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New insights into Cdk2 regulation during meiosis

Michitaka Isoda[a], Petra Mikolcevic[a], and Angel R. Nebreda[a,b]

[a]Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology, Barcelona, Spain; [b]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

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Cyclin dependent kinases (CDKs) are proline-directed serine/threonine kinases that play a central role in regulating cell cycle progression. Since the activity of CDKs depends on the binding of regulatory subunit named cyclins, the analysis of the CDK functions that have been studied so far has usually gone in parallel to the study of cyclins. However, the proteins referred to as RINGO or Speedy, which have no amino acid sequence homology to cyclins, have been found to function as atypical CDK activators.

The first RINGO protein was identified as a new activator of Cdk1 and Cdk2, which induced the meiotic maturation of frog (*Xenopus*) oocytes. Interestingly, CDKs activated by *Xenopus* RINGO were found to phosphorylate different sites on the kinase Myt1 than those phosphorylated by cyclin-CDK complexes.[1] In fact, Myt1 is much more efficiently inhibited by RINGO-CDK than by cyclin-CDK, supporting the idea that RINGO-activated CDKs may have different functions. RINGO proteins are conserved in metazoans and several mammalian RINGO family members have been identified. The best-studied mammalian family member is RingoA, whose mRNA is highly expressed in mouse gonads, suggesting that RingoA might regulate meiotic progression, as reported for *Xenopus* RINGO in oocytes. Genetic studies published during the past decade have provided good evidence that Cdk1 is the only CDK family member that is essential for mouse cell proliferation, and genetic inactivation of Cdk1 has been shown to cause mouse embryonic lethality.[2] In contrast, Cdk2 is not essential for somatic cell proliferation in mouse but it is indispensable for male and female meiosis. Interestingly, the meiotic phenotypes that are observed in Cdk2 knockout spermatocytes and oocytes have not been reported in any of the mice deficient for particular cyclins. A recent report has shown that the combined deletion of cyclins E1 and E2 produces similar meiotic phenotypes in spermatocytes as the deletion of Cdk2.[3] However, cyclins E1 and E2 do not co-localize with Cdk2 during prophase I of meiosis, neither at telomeres nor at crossing-over sites, suggesting that they are unlikely to be involved in Cdk2 activation at these specific locations. These findings support the existence of a cyclin-independent mechanism of Cdk2 activation in germ cells.

We have recently reported that RingoA knockout mice are born with the expected Mendelian frequency and do not show any overt differences compared to their wild-type littermates. However, they are sterile and have hypoplastic testes and ovaries, supporting an important role for RingoA in mammalian meiotic progression.[4] Importantly, spermatocytes and oocytes that are deficient in RingoA show identical phenotypes as those deficient in Cdk2,[5] namely they are mostly arrested in a pachytene-like stage of prophase I with non-homologous chromosome pairing, telomere detachment from the inner nuclear membrane (INM) and telomere fusion (Fig. 1). In addition, RingoA-deficient spermatocytes and oocytes show strong accumulation of γH2AX, which is a hallmark of unrepaired double strand breaks. The arrested germ cells then undergo apoptosis probably due to the pachytene checkpoint, which is activated by the accumulation of unrepaired DNA.[4]

RingoA localizes to the telomeric regions in pachytene spermatocytes, as it has been reported for Cdk2,[5] co-localizes with Cdk2 from the leptotene stage and then disappears from telomeres as cells enter the diplotene stage. RingoA and Cdk2 also co-localize along the asynapsed sex chromosome arms in pachytene spermatocytes. Interestingly, RingoA-deficient spermatocytes show impaired localization to telomeres of Sun1, a protein required for telomere tethering to the INM, whereas the telomeric localization of TERB1, another protein required for telomere-INM tethering, is maintained.[4] RingoA-Cdk2 can phosphorylate *in vitro* the N-terminus of Sun1, which is the domain involved in binding to TERB1, so it is possible that RingoA-Cdk2 regulates the tethering of telomeres to the INM through phosphorylation of Sun1, but the detailed physiological mechanism remains unclear. In contrast to the co-localization of RingoA and Cdk2 in telomeres and sex chromosomes, RingoA does not co-localize with Cdk2 at crossing-over sites. Since Cdk2 has been reported to bind the late-recombination marker protein Mlh1,[6] Cdk2 might participate in late-recombination events through the binding to a regulatory subunit other than RingoA.

In addition to the regulation of Sun1 localization, RingoA seems to control chromatin methylation. RingoA-deficient spermatocytes show decreased levels of the histone H3

CONTACT Michitaka Isoda michitaka.isoda@irbbarcelona.org; Angel R. Nebreda angel.nebreda@irbbarcelona.org

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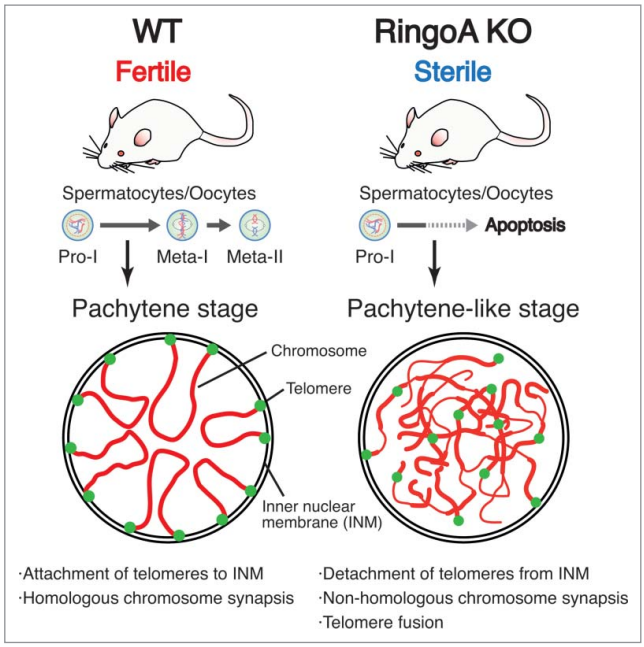

Figure 1. The Cdk2 activator RingoA is essential for the progression of germ cells through meiotic prophase I. Loss of RingoA arrests mouse germ cells in a pachytene-like stage with defective telomere tethering to the inner nuclear membrane (INM), non-homologous chromosome synapsis and telomere fusion, eventually leading to apoptosis.

trimethylated at Lys9 (H3K9-3me), whereas the amount of the histone H3 trimethylated at Lys4 (H3K4-3me) is increased.[4] Reduction of H3K9-me3 is thought to cause telomere shortening, which is actually observed in RingoA-deficient spermatocytes.[4] Moreover, aberrant chromosome methylation has been associated with non-homologous meiotic chromosome pairing,[7] and might be also related to the telomere fusion and non-homologous chromosome pairing that are observed in RingoA-deficient germ cells. How RingoA could modulate histone H3 methylation during meiosis remains unclear, but it is interesting to speculate that histone H3 phosphorylation by RingoA-Cdk2 could be involved.

Our results suggest that RingoA regulates the telomere length, which is critical for meiotic progression.[4] Since the maintenance of telomere length is important for cell immortalization and malignant transformation, further elucidation of RingoA functions may help to understand tumorigenesis mechanisms.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Ruiz EJ, Hunt T, Nebreda AR. Meiotic inactivation of Xenopus Myt1 by CDK/XRINGO, but not CDK/cyclin, via site-specific phosphorylation. Mol Cell 2008; 32:210-20; PMID:18951089; http://dx.doi.org/10.1016/j.molcel.2008.08.029

[2] Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nature reviews Cancer 2009; 9:153-66; PMID:19238148; http://dx.doi.org/10.1038/nrc2602

[3] Martinerie L, Manterola M, Chung SS, Panigrahi SK, Weisbach M, Vasileva A, Geng Y, Sicinski P, Wolgemuth DJ. Mammalian E-type cyclins control chromosome pairing, telomere stability and CDK2 localization in male meiosis. PLoS Genet 2014; 10:e1004165; PMID:24586195; http://dx.doi.org/10.1371/journal.pgen.1004165

[4] Mikolcevic P, Isoda M, Shibuya H, Del Barco Barrantes I, Igea A, Suja JA, Shackleton S, Watanabe Y, Nebreda AR. Essential role of the Cdk2 activator RingoA in meiotic telomere tethering to the nuclear envelope. Nat Commun 2016; 7:11084; PMID:27025256; http://dx.doi.org/10.1038/ncomms11084

[5] Viera A, Rufas JS, Martinez I, Barbero JL, Ortega S, Suja JA. CDK2 is required for proper homologous pairing, recombination and sex-body formation during male mouse meiosis. J Cell Sci 2009; 122:2149-59; PMID:19494131; http://dx.doi.org/10.1242/jcs.046706

[6] Liu W, Wang L, Zhao W, Song G, Xu R, Wang G, Wang F, Li W, Lian J, Tian H, et al. Phosphorylation of CDK2 at threonine 160 regulates meiotic pachytene and diplotene progression in mice. Dev Biol 2014; 392:108-16; PMID:24797635; http://dx.doi.org/10.1016/j.ydbio.2014.04.018

[7] Mahadevaiah SK, Bourc'his D, de Rooij DG, Bestor TH, Turner JM, Burgoyne PS. Extensive meiotic asynapsis in mice antagonises meiotic silencing of unsynapsed chromatin and consequently disrupts meiotic sex chromosome inactivation. J Cell Biol 2008; 182:263-76; PMID:18663141; http://dx.doi.org/10.1083/jcb.200710195