Developmental Biology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/locate/developmentalbiology

Epithelial and neural cadherin expression in the mammalian reproductive tract and gametes and their participation in fertilization-related events

Mónica Hebe Vazquez-Levin*, Clara Isabel Marín-Briggiler, Julieta Natalia Caballero, María Florencia Veiga

Instituto de Biología & Medicina Experimental (IBYME), National Research Council of Argentina (CONICET), Vuelta de Obligado 2490, Zip Code C1428ADN Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 15 November 2014
Received in revised form
23 December 2014
Accepted 28 December 2014

Keywords:
Fertilization
Cell–cell adhesion
Sperm
Oocyte
Epithelial cadherin
Neural cadherin

ABSTRACT

Mammalian fertilization involves a series of well-orchestrated cell–cell interaction steps between gametes, as well as among spermatozoa and somatic cells of both the male and female reproductive tracts. Cadherins are Ca^{2+}-dependent glycoproteins that have been involved in cellular adhesion and signaling in somatic cells. Taking into account that Ca^{2+} ions are required during fertilization, the involvement of these proteins in adhesion events during this process can be anticipated. This report presents an overview on two members of classical cadherins, Epithelial (E-) and Neural (N-) cadherin in reproductive biology. Its provides evidence of studies done by several research groups about the expression of E- and N-cadherin during spermatogenesis, oogenesis and folliculogenesis, and their involvement in gamete transport in the reproductive tracts. Moreover, it describes current knowledge of E- and N-cadherin presence in cells of the *cumulus*-oocyte complex and spermatozoa from several mammalian species, and shows gathered evidence on their participation in different steps of the fertilization process. A brief summary on general information of both proteins is also presented.

Fertilization-related events: An overview

Mammalian fertilization involves a series of well-orchestrated steps of cell–cell interaction between spermatozoa and the oocyte as well as spermatozoa and somatic cells of the female reproductive tract while they transit to the fertilization site. The accomplishment of this process lies in the success of these interactions, which are based on complementary molecules present in the surface of both gametes. These events have been investigated at both the structural and molecular level, providing enormous insights toward establishing a "molecular pathway" for mammalian fertilization. The current view of this fascinating biological process involves the recognition and interaction of a group of proteins present in both gametes, resulting in generation of a viable zygote. This highly complex process begins with gamete production in the female and male gonads long time before gametes meet.

Oocytes arrested in meiotic prophase are stored in the ovary before birth as primordial follicles, surrounded by granulosa cells that support their growth after *oogenesis* and *folliculogenesis*. Following ovulation, the *cumulus*-oocyte complex transiently associates with the *fimbriae* oviductal cells; subsequently, the complex enters the *ampulla* portion of the oviduct, where they meet with spermatozoa to accomplish fertilization. On the other hand, spermatozoa complete their morphogenesis in the testis; the *spermatogenesis* is a multistep process that involves sequential mitosis and meiosis divisions by which the developing germ cell differentiates from spermatogonial stem cell to spermatogonia, spermatocyte, spermatid and then to spermatozoon. However, testicular spermatozoa are immature and must reside for some time in the epididymis, where they develop progressive motility and acquire ability to recognize and interact with the female gamete, in a process called *epididymal sperm maturation*. Spermatozoa that leave the epididymis mix with the secretions of the accessory glands at ejaculation and initiate a journey through the female reproductive tract. The male gametes are transported following guidance mechanisms as thermotaxis, rheotaxis and chemotaxis. During their transit, spermatozoa interact with the oviduct epithelial cells and undergo several structural and molecular modifications, collectively known as sperm capacitation, resulting in full acquisition of sperm fertilizing competence. Capacitated spermatozoa arrive to the *ampulla* to accomplish *fertilization*. They interact with the vestments that surround the oocyte in the *cumulus*-oocyte complex; sperm first interact with the *cumulus* cells and later with the oocyte extracellular matrix or *zona pellucida*, to finally bind and

* Corresponding author. Fax: +54 1147862564.
E-mail address: mhvazl@gmail.com (M.H. Vazquez-Levin).

http://dx.doi.org/10.1016/j.ydbio.2014.12.029
0012-1606/

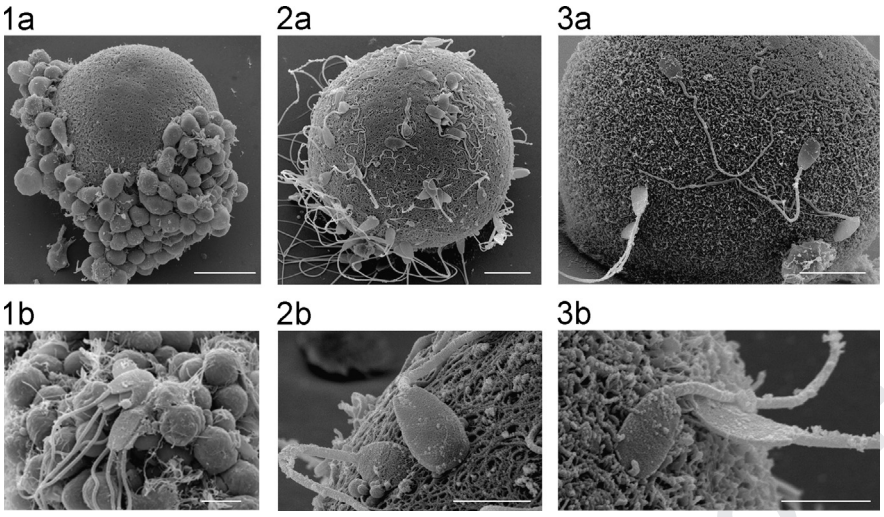

Fig. 1. Cell–cell adhesion events during bovine fertilization. Scanning electron microscopy images showing sperm–*cumulus* cells interaction (1a, detail in 1b), sperm–*zona pellucida* interaction (2a, detail in 2b) and sperm–oolemma interaction (3a, detail in 3b). Bar = 1a: 30 μm; 2a, 3a: 20 μm; 1b, 2b, 3b: 10 μm.

fuse to the oocyte plasma membrane or oolemma. Before interacting with the oolemma, spermatozoa must undergo acrosomal exocytosis, a process wherein the sperm plasma and outer acrosomal membranes fuse and the acrosomal contents are released. Following sperm–oolemma fusion, sperm nucleus decondensation occurs, the male and female haploid pronucleae form, migrate towards each other and combine, generating the zygote. Fig. 1 shows a set of scanning microscopy images illustrating some of the cell–cell interaction events between sperm and vestments of *cumulus*-oocyte complex cells in the bovine model. The reader may access to publications from highly recognized experts in the field that summarize the molecular events mentioned above (some of them are listed in the following reviews: Yanagimachi, 1994; Wassarman, 1999; Primakoff and Myles, 2002; Talbot et al., 2003; Bedford, 2004; Eisenbach and Giojalas 2006; Vazquez-Levin and Marín-Briggiler, 2009; Visconti et al., 2011; Evans, 2012; Gadella, 2012; Okabe, 2013; Clift and Schuh, 2013; Klinovska et al., 2014).

Throughout these years, numerous efforts have been made toward the identification and functional characterization of the molecular entities involved in *cell–cell adhesion events* leading to the fertilization process. Regarding the identity of these proteins, some members of the immunoglobulin, integrin, and the selectin superfamilies have been found to be expressed in the gonads and gametes, and have been shown to participate in gamete production and interaction during fertilization. Table 1 presents some examples of cell–cell adhesion proteins found in spermatozoa and oocytes and, when found, evidence of their participation in fertilization-related events. The list includes some examples of members from the *cadherin* cell–cell adhesion molecules superfamily, a vast group of proteins that mediate calcium (Ca^{2+})-dependent adhesion and signaling.

Taking into account that gamete interaction requires the presence of Ca^{2+} ions (Fraser, 1987; Marín-Briggiler et al., 2003; Boni et al., 2007; Chen et al., 2013; Rahman et al., 2014) and that cadherins participate in Ca^{2+}-dependent cell–cell adhesion (Takeichi, 1995), the involvement of these proteins in adhesion events during fertilization could be anticipated. The present report summarizes a group of studies done by several research groups showing evidence on the expression of E- and N-cadherin during gametogenesis in both male and female gonads, and gamete transport in the male and female tracts, and their presence in cells from the *cumulus*-oocyte complex and spermatozoa, as well as evidence gathered on their participation in fertilization-related events. A brief overview on both proteins is first presented in the next section.

The cadherin superfamily: epithelial and neural cadherin

The cadherin superfamily is composed of a large group of cell surface (transmembrane or membrane-associated) glycoproteins. This superfamily is organized in at least five major families, among them type I or classical cadherins, type II closely related cadherins, desmosomal cadherins (desmocollins and desmogleins), protocadherins, and a variety of cadherin-related molecules. Members of this superfamily perform numerous functions that involved cell–cell recognition. Even though they have been mainly associated to cell–cell adhesion events, cadherins participate in numerous functions, among them cell–cell recognition, cytoskeletal organization, signal transduction and growth control (Takeichi, 1995; Gumbiner, 1996; Angst et al., 2001).

Epithelial cadherin (E-Cadherin, Cadherin-1 (CDH1), L-CAM, ARC-1, uvomorulin) is the founder member of the cadherin superfamily (Takeichi, 1977). E-cadherin, a classical or type I cadherin, has been considered to be a paradigmatic classical cadherin and the prototype of all cadherin proteins because of its early identification and thorough characterization, both in normal and in pathological conditions. It was initially named uvomorulin based on early studies that described the ability of antibodies against the adhesion protein to block interactions between murine blastomeres, resulting in changes in embryo appearance that resemble a bunch of grapes (from latin "uva") (Hyafil et al., 1981; van Roy and Berx, 2008). Later studies demonstrated its role as a ubiquitous cell adhesion glycoprotein (Vestweber and Kemler, 1984). In the early 1980s, the name "cadherins" was introduced for this class of cell–cell adhesion molecules (Yoshida-Noro et al., 1984). E-cadherin is an essential glycoprotein for development, cell differentiation and tissue homeostasis, as well as for maintenance of epithelial polarity and structural integrity (van Roy and Berx, 2008).

The *CDH1* gene encodes human E-cadherin, is located on chromosome 16q22.1, and spans a region of approximately 100 kb; it comprises 16 exons and 15 introns and is highly conserved among species (Berx et al., 1995). Cloning of mouse E-cadherin led to the prediction of its structure composed of a signal sequence, a propeptide and a one-pass-transmembrane glycopolypeptide (Nagafuchi et al., 1987) and cloning of the human

Please cite this article as: Vazquez-Levin, M.H., et al., Epithelial and neural cadherin expression in the mammalian reproductive tract and gametes and their participation in fertilization-related events. Dev. Biol. (2015), http://dx.doi.org/10.1016/j.ydbio.2014.12.029