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Review

Modes of acrosin functioning during fertilization

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ABSTRACT

Mammalian fertilization is a complex process that involves gamete recognition, penetration, and fusion. Biochemical studies that identified the role of acrosome components during sperm–ova interaction especially the zona pellucida (ZP) provided major advances in sperm cell biology. Acrosin (a typical serine protease) functions during fertilization in several significant ways which include: a) activation of acrosome components, b) secondary binding with the ZP, and c) hydrolysis of the ZP. However, studies using knockout (KO) acrosin-deficient mice cast doubt on the traditional role of acrosin in fertilization. The KO acrosin-deficient mice exhibit normal fecundity except for delayed fertilization. Despite the doubt cast on the traditional role of acrosin by the KO acrosin-deficient mouse studies, acrosin still remains a major protease involved in multiple processes of fertilization. In this review, we assess the functional profile of acrosin and briefly summarize recent findings on proteases involved in fertilization. We propose a refined scheme for the functional role of acrosin in fertilization. We particularly emphasize the role of acrosin in acrosome exocytosis and activation of other acrosome components based on advanced technology like structural X-ray analysis.

Contents

1. Introduction

Mammalian fertilization involves sperm–ova interactions and fertilization reactions both of which contribute to the synchronicity of fertilization whereby biochemical and molecular events of the sperm and ova occur in an organized fashion. The study of these processes has elucidated the mechanisms involved in sperm–ova recognition, the development of infertility therapies, and strategies for non-hormonal contraception in humans. However, many molecular mechanisms involved in fertilization remain un-resolved, especially in the area of sperm–ova interactions.

In most placental mammals, fertilization is a highly orchestrated process that involves a number of events which include: a) sperm penetration of the cumulus cell layer, b) sperm binding to the zona pellucida (ZP), c) the acrosome reaction, d) ZP hatching, and d) sperm fusion with the oocyte cell membrane (Fig. 1). The acrosome (Gr. *akros* = extreme or tip, *soma* = body) is a Golgi-derived

Abbreviations: AR, acrosome reaction; ES, equatorial segment; GMF, gamete membrane fusion; IAM, inner acrosomal membrane; KO, knockout; MP, middle piece; OAM, outer acrosomal membrane; PB, polar body; PVS, perivitelline space; SZB, sperm–ZP binding; ZP, zona pellucida.

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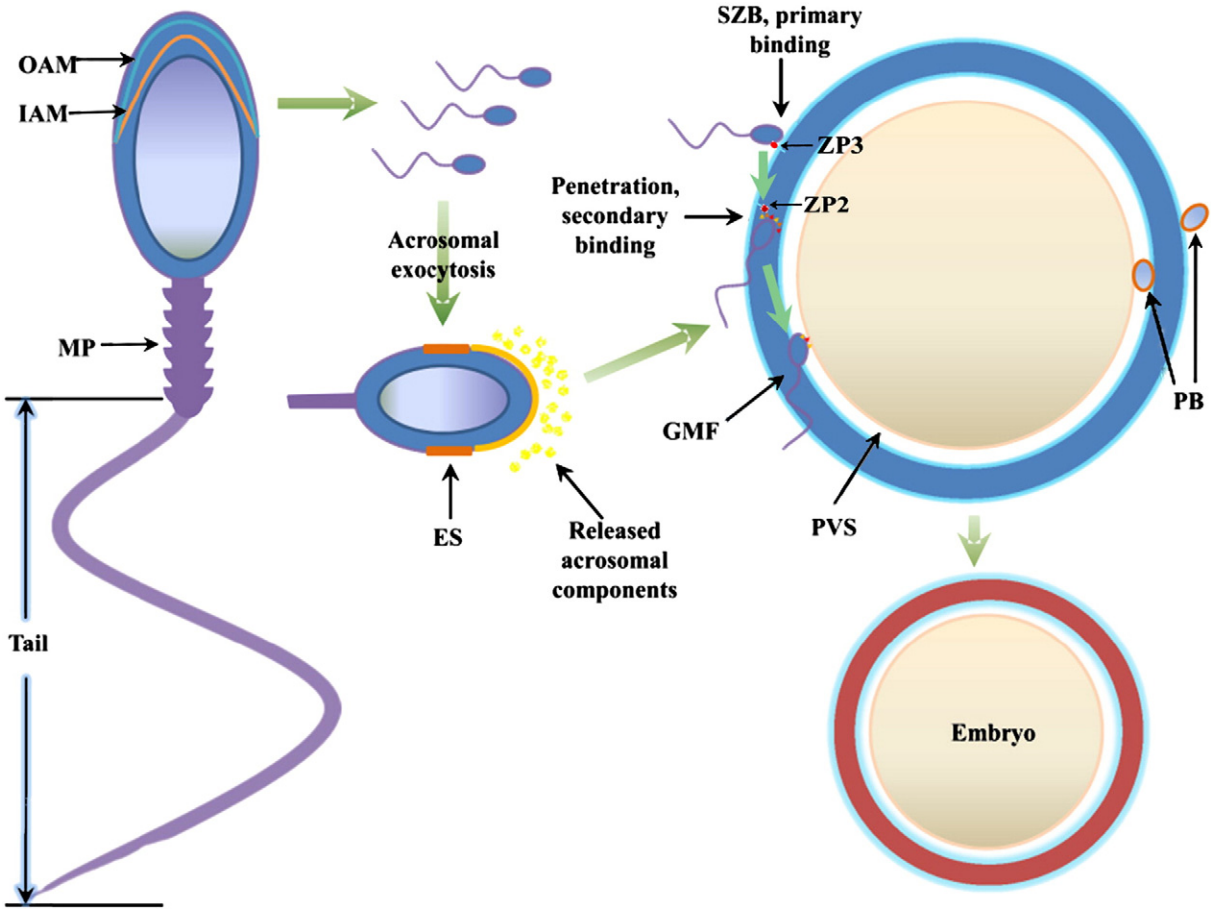

Fig. 1. Sperm–egg interaction. Sperm–ZP primary binding and secondary binding are shown during the SZB and penetration. OAM: outer acrosomal membrane; IAM: inner acrosomal membrane; MP: middle piece; ES: equatorial segment; SZB: sperm–ZP binding; GMF: gamete membrane fusion; PVS: perivitelline space; PB: polar body.

organelle that stores enzymes necessary for sperm penetration and is located at the anterior end of the spermatozoon between the cell membrane and the compact nucleus. The acrosome stores enzymes necessary for sperm penetration. The sperm undergoes an acrosome reaction as a result of sperm–ZP binding whereby the acrosome matrix is not only activated but also released. Some distinctive proteases have been identified as likely candidates in this process.

Acrosin is one of these distinctive proteases that plays multiple roles in fertilization and is a long-known component of the acrosome matrix (Adham et al., 1989; Tyler, 1939). As a typical serine endoprotease with trypsin-like activity, acrosin is stored in its inactive zymogen form (called proacrosin) and is secreted as a serine protease after sperm–ZP binding. Acrosin plays key roles in a number of processes which include: a) acrosome matrix dispersal, b) sperm–ZP binding, c) the acrosome reaction, d) secondary binding, and e) ZP penetration.

In this review, we discuss the biochemical features of acrosin and its participation in sperm–ova interactions. We highlight how various studies on acrosin have expanded our knowledge of fertilization in the past decades.

2. Acrosin in the acrosome reaction and acrosome matrix dispersal

During the acrosome reaction, surface remodeling events occur on the sperm cell membrane. In addition, acrosome components are activated and released from the acrosome vesicle in order to hydrolyze and penetrate the vestments surrounding the oocyte. In this regard, acrosin participates in the process of acrosome exocytosis.

In humans, *in vivo* sperm–ZP binding remains relatively normal after treatment with monoclonal anti-acrosin/proacrosin antibody (AcrC5F10) even though AcrC5F10 blocks proacrosin causing a defect in proacrosin–ZP binding. Nonetheless, an acrosome reaction occurs in spite of AcrC5F10 treatment (Veaute et al., 2010).

Subcellular localization studies of proacrosin revealed that proacrosin associates with other components of the acrosome matrix (Hardy et al., 1991). This may indicate that activated acrosin participates in acrosome exocytosis *via* its serine proteolytic function by releasing a variety of acrosome matrix components. That is to say, various acrosome matrix components may serve as substrates of activated acrosin and then undergo release from the matrix. Furthermore, male Acr −/− mice with a disruptive mutation in acrosin demonstrate a delayed release of several acrosome proteins (*e.g.*, sp56, MC101) compared to wild type mice using immunocytochemical approaches (Yamagata et al., 1998). These studies suggest that acrosin accelerates the dispersal of the acrosomal matrix.

There is compelling evidence to unequivocally implicate proacrosin/acrosin in the acrosome reaction and acrosome exocytosis. The proteolytic activity of acrosin results in the activation and accelerated release of other acrosome components. Since the acrosome proteases are stored as proenzymes, the likelihood that acrosin may cleave and activate other acrosome proteases becomes apparent. In the absence of acrosin proteolytic activity of acrosin, the acrosome reaction may become delayed and hence the sperm–ZP binding may be affected (Adham et al., 1997). Consequently, the assessment of acrosin proteolytic activity by spectrocolorimetry may be a good way to measure the acrosome reaction (Liu et al., 2008).