26S PROTEASOME AND PKA MODULATE MAMMALIAN SPERM CAPACITATION BY CREATING AN INTEGRATED DIALOGUE: A COMPUTATIONAL ANALYSIS

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Recent experimental evidence suggests the involvement of the 26S proteasome, the main protease active in eukaryotic cells, in the process that leads mammalian sperm to become fully fertile, so-called capacitation. Unfortunately, its role in male gametes signaling is still far from being completely understood. For this reason, here, we realized a computational model as an attempt to rebuild and explore 26S proteasome signaling cascade, aggregating all the molecular data available to date and realizing the Proteasome Interactome Network (PIN). Once obtained the network (i.e., a graph to represent the molecules as nodes and the interactions among them as links), we assessed its topology to infer important biological information.

PIN is composed of 157 nodes, 248 links and it is characterized by a scale-free topology, following the Barabasi Albert model. In other words, it possesses a large amount of scarcely linked nodes and a small set of highly linked nodes, the hubs, which act as system controllers. This peculiar topology confers to the network relevant biological features: it is robust against random attacks, easily navigable and controllable and it is possible to infer new information from it. Indeed, the analysis of PIN showed that PKA and 26S proteasome were strongly interconnected and both were active in sperm signaling by influencing the protein phosphorylation pattern and then controlling several key events in sperm capacitation, such as membrane and cytoskeleton remodeling.

In conclusion, the network model could explain many biological aspects of sperm physiology that are out of focus looking at the single molecular determinant, overcoming the reductionist approach which did not consider the complexity of molecules and their interactions. This could be helpful to identify potential diagnostic markers and therapeutic strategies concurring in explaining and approaching male infertility.