Deciphering the Metabolic Reprogramming during Sperm Capacitation

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Mammalian sperm are stored in the epididymis in a dormant state. Upon ejaculation, they must immediately start producing sufficient energy to maintain motility and support capacitation. While this increased energy demand during capacitation is well-established, it remains unclear how mammalian sperm modify their metabolism to meet this need. Capacitation is regulated by changes in intracellular calcium (Ca^{2+}), sAC-mediated cAMP increase and protein phosphorylation via PKA. However, the interplay between these signaling pathways regulating sperm capacitation and sperm metabolism remains mostly unexplored.

Using an extracellular flux analyzer, metabolomics and metabolic flux analysis we compare the metabolism of non-capacitated and capacitated mouse and human sperm, sperm with impaired Ca^{2+} signaling, sperm treated with soluble adenylate cyclase (sAC) inhibitors and sperm from sAC knockout mice.

By combining these techniques we show that glycolysis and oxidative phosphorylation increase during capacitation in mouse and human sperm and that there is a functional link between glycolysis and oxidative phosphorylation. We discovered that the flux through glycolysis, pentose phosphate pathway and citrate cycle is altered during capacitation and that also endogenous substrates like amino acids are utilized for energy production. Furthermore, we identified a subset of glycolytic steps regulated by sAC and Ca^{2+}.

Our study provides new insights into the energy production during mammalian sperm capacitation and experimental evidence for a link between Ca^{2+}/sAC/protein kinase A-regulated signaling pathways and mammalian sperm metabolism.