Examining the role of α-ketoglutaric acid (AKG) and its receptor OXGR1 in male sperm maturation

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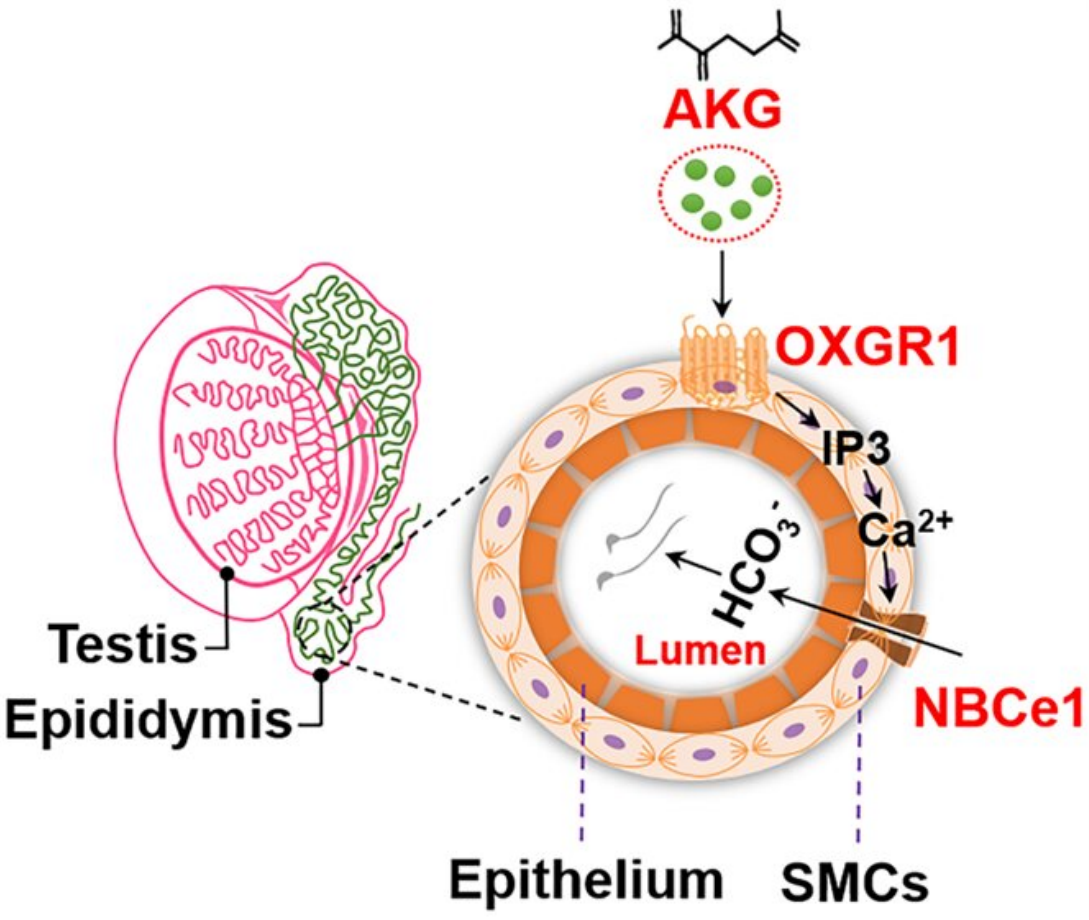

Schematic diagram of OXGR1-mediated AKG regulating the epididymal fluid

acid–base balance. Credit: Chang Xu et al

Infertility is a global public health problem caused by genetic defects, lifestyle, nutrition, and factors affecting the local metabolism and microenvironment of the reproductive system. Sperm from the testis must enter the epididymis to undergo a series of structural, biochemical and functional changes before they can gain maturity and become capable of fertilization. The influence of the epididymis on sperm maturation is highly susceptible to aging, stress and local metabolic factors.

On July 15, 2022, Professors Gang Shuang and Qingyan Jiang at South China Agricultural University published a study in *Life Metabolism* entitled "Smooth muscle AKG/OXGR1 signaling regulates epididymal fluid acid-base balance and sperm maturation," revealing the important role of AKG/OXGR1 signaling pathway in maintaining the male reproduction.

This study confirms for the first time that Oxoglutarate receptor 1 (OXGR1) is expressed in the smooth muscle of the epididymis and its levels decrease with aging and heat stress. Studies in global knockout of OXGR1 and epididymis-specific knockout of OXGR1 mouse models revealed that OXGR1 is essential for epididymal sperm maturation by regulating acid-base homeostasis in the renal tubular fluid. More importantly, AKG supplementation is beneficial for epididymal sperm maturation disorders caused by aging and heat stress.

OXGR1 is an endogenous receptor for AKG, a key metabolic intermediate of the Tricarboxylic acid (TCA) cycle. Previous studies have found that OXGR1 is most highly expressed in the testis, but its cellular distribution and biological functions in the male reproductive

system are unknown. Therefore, revealing the potential functions of OXGR1 in the male reproductive system is of great clinical significance and application.

As an endogenous agonist of OXGR1, AKG has been shown to have important regulatory roles in extending lifespan, maintaining intestinal health, reducing the risk of obesity, and activating macrophages. In the present study, supplementation of 2% AKG to drinking water significantly reduced the sperm malformation rate of epididymis, and increased the sperm capacitation and spontaneous acrosome reaction rate in aging mice. The similar effects were observed in the heat stress mouse model, but supplementation of AKG failed to effectively improve the reduction in sperm capacitation caused by heat stress.

This study revealed for the first time that epididymal smooth muscle can regulate local microenvironmental acid-base homeostasis and sperm maturation through the AKG/OXGR1 signaling pathway, suggesting a new function of smooth muscle cells in male fertility health. It also showed that the smooth muscle AKG/OXGR1 signaling pathway can reverse aging and heat stress-induced reduction in male fertility, providing a potential strategy for targeting aging and heat stress-induced reduction in male fertility.

More information: Chang Xu et al, Smooth muscle AKG/OXGR1 signaling regulates epididymal fluid acid–base balance and sperm maturation, *Life Metabolism* (2022). DOI: 10.1093/lifemeta/loac012

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