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# In the Spotlight

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## New Insights Into Oocyte Activation

Activation of the metaphase II-arrested oocyte after the spermatozoid–oocyte fusion takes place is key for normal fertilization to occur. This activation process is known to involve a cascade of events that is triggered by a transient rise in oocyte intracellular calcium levels, which eventually leads to exocytosis of cortical granules, completion of meiosis II, decondensation of sperm nucleus, pronuclei formation, and, finally, embryo cleavage.

Although many steps of the oocyte activation process are clearly understood, the nature of the sperm factors that act upstream the intracellular calcium release has remained to be elucidated.

Interestingly, in a recent issue of the *Journal for the Federation of American Societies for Experimental Biology* (*FASEB J.* 2014;28:4434-4440) Aarabi and colleagues report the identification of a sperm-derived protein that is essential for calcium oscillations and oocyte activation in mice and humans.

Aarabia et al showed that the sperm postacrosomal WW binding protein (PAWP), which is stored in the sperm compartment whose content is first released into the oocyte cytoplasm, is able to trigger oocyte calcium oscillations and pronuclear formation in human and mouse oocytes similar to what is observed during intracytoplasmic sperm injection. In addition, the authors demonstrated that the sperm-induced calcium oscillations are blocked upon coinjection of a competitive inhibitor, derived from the WWI domain-binding motif of PAWP. These results indicate that PAWP is both required and essential for successful fertilization and zygotic development.

These findings not only help elucidate the process of oocyte activation but also suggest that deficiencies in PAWP may constitute a previously unrecognized etiology for some cases of idiopathic infertility, indicating that it may also be a promising target for the development of new therapeutic strategies to combat infertility.

## A Closer Look at BRCA2

Mutations in the gene BRAC2 have long been associated with an increased susceptibility to breast, ovarian, and prostate cancer. Although the BRAC2 protein is known to play an important role in DNA repair, specifically acting in the repair of DNA double-strand breaks that occur due to inevitable daily exposure to toxic chemicals, metabolic by-products, and radiation, its characterization and mechanism of action have been hard to elucidate. This lack of information has impaired the development of much needed BRAC2-targeted prophylactic and therapeutic strategies to defeat certain types of cancer.

Fortunately, with a recent publication in *Nature Structural and Molecular Biology* (*Nature Structural & Molecular Biology*. 2014; doi:10.1038/nsmb.2899) by Shahid et al, the improvement in a BRAC2-targeted cancer fighting approach may be closer to reach. Shahid and colleagues have been able to present for the first time the biochemical and structural characterization of the full-length BRAC2 protein, alone and forming a complex with its counterpart RAD51.

The authors' studies reveal that BRAC2 facilitates the nucleation of RAD51 filaments at multiple sites on single-strand DNA, which then searches for matching DNA strands in order to repair the break. This concomitant assembly of filaments at multiple sites suggests an increased efficiency to search for matching strands.

Shahid and colleagues also show that the extremely large (3418 amino acids long) BRAC2 protein acts as a dimer, which additionally binds to 2 sets of RAD51 that run in opposite directions. The authors further demonstrate that single-strand DNA binds along the long axis of BRAC2, in a way that assures that only 1 set of RAD51 monomers can form a productive complex with the DNA and establish the filament formation.

Thus, the findings by Shahid et al provide a closer look at the molecular mechanisms involved in homologous recombinational repair, which will hopefully on one hand lead the way to the discovery of new approaches to correct or overcome BRAC2 defects, and on the other to manipulate cancer cells to become less efficient in DNA repair to prompt their death.