Yes Fyn Can: Individual or team player in SFKs?

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Oocyte maturation is the key period in female gamete formation. Two successive meiotic divisions ensure that mature oocytes will contain a haploid number of chromosomes, while highly asymmetric cleavages make sure that the majority of cytoplasmic resources necessary for embryo development will remain within the oocyte and will not be lost within the polar bodies. Therefore, the cell divisions during oocyte maturation differ fundamentally from all other cell divisions by the absence of S phase between the two M phases, and by an extreme polarization of the dividing cell. In addition, all this happens in a huge cell, making rigorous temporal and spatial coordination both necessary and extremely difficult. To this end, the sequence of events upon oocyte maturation must be carefully controlled and constantly corrected. A part of this control relies on protein phosphorylation, orchestrated by kinases and phosphatases, of which a major role is attributed to serine-threonine kinases. Among them CDK1 (Cyclin-Dependent Kinase 1), Mos proto-oncogene and MAP kinases ERK1/2 (Extracellular-Regulated Kinases 1/2) play pivotal roles. CDK1/cyclin B inactivation requires cyclin B ubiquitination and separation from CDK1,[1] which is finely controlled by Mos/…/ERK1/2 pathway.[2] However, serine and threonine phosphorylations are not the only players in this game. Tyrosine phosphorylations are also involved in oocyte maturation. These phosphorylations are executed, among others, by a family composed of nine closely related tyrosine kinases, known also as SFKs (Src Family Kinases), named after the Src proto-oncogene, the first family member described. Src, Yes and Fyn are expressed in a broad range of tissues, and are present in oocytes. This family was first studied using inhibitors (e.g., PP2 or SU6656) that interfere with the function of all SFKs, due to intra-familial structural similarities. Pharmacological inhibition of SFKs has demonstrated their involvement in a wide variety of cell functions, including the cell cycle. Moreover, SFK members are able to compensate for one another.[3,4] In MII-arrested rat oocytes, the SFKs clearly interfere with the CDK1 and Mos/…/ERK1/2 pathways. For example, a dominant-negative form, either of Yes or Fyn, inhibits cyclin B degradation and oocyte activation.[5] The question remained as to whether or not each of the family members has a specific role to play during oocyte maturation. To answer this question, more subtle methods had to be applied. Deletion of the Fyn gene from mice has shown that this kinase is essential for embryo development, and has recently provided key information on the function of Fyn in oocyte maturation.[6] The pharmacological and genetic studies were completed by siRNA knock-down experiments, performed specifically in oocytes,[7] showing that Fyn inhibition has a drastic impact on oocyte maturation. $Fyn^{-/-}$ oocytes have defects in both the spindle organization and chromosome segregation that, in some cases, brought meiotic maturation to a halt, whereas in other cases, permitted advancement of the cell cycle to M II, albeit with significant spindle distortions. Do other SFK members rescue the oocytes from complete penetrance of the most severe phenotype?

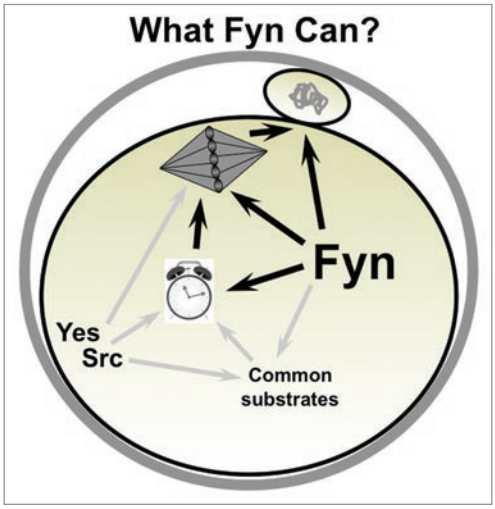

Figure 1. Fyn kinase regulates timing of events during oocyte maturation participates in meiotic spindle function and in polar body extrusion (black arrows). How Fyn collaborates with other members of the SFKs tyrosine kinase family remains to be elucidated (grey arrows).

For a better insight into the specific functions of Fyn in mouse oocytes and its regulation, Levi, Maro and Shalgi (*Cell Cycle* Volume 9, Issue 8) used Western blot and immunofluorescence analysis of Fyn coupled with expression of RNAs coding for wild type and mutants of Fyn (dominant-negative and constitutively active), followed by confocal imaging of live oocytes. These approaches, together with previous analyses of genetic knock-out and siRNA-mediated knock-down, enabled them to demonstrate specific roles of Fyn during key stages of mouse oocyte maturation. Partial degradation of Fyn might be crucial for meiotic resumption and for oocyte nucleus (GV for Germinal Vesicle) breakdown (GVBD). The strong accumulation of Fyn within the meiotic spindle and at the oocyte cortex before polar body extrusion helps in the accurate orchestration of chromosome separation and polar body extrusion, especially in determining its precise sizing and timing. Fyn seems therefore to have a strong impact on both temporal and spatial coordination of oocyte maturation. However, it is still not clear whether it is alone in this regulation, or if it operates in concert with other family members. The structural similarities between Fyn, Src and Yes suggest that they may act as a family. For this reason it would be of great importance to learn the role played by each member of this orchestra (**Fig. 1**).

Given the complex role of Fyn during oocyte maturation it would be of great importance to identify substrates of Fyn. Numerous substrates are known in other types of cells

(e.g. Rho GTPase-activating protein called TCGAP for Tc10/Cdc42 GTPase-activating protein),[8] and some in oocytes (e.g. tr-kit proto-oncogene).[9] Levi et al suggest that γ-tubulin located at the spindle poles and involved in spindle organization could be another potential substrate within the meiotic spindle. Further questions are whether Fyn substrates differ from those of Src and Yes, and how are they localized during the spindle formation and polar body extrusion? Full understanding of SFKs role in oocytes will also require identification of phosphatases counterbalancing the effects of Fyn, Src and Yes. These questions and problems will certainly not wait a long time for answers. The understanding of tyrosine phosphorylation in oocyte maturation follows the well-established knowledge of serine and threonine phosphorylation today. The real challenge for tomorrow will be to get an insight into the precise role of their phosphatases. These extremely important enzymes are just now entering the stage.

References

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