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New insights into transduction pathways that regulate boar sperm function

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ABSTRACT

Detailed molecular mechanisms mediating signal transduction cascades that regulate boar sperm function involving Ser/Thr and tyrosine phosphorylation of proteins have been reviewed previously. Therefore, this review will focus in those kinase pathways identified recently (<10 years) in boar spermatozoa that regulate different functional spermatozoa processes. AMP-activated protein kinase (AMPK) is a cell energy sensor kinase that was first identified in mammalian spermatozoa in 2012, and since then it has emerged as an essential regulator of boar sperm function. Signaling pathways leading to AMPK activation in boar sperm are highlighted in this review (PKA, CaMKKα/β, and PKC as well as Ca^{2+} and cAMP messengers as upstream regulators). Interestingly, stimuli considered as cell stress (hyperosmotic stress, inhibition of mitochondrial activity, absence of intracellular Ca^{2+}) markedly activate AMPK in boar spermatozoa. Moreover, AMPK plays a remarkable and necessary regulatory role in mammalian sperm function, controlling essential boar sperm functional processes such as motility, viability, mitochondrial membrane potential, organization and fluidity of plasma membrane, and outer acrosome membrane integrity. These mentioned processes are all required under fluctuating environment of spermatozoa when transiting through the female reproductive tract to achieve fertilization. An applied role of AMPK in artificial insemination techniques is also suggested as during boar seminal doses preservation at 17 °C, physiological levels of AMPK activity markedly increase (maximum on Day 7) and result essential to maintain the aforementioned fundamental sperm processes. Moreover, regulation of sperm function exerted by the glycogen synthase kinase 3 and Src family kinase pathways is summarized.

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1. Introduction

Most of the epididymal boar sperm acquire progressive motility in the middle (corpus) and terminal (cauda) regions. In this later terminal region of epididymis, boar sperm are stored in a quiet state to minimize possible premature membrane instability that could lead to nonphysiological acrosome reaction [1]. After ejaculation, mammalian sperm initiate flagellar beating and become actively motile although they are still unable to penetrate the egg layers. Motility activation is partially regulated by changes in the ionic media surrounding the spermatozoa. This motility pattern is later on modified to achieve hyperactivation, which exact role is not totally defined yet, although it is suggested to be related to spermatozoa release from the oviduct reservoirs and to aid sperm to penetrate the extracellular matrix of the oocyte. The physiological modifications that take place in sperm after epididymal maturation during their transit through the female reproductive tract that confers on sperm the ability to fertilize the oocyte have

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been collectively named as capacitation, which was first independently reported by Austin [2] and Chang [3]. Molecular events accompanying capacitation are still poorly understood; however, some processes are mostly pointing to a key spermatozoa compartment: the plasma membrane. Thus, capacitation correlates with increased plasma membrane fluidity and hyperpolarization, cholesterol efflux from the sperm plasma membrane as well as changes in intracellular ion concentrations and increased protein tyrosine phosphorylation [4]. These mentioned sperm physiological processes are necessary for the subsequent stimulation of hyperactivation and acrosome reaction [1]. The sperm progressive motility achieved after ejaculation occurs in response to exposure to the extracellular medium stimuli, especially bicarbonate which enters the spermatozoa through the plasma membrane *via* the actions of carbonic anhydrase, sodium bicarbonate cotransporter, and bicarbonate–chloride exchanger [5]. In the cytosol, bicarbonate binds and stimulates soluble adenylyl cyclase 10, also called sAC or SACY, which catalyzes the production of cAMP using ATP as substrate. The produced cAMP represents an intracellular messenger for the protein kinase A (PKA) that becomes allosterically activated and subsequently mediates downstream signaling pathways by stimulation of Ser/Thr phosphorylation of different substrate proteins [5,6]. More detailed molecular events in those transduction cascades mediated by cAMP involving PKA, PKC, PDK1, PLCgamma1-IP(3), and also tyrosine phosphorylation of proteins in boar sperm have been reviewed before [5]. Recently, it has been reported the presence of integral membrane water channels, aquaporins 7 and 11 in boar sperm. The amount of aquaporin 11 shows a correlation with sperm motility and membrane integrity [7].

Besides motility, the transit through the female reproductive tract exposes spermatozoa to different stimuli able to trigger those physiological and biochemical modifications that accompany the sperm capacitation process and ultimately confer on it the ability to fertilize the oocyte. Very recently, a proteomic approach in identifying numerous capacitation-related proteins in boar sperm has been performed [8]. Regarding kinases, it has been identified the extracellular signal–regulated kinases pathway in boar sperm where it regulates tyrosine phosphorylation during capacitation [9] and also the activation of AKT induced by dopamine along this process [10]. General signaling mechanisms underlying sperm modifications during capacitation have been the main subject of previous reviews [5,11,12]. Special relevance deserves recent studies aimed to elucidate mechanisms involved in boar sperm hyperactivation [5,13,14], changes in the plasma membrane organization [15], which may be induced by endocannabinoid-binding type-1 cannabinoid receptor CB1 and transient receptor potential vanilloid 1 (TRPV1) [16], Ser/Thr phosphorylation [17], tyrosine phosphorylation [13,18], and finally those leading to the acrosome reaction [5,12,19,20], which may be partially mediated by reactive oxygen species (ROS) and phospholipase A [21]. Besides phosphorylation, another posttranslational modification of proteins, ubiquitination, modulates boar sperm capacitation [22].

This review will focus in recent (<10 years) research signaling pathways that regulate different aspects of boar sperm function, including motility, viability, mitochondrial membrane potential, plasma membrane fluidity, and acrosome membrane integrity.

2. AMP-activated protein kinase

2.1. Structure and upstream signaling

AMP-activated protein kinase (AMPK) is a cellular fuel gauge that acts regulating energy balance at the cellular and whole body levels [23,24]. AMP-activated protein kinase is present in all eukaryotes as heterotrimeric complexes comprising a catalytic α subunit and regulatory β and γ subunits, each of which occurs in mammals as alternate isoforms encoded by distinct genes [25]. In mammalian cells, there are two isoforms of the α subunit, two isoforms of the β subunit, and three isoforms of the γ subunit [23]. The α subunit contains a typical serine/threonine protein kinase domain at the N-terminus and a C-terminal regulatory domain. Within the β subunit, there is a domain that has been termed the glycogen-binding domain or carbohydrate-binding module. The C-terminal region of the β subunit interacts with the α and γ subunits, acting as a scaffold for the interaction of the heterotrimeric complex [23]. Finally, the γ subunit contains four copies of a cystathionine-β-synthase domain [26] which forms four potential adenine nucleotide–binding sites [27].

Like most kinase cascades, AMPK is activated by phosphorylation of a residue (Thr172) within the activation loop of the kinase domain [28]. Several kinases have been described to phosphorylate AMPK at Thr172: LKB1 [29], α and β isoforms of the calcium-calmodulin kinase kinase (CaMKK) [30], TGF-beta-activating kinase 1, [31], and kinase suppressor of Ras 2 [32]. Moreover, AMPK becomes also activated by AMP *via* a tripartite mechanism: (1) promotion of Thr172 phosphorylation; (2) inhibition of Thr172 dephosphorylation and (3) allosteric activation. Only the second effect is mimicked by ADP, although all three AMP effects are antagonized by ATP [24].

2.2. AMPK functions

A vast majority of works investigating cellular functions of AMPK have been conducted in somatic cells [23–25]. Given its key role as a sensor of the cell energy status (through its activation by high AMP levels), one of the main known functions of AMPK is the control of metabolic pathways under different energy or stressful conditions. This metabolic regulator role of AMPK has been reported in different tissues including cardiac and skeletal muscle, adipose tissue, pancreas, liver, and brain [33,34]. In the reproduction realm, AMPK role has been studied in hypothalamic–hypophysis axis [35,36], epididymis and vas deferens function [37], and mouse oocyte meiotic maturation [38].

2.3. AMPK in boar spermatozoa

Until 2012, no works aimed to study the function of AMPK in spermatozoa had been conducted, although some AMPK-related kinases had been reported in these germ

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