of the NE component during meiosis. Indeed, when the movement of telomeres is visualized using a GFP-fusion protein of Rap1 (a telomere binding protein), the treatment of the *cdc28-as1* and *cdc7-as3* mutants with the inhibitors hampers the movement of Rap1 on NE as well as bouquet resolution. In fact, rapid prophase movements of telomeres are absent in the *mps3-3A* (188T-A, 189S-A, 190S-A substitutions) mutant, which lacks putative CDK-DDK phosphorylation sites. The *mps3-3D* (188T-D 189S-D,190S-D) phosphomimic mutant suppresses CDK and DDK requirement for rapid prophase movements. While, the SUN domain of Mps3 is partially required for telomere and chromosome movements. Interestingly deletion of nuclear pore proteins Nup152 and Pom152 completely suppresses *mps3-aaa* defects in Mps3 relocalization but not in movements. In the absence of these nucleoporins, Mps3 completely relocalizes on the NE during mitosis in both wild type as well as mps3-aaa mutant.

It is likely that CDK and DDK collaborate to regulate telomere clustering, bouquet resolution and rapid prophase movements by phosphorylating Mps3-containing complex on NEs and Mps3 functions such as relocation is negatively regulated by the nuclear pores.

In my thesis, I revealed a novel control pathway of a NE-bound protein during meiosis, which plays a critical role in events in meiosis prophase-I such as pairing of chromosomes and the recombination.

論 文 審 査 の 結 果 の 要 旨

H. B. D. Prasada Rao 氏は Mps3 (Sun domain protein) phosphorylation dependent nuclear envelope remodeling facilitates rapid movements of chromosomes during meiosis（SUN ドメインタンパク質 Mps3 のリン酸化に依存した減数分裂期の核膜リモデリングと染色体運動）というテーマで研究を行った．配偶子形成に必要な減数分裂期では、染色体が核内で再配置され、ダイナミックに動くことが知られている。その機能や分子レベルでの機能については不明な点が多い。本研究で、核膜タンパク質の１つ Mps3 が２つのリン酸化酵素、CDK（サイクリン依存性キナーゼ）と DDK（Dbf1 依存性キナーゼ）により直接リン酸化されることが、Mps3 の核膜への再局在、ならびに運動に重要な役割を果たすことを実験的に示した。また、この Mps3 のリン酸化が減数分裂の核内でおこる染色体運動のみならず、組換え、そして核膜の拡張を制御することを見出した。加えて、この制御に核膜孔のタンパク質も関与することを見出した。

タンパク質のリン酸化による核膜の remodeling が減数分裂の核内でおこる種々の事象のグローバルな制御形態であることを示した．極めて独創性の高い研究と断言できる。

よって、本論文は博士（理学）の学位論文として十分価値あるものと認める。