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Cell Cycle New and Views

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The fine spatial and temporal resolution of translation control can have a rapid and subtle effect on the microenvironment of the cell in comparison with transcriptional regulation. Mammalian oocyte represents a relevant model that allows addressing the spatial control of translation during meiotic maturation. The fully-grown mammalian oocyte is transcriptionally quiescent and stored maternal RNAs are used for the completion of meiosis and early embryo development. It was shown three decades ago that during resumption of meiosis, protein synthesis is not necessary for the nuclear envelope breakdown (NEBD) but active protein synthesis is required for the correct formation of the meiotic spindle and progression to metaphase II (1). Therefore mammalian oocyte represents a suited system to address translation control in relation with the cell cycle in general and with the spindle formation in particular. In this issue of the Cell Cycle the study by Jansova et al. gains new insight into the role of the eukaryotic initiation factor 4E-Binding Protein 1 (4E-BP1) in the meiotic spindle formation in mouse oocyte (2).

4E-BP1 has been shown to undergo a dynamic and fine spatially regulated pattern of phosphorylation at sites that control its binding to eIF4E and consequently its efficiency to inhibit translation (3, 4). Then, it has been proposed that the localization of specific phosphorylated 4E-BP1 isoforms at the spindle pole or on the spindle represents a novel mechanism supporting localized protein synthesis related to mRNA localized at the spindle. The study by Jansova et al. goes further in demonstrating the implication of the 4E-BP1-phosphorylation status in forming a well-structured meiotic spindle. Microinjection of mRNA encoding for a dominant negative 4E-BP1 mutant (replacement of key serine/threonine residues by non-phosphorylatable alanine residues) affects translation activity and promotes aberrant spindle formation. Their data demonstrate that 4E-BP1-phosphorylation is essential to ensure correct meiotic progression.

In this regard, the identification of the kinases, which are involved in the phosphorylation of 4E-BP1, represents a major challenge. Kubelka's group previously showed that chromosomal translational hotspots are controlled by the activity of the mTOR-signalling pathway during the first meiotic division in maturing mouse oocytes (5). The current study adds new information by investigating the role of CDK1 on the phosphorylation of 4E-BP1 in mouse oocytes (2). Using specific kinase inhibitors, they showed that CDK1 and mTOR kinases are the main positive regulators of 4E-BP1

phosphorylation following NEBD (Fig. 1). The Western blot data shown by Jansova et al., indicate that CDK1 influences the activity of mTOR in mouse oocytes suggesting that CDK1 acts indirectly on 4E-BP1 phosphorylation via mTOR activation. Interestingly, both CDK1 and mTOR co-localize with specific 4E-BP1-phosphorylation isoform on the spindle at the onset of meiotic resumption. The fact that CDK1 is a positive regulator of the 4E-BP1-phosphorylation during mouse oocyte maturation will add fuel to the complicated debate of the link between the translational activity and the stages of the cell cycle. Indeed, many discrepancies that have been reported when observing translation mechanisms linked with the cell cycle might be related to direct effect of the different pharmacological agents used to synchronize cells rather than cell cycle status (6). Therefore, oocyte meiotic maturation, where the synchronism of cell divisions occurs physiologically, represents a pertinent model for the analysis of the control of the phosphorylation of 4E-BP1 by CDK1. The work by Jansova et al., revealing CDK1 activity towards 4E-BP1 phosphorylation via unexpected phosphorylation and activation of mTOR, adds more to the complexity of the signalling pathway acting upstream 4E-BP1 and may initiate further research.

In view of these works, it now appears that fine control of translation activity within the spindle can play an important role in maintaining genomic stability. However, many points remain to be clarified. Among others, one can still wonder how the phosphorylations are controlled spatially on specific sites of 4E-BP1 and what their consequences on specific translation activity are. Which mRNAs are actively translated in this spatial and temporal context? The integration of 4E-BP1-phosphorylation knowledge at different levels of scales (molecular / structural (7) and intracellular compartments (2-6)) opens up a promising field of investigation for systemic approaches that focus on spatio-temporal control of the mRNA translation. It is almost sure that the mammalian oocyte meiotic maturation system, by its characteristics: size and round shape, synchronism and asymmetry of meiotic divisions, its links with translation, represents an interesting future model in this context.

References

1. Hashimoto N, Kishimoto T. Regulation of meiotic metaphase by a cytoplasmic maturation-promoting factor during mouse oocyte maturation. Dev Biol. 1988;126(2):242-52. PubMed PMID: 3350209.
2. Jansova D, Koncicka M, Tetkova A, Cerna R, Malik R, del Llano E, et al. Regulation of 4E-BP1 activity in the mammalian oocyte. Cell Cycle 2017; In press; http://dx.doi.org/10.1080/15384101.2017.1295178.
3. Romasko EJ, Amarnath D, Midic U, Latham KE. Association of maternal mRNA and phosphorylated EIF4EBP1 variants with the spindle in mouse oocytes: localized translational control supporting female meiosis in mammals. Genetics. 2013;195(2):349-58. doi: 10.1534/genetics.113.154005. PubMed PMID: 23852387; PubMed Central PMCID: PMCPMC3781964.
4. Shang ZF, Yu L, Li B, Tu WZ, Wang Y, Liu XD, et al. 4E-BP1 participates in maintaining spindle integrity and genomic stability via interacting with PLK1. Cell Cycle. 2012;11(18):3463-71. doi: 10.4161/cc.21770. PubMed PMID: WOS:000308907600025.
5. Susor A, Jansova D, Cerna R, Danylevska A, Anger M, Toralova T, et al. Temporal and spatial regulation of translation in the mammalian oocyte via the mTOR-eIF4F pathway. Nat Commun. 2015;6:6078. doi: 10.1038/ncomms7078. PubMed PMID: 25629602; PubMed Central PMCID: PMCPMC4317492.

6. Coldwell MJ, Cowan JL, Vlasak M, Mead A, Willett M, Perry LS, et al. Phosphorylation of eIF4GII and 4E-BP1 in response to nocodazole treatment: a reappraisal of translation initiation during mitosis. Cell Cycle. 2013;12(23):3615-28. doi: 10.4161/cc.26588. PubMed PMID: 24091728; PubMed Central PMCID: PMCPMC3903713.
7. Bah A, Vernon RM, Siddiqui Z, Krzeminski M, Muhandiram R, Zhao C, et al. Folding of an intrinsically disordered protein by phosphorylation as a regulatory switch. Nature. 2015;519(7541):106-9. doi: 10.1038/nature13999. PubMed PMID: 25533957.

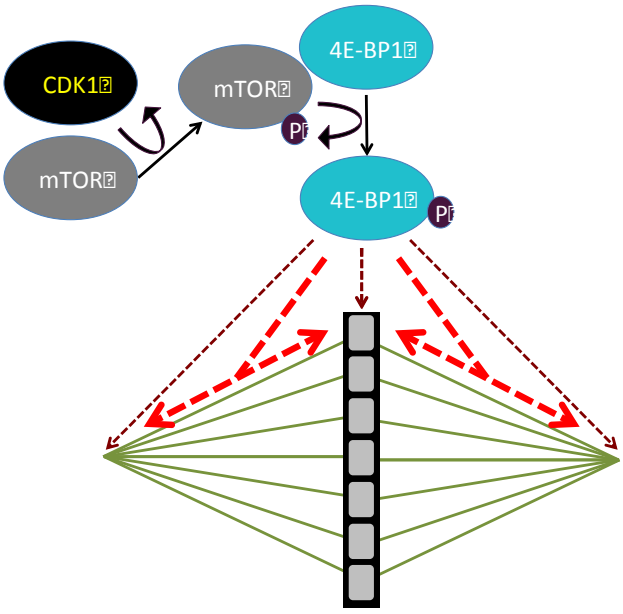

Figure 1 legends: CDK1 phosphorylates and activates mTOR, which phosphorylates 4E-BP1 on different sites (after (2)). Depending on the phosphorylated sites, 4E-BP is localized in the vicinity of the chromosomes and at the spindle poles (brown dashed arrows) or is distributed along the whole spindle (red dashed arrows).