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Phase Separation of FXR1 Activates Dormant mRNAs and Drives Sperm Development

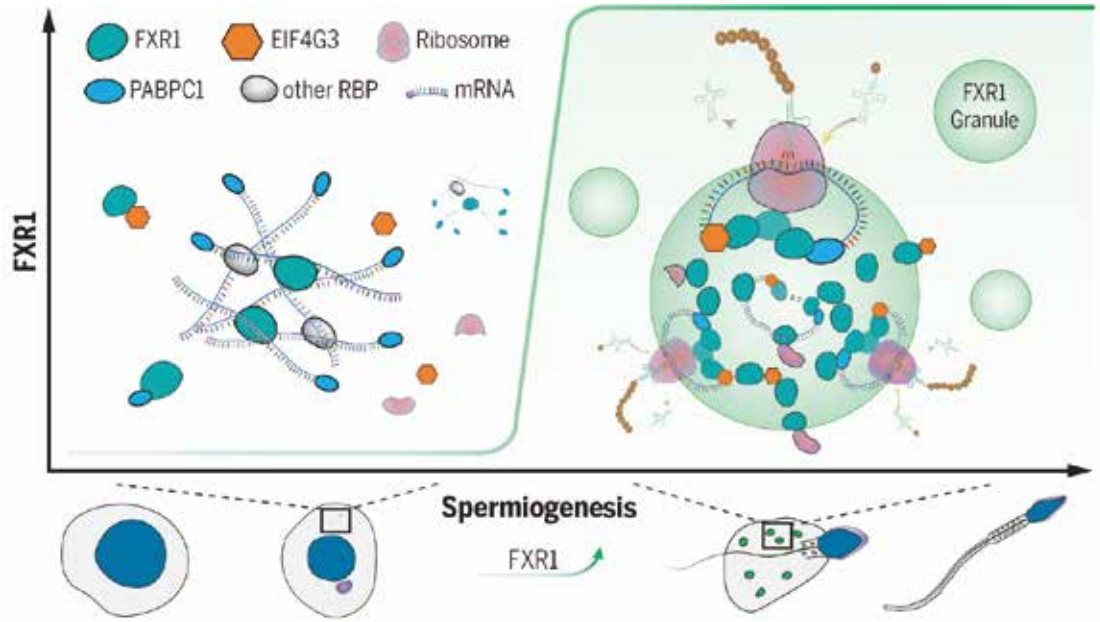
By YAN Fusheng (Staff Reporter)

Chinese researchers pinpoint an RNA-binding protein called FXR1 to be the key to wake up the dormant mRNAs required for late sperm maturation in mice, which may shed light on how to reverse male infertility in humans.

In mammals, spermiogenesis (the maturation of spermatids into mature, motile 'tadpole-like spermatozoa) is highly orchestrated and controlled by a group of genes collectively referred to as spermiogenic genes. As the nucleus condenses at the head part during spermiogenesis, transcription gradually halts. The spermiogenic genes transcribed in advance during the earlier stages of spermiogenesis are stored as translationally inert messenger ribonucleoproteins (mRNPs, an assembly of mRNAs and RNA binding proteins) until they are needed for translation.

Such mRNPs are usually organized into mRNP granules, which serve as membraneless storage facilities for non-translating mRNAs. They remain inert till a specific moment at the late stage when they are activated and kicked into translation. However, the mechanism by which they are activated is poorly understood.

In the August 12 issue of *Science*, a Chinese team,



FXR1-containing granules (membraneless biomolecular condensates) mediate translation activation in late spermatids. During late spermiogenesis, elevated FXR1 (an RNA binding protein) undergoes liquid-liquid phase separation to assemble target mRNAs as FXR1 mRNP granules that recruit translational machinery to activate the stored mRNAs in late spermatids. These phase-separated FXR1 granules drive an extensive translation program to instruct mouse spermatid development and sperm maturation. (Image by CEMCS)

jointly led by Dr. LIU Mofang from the Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science (CEMCS) under the Chinese Academy of Sciences, and Dr. HUANG Ying from the Xinhua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, pins down a particular RNA binding protein called FXR1 to be the key to turn on the translation of the mRNAs and usher the further sperm maturation in mice.

The study shows that FXR1 is highly expressed in late spermatids and undergoes liquid-liquid phase separation (LLPS) to merge mRNP granules with the translation machinery, converting stored mRNAs into a translationally activated state.

As they suggested, in mouse late spermatids, elevated FXR1 protein may "invade" these mRNPs using phase separation to gradually disrupt existing RNA-RNA interactions and/or replace other RNA binding proteins to transform the stored mRNAs into new FXR1-dominated mRNP granules. During this transformation process, FXR1 recruits the translation machinery through its direct interaction with translation initiation factor EIF4G3, thereby converting its target mRNAs into a translationally activated state. The proposed mechanism suggests a crucial role of FXR1 granules in enriching both mRNA transcripts and the translational machinery, whereby it induces the translation of spermiogenic mRNAs in late spermatids.

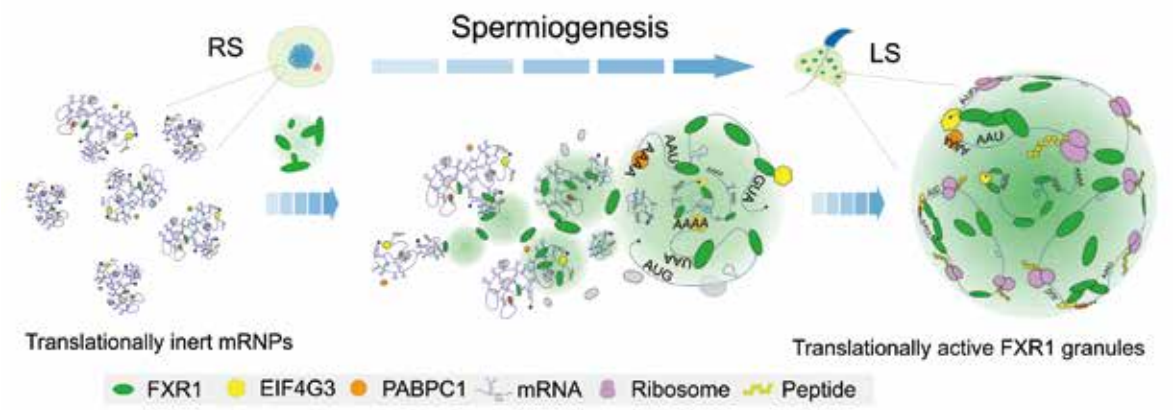
Germline-specific *Fxr1* ablation in mice impaired the translation of target spermiogenic mRNAs and caused defective spermatid development and male infertility. Mutant mice with phase separation deficiency caused by a genetic mutation at *Fxr1* suffered the same developmental defects.

"These findings demonstrate that FXR1 is an essential translation activator that instructs spermiogenesis in mice and unveils a key contribution of FXR1 LLPS to the translation activation of stored mRNAs in mouse spermatid and male fertility in mice," said the authors in the article. "The study also pinpoints the importance of liquid-liquid phase separation in a developmental process *in vivo*."

Indeed, phase separation allows cellular organization by coordinating biochemical reactions into membraneless biomolecular condensates, such as ribonucleoprotein (RNP) granules.

"RNP granules are classically associated with translational repression…, but this new work reports translational activation as a previously unknown function of biomolecular condensates," commented Dr. Martine Simonelig, a French human geneticist from Université Montpellier, on this work in the same *Science* issue.

"Now, a key issue to address is the biological functions of these condensates: Can phase separation induces specific functions and, if so, how?…understanding how granule formation contributes to biological functions in vivo remains a major challenge."



A schematic model shows that FXR1 activates the translation of spermiogenic mRNAs in late spermatids (LS) through phase separation and interaction with translation machinery components. (Image by CEMCS)

Reference

Kang, J. Y., Wen, Z., Pan, D., et al. (2022). LLPS of FXR1 drives spermiogenesis by activating translation of stored mRNAs. *Science, 377*(6607), eabj6647. doi:10.1126/science.abj6647