**Review**

# Function of the cell surface molecules (CD molecules) in the reproduction processes

Katarína Fábryová and Michal Simon

*Institute of Animal Biochemistry and Genetics, Slovak Academy of Sciences, Ivanka pri Dunaji, Bratislava, Slovakia*

**Abstract.** Recent studies brought the evidences that some cell surface molecules associated with immune system (cluster of differentiation (CD) molecules) may be involved in the fertilization process. The experimental observations regarding the function of CD9, CD49f/CD29, CD46 and CD11b/CD18 have led to the construction of general hypothesis of fertilization comprising the interaction of these CD molecules in binding and fusion of sperm and egg. The models for the role of CD9 and CD49f/CD29 in the fertilization are based on the interaction of tetraspanin CD9 and integrin α6β1 (CD49f/CD29) *via* fertilin in sperm-egg binding and fusion. The model for the role of integrin CD11b/CD18 and CD46 in fertilization is based on the interaction of these two molecules through complement C3 fragments which may serve as bridging ligands between sperm CD46 and oocyte CD11b/CD18 and facilitate apposition of the sperm inner acrosomal membrane with oolemma.

**Key words:** Reproduction — Sperm-egg interaction — CD molecules

## Introduction

The process of fertilization in mammals requires the successful completion of many steps, starting with the development and the transport of gametes in the reproductive tracts of both male and female organisms until they arrive close to each other in the female reproductive tract. The subsequent interaction between the two gametes requires several steps that result in gamete fusion to produce a zygote. Cell adhesion is a major part of these unique processes; it is involved in the transport of both egg and sperm, and it is also integral to the steps in sperm-egg interaction (Talbot et al. 2003). There are many involvements of the immune system in the physiology of mammalian reproduction. Two of them are the complex tolerance of "foreign" fetuses or the selection and physiological destruction of vast majority spermatozoa (directly) not participating in sperm-egg fusion by immune system mechanisms. Therefore, immunology is a powerful tool for studying the fertility of man and animals and the underlying physiological processes of reproduction.

Correspondence to: Katarína Fábryová, Institute of Animal Biochemistry and Genetics, Slovak Academy of Sciences, Moyzesova 61, 900 28 Ivanka pri Dunaji, Slovakia
E-mail: katarina.fabryova@savba.sk

One of the aims of the immunological studies in reproduction was to discover genes expressed on gametic cells and reproductive tissues that encode proteins which are important in whole procedure or in some steps of gametic maturation and fertilization of eggs. In the last period a set of such proteins have been described.

In this review we focus on the role of sperm and egg surface cluster of differentiation (CD) molecules, especially integrins and tetraspanins, which could be involved in the adhesion/fusion of egg and sperm membranes.

## CD molecules in fertilization

CD molecules are antigens appearing in the cell membrane in a specific stage of their development. They remain there in a specific development period or they remain there as a characteristic marker till destruction of the cell membrane. Because most of them have a restricted cell or tissue distribution they are also marked as "differentiation antigens" (Buc 2001).

To date, more than 300 surface antigens defined on human leucocytes are known and their number is still increasing. There is a large heterogenity in the structure and functions of CD antigens. Majority of CD antigens are involved in the immune functions of organism. They comprise the

receptors for antigens, MHC (major histocompatibility complex) glycoproteins, adhesive molecules, receptors for immunoglobulins, receptor for complement, receptors for lymphokines and other growth and differentiation factors, membrane enzymes or transport molecules and other molecules, with well-characterized structure and expression but the function of which has not been defined yet (Hořejší 1991; Barclay et al. 1997).

Some of CD molecules are also expressed on the tissues and cells of the male and female genital tract (Fábryová et al. 2008; Jankovičová et al. 2008). They could be involved in the reproductive immunity but their exact role is mostly unknown.

However, recent studies brought the evidences that some CD molecules may participate in the fertilization process. The main candidates for this function are some CD molecules belonging to the superfamilies of tetraspanins, integrins and complement regulatory proteins. The aim of this review is to yield and summarize the data about the structure and functional properties of this molecules and suggest the mechanism how they could influence the reproduction processes of man and animals.

Tetraspanin superfamily is characterized by the existence of four transmembrane domains delimiting two extracellular regions of unequal size (Lagaudrière-Gesbert et al. 1997). Tetraspanins interact with other proteins including integrins, immunoglobulins, proteoglycans, complement-regulatory proteins and growth factor receptors. For this reason, they are thought to form multi-molecular complexes with these associated molecules on the plasma membrane (Boucheix and Rubinstein 2001) and are implicated in a variety of normal and pathological processes, such as cell motility, metastasis, cell proliferation and differentiation (Berditchevski 2001), and also in sperm-egg fusion (Le Naour et al. 2000; Miyado et al. 2000).

Integrins comprise a large family of cation-dependent heterodimeric transmembrane receptors composed of noncovalently linked α and β subunits (Hynes 1992). It is a large family of cell adhesion receptors, involved in cell-cell and cell-matrix interactions. At present, 20 different integrin heterodimers are known. They not only anchor cells to their proper locations, but also activately mediate the passage of information into the cell. They are involved in such diverse processes as immune response, lymphocyte homing, platelet aggregation, metastatic spread of certain malignancies, healing process of tissue injures, embryologic development and reproduction (Vinatier 1995).

Proteins which belong to the family of complement regulatory proteins could regulate the function of a complement system by cleavage of complement cascade (see Valentovičová et al. 2005). The complement system plays an important role in host defense. However, if not properly regulated, activated complement can also cause significant damage to host tissues. To prevent complement-mediated autologus tissue damage, host cells express a number of membrane-bound complement regulatory proteins (Miwa and Song 2001). These include also some of the CD molecules, which are present on many tissues in male and female reproductive tracts and gametes.

The experimental data accumulated recently have shown that at least some CD molecules belonging to these 3 superfamilies of CD molecules could be involved in reproduction processes.

## Interaction of CD9 and CD49f/CD29 (α6β1, VLA-6) *via* fertilin in sperm-egg binding and fusion

CD9 is a widely expressed cell molecule that belongs to the tetraspanin superfamily of proteins (Le Naour et al. 2000). CD9 is mainly expressed by platelets and extent by other blood cells (Barclay et al. 1997) it is also present on oocytes (Chen et al. 1999). Expression of CD9 enhances membrane fusion (Loffler et al. 1997; Willett et al. 1997). It seems to be likely that one of the role of CD9 is in cell adhesion through the regulation of integrin function CD49f/CD29 (α6β1; VLA-6) (Berditchevsky et al. 1996).

Fertilization involves the membrane fusion between gametes. Previous studies in mice have reported that CD9 has a key role in sperm-egg fusion (Kaji et al. 2000; Le Naour et al. 2000; Miyado et al. 2000) or binding and fusion (Chen et al. 1999). The following specific effect of CD9 molecule to reproduction processes was found: CD9 knockout mice (the mice in which the CD9 gene was inactivated) female appeared to ovulate normally, and yields of oocytes from super-ovulated animals were similar to yields from knockouts. Oocyte maturation to metaphase II also appears to be normal. However, oocytes from CD9 knockout mice were rarely fertilized. Sperm were able to adhere to the plasma membrane of zona pellucida (ZP)-free CD9 knockout oocytes, but very rarely fused with the oocyte membrane (Kaji et al. 2000; Le Naour et al. 2000; Miyado et al. 2000).

The effect of anti-CD9 antibodies from *in vitro* fertilization studies is not unequivocal. There is different response to antibody treating in man and in mice. ZP-free oocytes treated with anti-CD9 monoclonal antibodies have been reported to have reduced numbers of bound sperm (Chen et al. 1999; Li et al. 2004), whereas another report states that sperm binding was unaffected by an anti-CD9 antibody (Le Naour et al. 2000; Miller et al. 2000; Miyado et al. 2000). Anti-human CD9 mAb failed to inhibit the fusion of human ZP-free oocytes with sperm, when added at the time of insemination, under conditions in which anti-mouse CD9 mAb inhibits the fusion in mouse. However, anti-CD9 mAb strongly inhibited the fusion when added to human intact oocytes and kept continuously present during ZP removal

and fusion, indicating that mechanical ZP removal induces on the oocyte the stage when CD9 is no longer required for fusion (Ziyyat et al. 2006).

Integrins have been speculated to mediate sperm-oocyte adhesion, as they mediate somatic adhesion (Evans 2002). CD49f is the α6 integrin subunit which can combine with CD29 (the β1 integrin subunit) to form integrin VLA-6 (CD49f/CD19; α6β1) to be expressed on T lymphocytes, thymocytes on the epithelia of non-lymphoid tissues and also on the surface of oocytes of man and mice (Barclay et al. 1997).

Based on antibody-inhibition assays, it has been suggested that the integrin α6β1 could be a receptor for sperm binding to egg (Almeida et al. 1995), but this conclusion was not reached in a later study using a different method of removing the zona pellucida surrounding the egg (Evans 1999).

Recently, the analysis of oocytes from mice lacking the integrin α6 gene showed that this integrin was not essential for sperm-oocyte binding and fusion in the mouse might be due to the substitution of α6β1 by another integrin in those mice. The interpretation of this finding needs further studies. One possibility might be the existence of different α6β1 integrin. The alternative possibility is that a novel integrin or receptor may be present on the surface of the egg and binds sperm (Miller et al. 2000).

The fusion of human gametes is more dependent on α6β1 integrin than the fusion of mouse gamete. Up to 96% inhibition of sperm-egg fusion was recorded after treatment with α6β1 monoclonal antibody. This finding has clearly shown the crucial role of α6β1 in human gamete fusion (Ziyyat et al. 2006).

Fertilin α, fertilin β and cyritestin are members of a disintegrin and a metalloprotease domain (ADAM) family, being ADAM1, ADAM2, and ADAM3, respectively, each of which has a disintegrin and a metalloprotease domain (Blobel et al. 1992). The fertilin β subunit has been hypothesized to be involved in binding of the sperm to the egg in a mechanism that leads to sperm-egg fusion (Ramarao et al. 1996; Vidaeus et al. 1997). The fertilin α subunit has been hypothesized to be involved in fusion of the egg and sperm plasma membranes (Evans et al. 1997). Their putative receptors, oocyte integrins, are necessary for the sperm-oocyte interaction (Kaji and Kudo 2004).

The experimental observations mentioned above regarding the function of CD9, CD49f/CD29 and fertilin in reproduction processes have led to the construction of general hypothesis of fertilization comprising the interaction of the CD molecules in binding and fusion of sperm and egg.

The adhesion of mouse gametes requires an interaction between fertilin and integrin α6β1 (Almeida et al. 1995) on the plasma membranes of the sperm and egg, respectively.

According to Chen and Sampson (1999) fertilin β binds directly to the α6β1 integrin on the egg surface and this partnership mediates sperm-egg fusion. The tetraspan protein CD9 facilitates α6β1-mediated binding of fertilin β (ADAM2) to eggs. Perhaps CD9, or other integrin associated proteins, facilitate binding of other ADAMs to their respective integrin coreceptors (Nakamura et al. 1995).

Two models for the role of CD9 in binding of fertilin to α6β1 have been considered by Chen et al. (1999) (Fig. 1). In model I, fertilin β binds to α6β1 that is physically associated with CD9 and tethered to the actin cytoskeleton. In model II, fertilin β binds to α6β1 that is tethered to the actin cytoskeleton; CD9 indirectly influences the association of α6β1 with the actin cytoskeleton and, therefore, its ability to bind fertilin β.

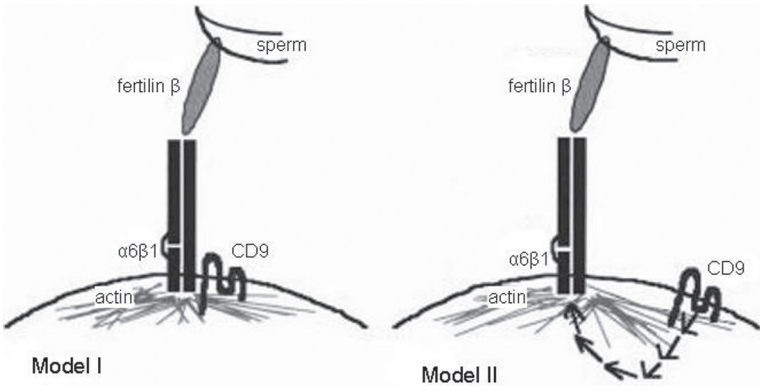


**Figure 1.** Models for the role of CD9 in binding of fertilin to α6β1. In Model I, fertilin β (ADAM 2) binds to α6β that is physically associated with CD9 and tethered to the actin cytoskeleton. In Model II, fertilin β binds to α6β1 that is tethered to the actin cytoskeleton; CD9 indirectly influences the association of α6β1 with the actin cytoskeleton and, therefore, its ability to bind fertilin β (Chen et al. 1999).

**Binding of sperm-egg through CD11b/CD18 integrin and CD46**

The analysis of the function of CD molecules in the fertilization processes revealed the role of other CD molecules resulting in the "alternative way" of sperm-egg binding.

In the binding of the sperm and the egg has an important role integrin CD11b/CD18 ($\alpha_M\beta_2$, Mac-1, CR3), which belongs to the $\beta_2$ subfamily of integrins. CD11b/CD18 is expressed in white blood cells and has been implicated in diverse responses of these cells (Coxon et al. 1996; Ding et al. 1999), in addition to being the receptor for complement fragment iC3b (Arnaout 1990).

CD11b/CD18 is also expressed on human oocytes. Both ZP-intact and ZP-free oocytes were positive for plasma-membrane expression of CD11b/CD18 that binds C3 products (Anderson et al. 1993). Quite the opposite CD11b/CD18 expression has been reported as absent from both unreacted and acrosome-reacted spermatozoa (Anderson et al. 1993).

The antibodies against α and β integrin subunits, including $\alpha_M$ and $\beta_2$ subunits, only partially blocked sperm-oocyte binding (with maximum of 55% inhibition). In addition, the fusion of oocytes by sperm that had become bound to oolema (plasma membrane of the oocyte) was not blocked. These results suggest that one of the binding mechanism could be inhibited by integrin antibodies but that this mechanism does not play an essential role in the human sperm-oolemmal binding and fusion processes (Sengoku et al. 2004).

Complement is involved in cell-cell interactions in several systems (Joiner 1988; Ahearn and Fearon 1989; Springer 1990), and recent studies have suggested that it may play role in fertilization. C3 is secreted by rat and human uterine glandular epithelium; the highest levels are produced in fertilization (Kuivanen et al. 1989; Sundstrom et al. 1989; Isaacson et al. 1990). C3 fragments can serve as bridging ligands, facilitating apposition of the sperm inner acrosomal membrane with egg plasma membrane, but at high levels C3 fragments may block fertilization by saturating sperm and egg receptor. Human and hamster oocytes can activate the alternative pathway of complement and bind human C3 fragments. Dimeric C3b binds to acrosome-reacted sperm but not to acrosome-intact sperm that suggests that sperm CD46 binds C3 catabolites immediately before fertilization (Anderson et al. 1993).

CD46 / MCP (membrane cofactor protein) is a cell surface complement regulatory glycoprotein that facilitates enzymatic cleavage of complement component C3b (Taylor et al. 1994; Antalíková et al. 2007). The main function of the membrane glycoprotein is to protect essentially the host cells from an autologous complement attack (see Valentovičová et al. 2005).

This glycoprotein is present on all human peripheral blood cells (besides erythrocytes), on fibroblasts, endothelial and epithelial cells, and on tissues of reproductive system, including fallopian tube, uterine endometrium and placenta. CD46 is not expressed on unfertilized oocytes but it appears at the 6–8 cell stage embryo (Liszewski et al. 1991). In contrary, according to Taylor et al. (1994) CD46 is expressed on ZP-free human oocytes. In man, it is expressed by acrosome-reacted, but not acrosome-intact spermatozoa (Anderson et al. 1989). This finding may suggest that this antigen is particularly important in the process of fertilization. In orangutan and unlike to human analogues, it was described on all blood cells (Nicleks and Atkinson 1990). In guinea pig (Hokosawa et al. 1996) and mice (Tsujimura et al. 1998) it is selectively expressed in the testis, particularly in germ cells. CD46 molecule has been localized on the plasma membrane and in the acrosomal content or on the acrosomal membrane of bovine spermatozoa (Jankovičová et al. 2006). These facts suggest that this molecule is primarily important in reproduction.

CD46 is thought to be a factor in sperm-egg interaction, because human sperm binding and pronuclear formation in ZP-free human oocytes can be significantly inhibited by preincubation of both sperm and oocytes with anti-CD46 mAb. This effect was not observed when either of these gametes alone was incubated with mAb (Taylor et al. 1994). It was reported that the blocking of human sperm by CD46 monoclonal antibodies suppressed sperm binding to human and hamster oocytes (Okabe et al. 1990; Taylor and Johnson 1996). Kitamura et al. (1997) proposed a new category of infertility – a sperm-specific CD46 aberration. The same authors reported that the sperm lost the ability to adhere to oocytes due to the observed defects in the sperm CD46, thereby causing a failure of fertilization.

The expression of CD46 by ZP-free oocytes and acrosome-reacted sperm suggest a role for CD46 at the level of apposition of the inner acrosomal membrane and the oolemma (D'Cruz 1996). However, CD46 may not be involved directly in initial fusion events, as fusion begins in the equatorial or postacrosomal regions where the membrane remains intact after the acrosome reaction, rather than the inner acrosomal region where CD46 is expressed (Taylor et al. 1994).

From these evidences results a model for C3 and complement-binding proteins in gamete membrane apposition. CD46 on sperm that have undergone the acrosome reaction specifically binds dimeric C3b and human sperm acrosomal proteases released during the acrosome reaction directly cleave C3, facilitating its binding to CD46. At subsaturating levels of dimeric C3b, the interaction of sperm and egg was enhanced, whereas at saturating doses the interaction was inhibited. This result suggested that dimeric C3b at low levels could serve as a bridge between sperm (CD46) and oocyte (CD11b/CD18) complement receptor, facilitating

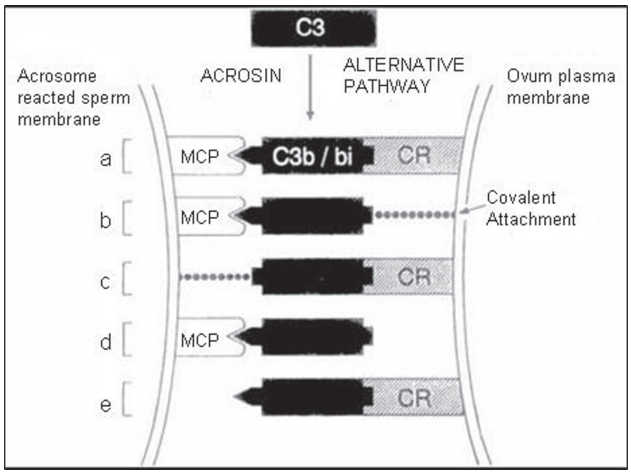


**Figure 2.** Model for role of C3 and complement-binding proteins in gamete membrane apposition. a) C3b/iC3b (C3b/bi) acting as a ligand between sperm MCP (CD46) and oocyte complement receptor (CR) (type 1 – CD35 or type 3 – CD11b/CD18). b) C3b/C3bi covalently attached to oocyte acting as a ligand for sperm MCP. c) C3b/C3bi is covalently attached to sperm acting as a ligand for oocyte CR. d) and e) excess C3b/C3bi saturating all MCP/CR sites and inhibiting membrane apposition (Anderson et al. 1993). MCP, membrane cofactor protein.

fertilization, whereas at high levels dimeric C3b saturated all receptor-binding sites for C3 fragments and inhibited the apposition of gamete membranes (Fig. 2). In addition, antibodies to both CD46 and C3 significantly inhibited penetration of hamster oocytes by human sperm (Anderson et al. 1993).

C3 fragments (C3b/iC3b) may serve as bridging ligands between sperm CD46 and oocyte CD11b/CD18 and facilitate apposition of the sperm inner acrosomal membrane with oolemma. Regulated gamete-induced generation of C3 fragments by selectively expressed receptors on sperm and oocytes may be an initial step in gamete interaction, leading to membrane fusion and fertilization (Anderson et al. 1993).

The experiments reviewed in this paper clearly have shown the function of some CD molecules in the reproduction processes. Simultaneously the species specific differences in the effect of discrete CD specifities during the sperm adhesion and fusion was suggested. Consequently, to understand better the molecular mechanism of fertilization, the identification of further CD molecules participating in reproduction processes and their interaction in distinct parts of the genital tract or reproductive fluids in different species would be required.

**Acknowledgements.** This work was supported by grants VEGA 2/0001/09 and APVV-VVCE-0064-07-07.

## References

Ahearn J. M., Fearon D. T. (1989): Structure and function of the complement receptors, CR1 (CD35) and CR2 (CD21). Adv. Immunol. **46**, 183–219

Almeida E. A., Huovila A. P., Sutherland A. E., Stephens L. E., Calarco P. G., Shaw L. M., Mercurio A. M., Sonnenberg A., Primakoff P., Myles D. G., White J. M. (1995): Mouse egg integrin α6β1 functions as a sperm receptor. Cell **81**, 1095–1104

Anderson D. J., Michalson J. S., Johnson P. M. (1989): Trophoblast/leukocyte-common antigen is expressed by human testicular germ cells and appears on the surface of acrosome-reacted sperm. Biol. Reprod. **41**, 285–293

Anderson D. J., Abbot A. F., Jack R. M. (1993): The role of complement component C3b and its receptors in sperm-oocyte interaction. Proc. Natl. Acad. Sci. U.S.A. **90**, 10051–10055

Antalíková J., Simon M., Jankovičová J., Horovská Ľ. (2007): Identification of MCP/CD46 analogue on bovine erythrocytes using the new monoclonal antibody IVA-520. Vet. Immunol. Immunopathol. **115**, 155–159

Arnaout M. A. (1990): Structure and function of the leukocyte adhesion molecules CD11/CD18. Blood **75**, 1037–1050

Barclay A. N., Brown M. H., Law S. K. A., Knight A. J., Tomlinson M. G., van der Merwe P. A. (1997): The Leucocyte Antigen Facts Book. Academic Press, Oxford, U.K.

Berditchevski F., Zutter M. M., Hemler M. E. (1996): Characterization of novel complexes on the cell surface between integrins and proteins with 4 transmembrane domains (TM4 aproteins). Mol. Biol. Cell **7**, 193–207

Berditchevski F. (2001): Complexes of tetraspanins with integrins: more than meets eye. J. Cell Sci. **114**, 4143–4151

Blobel C. P., Wolfsberg T. G., Turck C. W., Myles D. G., Primakoff P., White J. M. (1992): A potential fusion peptide and an integrin ligand domain in a protein active in sperm-egg fusion. Nature **356**, 248–252

Boucheix C., Rubinstein E. (2001): Tetraspanins. Cell. Mol. Life Sci. **58**, 1189–1205

Buc M. (2001): Immunology. Veda, publisher SAS, Bratislava (in Slovak)

Chen H., Sampson N. S. (1999): Mediation of sperm-egg fusion: evidence that mouse egg α6β1 integrin is the receptor for sperm fertilinbeta. Chem. Biol. **6**, 1–10

Chen M. S., Tung, K. S., Coonrod S. A., Takahashi Y., Bigler D., Chang A., Yamashita Y., Kincade P. W., Herr J. C., White J. M. (1999): Role of integrin-associated protein CD9 in binding between sperm ADAM 2 and the egg integrin α6β1: implications for murine fertilization. Proc. Natl. Acad. Sci. U.S.A. **96**, 11830–11835

Coxon A., Rieu P., Barkalow F. J., Askaris., Sharpe A. H., von Adrian U. H., Arnaout M. A., Maydas T. N. (1996): A novel role for the β 2 inregrin CD11b/CD18 in neutrophil apoptosis: a homeostatic mechanism in inflamation. Immunity **5**, 653–666

D'Cruz O. J. (1996): Adhesion molecules in human sperm-oocyte interaction: relevance to infertility. Front. Biosc. **1**, 161–176

Ding Z. M., Babensee J. E., Simon S. I., Luh. F., Perrard J. L., Bullard D. C., Dai X. Y., Bromley S. K., Dustin M. L., Entman M. L., Smith C. W., Ballantine C. M. (1999): Relative contribution of LFA-1 and Mac-1 to neutrophil adhesion and migration. J. Immunol. **163**, 5029–5038

Evans J. P., Schultz R. M., Kopf G. S. (1997): Characterization of the binding of recombinant mouse sperm fertilin α subunit to mouse eggs: evidence for function as a cell adhesion molecule in sperm-egg binding. Dev. Biol. **187**, 94–106

Evans J. P. (1999): Sperm disintegrins, egg integrins, and other cell adhesion molecules of mammalian gamete plasma membrane interactions. Front. Biosci. **4**, D114–131

Evans J. P. (2002): The molecular basis of sperm-oocyte membrane interactions during mammalian fertilization. Hum. Reprod. Update **8**, 297–311

Fábryová K., Antalíková J., Jankovičová J., Simon M., Horovská Ľ. (2008): Analysis of bovine cell surface antigen recognized by monoclonal antibody IVA-543. J. AgroBiol. **25**, 39–40

Hokosawa M., Nonaka M., Okada N., Nonaka M., Okada H. (1996): Molecular cloning of guinea pig membrane cofactor protein: preferential expression in testis. J. Immunol. **157**, 4946–4952

Hořejší V. (1991): Surface antigens on human leucocytes. Adv. Immunol. **49**, 75–147

Hynes R. O. (1992): Versatility, modulation, and signaling in cell adhesion. Cell **69,** 11–25

Isaacson K. B., Galman M., Coutifaris C., Lyttle C. R. (1990): Endometrial synthesis and secretion of complement component-3 by patients with and without endometriosis. Fertil. Steril. **53**, 836–841

Jankovičová J., Antalíková J., Simon M., Horovská Ľ. (2006): Identification and characterization of CD46 protein on bovine spermatozoa. Am. J. Reprod. Immunol. **56**, 45

Jankovičová J., Simon M., Antalíková J., Horovská Ľ., Fábryová K. (2008): Potential role of bovine CD46 in the reproduction processes. J. AgroBiol. **25**, 35–37

Joiner K. A. (1988): Complement evasion by bacteria and parasites. Annu. Rev. Microbiol. **42**, 201–230

Kaji K., Oda S., Shikano T., Ohnuki T., Uematsu Y., Sakagami J., Tada N., Miyazaki S., Kudo A. (2000): The gamete fusion process is defective in eggs of CD9-deficient mice. Nat. Genet. **24**, 279–282

Kaji K., Kudo A. (2004): The mechanism of sperm-oocyte fusion in mammals. Reproduction **127**, 423–429

Kitamura M., Matsumiya K., Yamanaka M., Takahara S., Hara T., Matsumoto M., Namiki M., Okuyama A., Saya T. (1997): Possible association of infertility with sperm-specific abnormality of CD46. J. Reprod. Immunol. **33**, 83–88

Kuivanen P. C., Capulong R. B., Harkins R. N., DeSombre E. R. (1989): The estrogen-responsive 110K and 74K rat uterine secretory proteins are structurally related to complement component C3. Biochem. Biophys. Res. Commun. **158**, 898–905

Lagaudrière-Gesbert C., Le Naour F., Lebel-Binay S., Billard M., Lemichez E., Boquet P., Boucheix C., Comjeaud H., Rubinstein E. (1997): Functional analysis of four tetraspans, CD9, CD53, CD81, and CD82, suggests a common role in costimulation, cell adhesion, and migration: only CD9 upregulates HB-EGF activity. Cell. Immunol. **182**, 105–112

Le Naour F., Rubinstein E., Jasmin C., Prenant M., Boucheix C. (2000): Severely reduced female fertility in CD9-deficient mice. Science **287**, 319–321

Liszewski M. K., Post T. W., Atkinson J. P. (1991): Membrane cofactor protein (MCP of CD46): newest member of regulators of the complement activation gene cluster. Annu. Rev. Immunol. **9**, 431–455

Li Y. H., Hou Y., Ma W., Yuan J. X., Zhang D., Sun Q. Y., Wang W. H. (2004): Localization of CD9 in pig oocytes and its effects on sperm-egg interactions. Reproduction **127**, 151–157

Loffler S., Lottspeich F., Lanza F., Azorsa D. O., ter Meulen V., Schneider-Schaulies J. (1997): CD9, a tetraspan transmembrane protein, renders cells susceptible to canine distemper virus. J. Virol. **71**, 42–49

Miller B. J., Georges-Labouesse E., Primakoff P., Myles D. G. (2000): Normal fertilization occurs with eggs lacking the integrin α6β1 and is CD9-dependent. J. Cell Biol. **149**, 1289–1295

Miwa T., Song W. C. (2001): Membrane complement regulatory proteins: insight from animal studies and relevance to human diseases. Int. Immunopharmacol. **1,** 445–459

Miyado K., Yamada G., Yamada S., Hasuwa H., Nakamura Y., Ryu F., Suzuki K., Kosai K., Inoue K., Ogura A., Okabe M., Mekada E. (2000): Requirement of CD9 on the egg plasma membrane for fertilization. Science **287**, 321–324

Nakamura K., Iwamoto R., Mekada E. (1995): Membrane-anchored heparin-binding EGF-like growth factor (HB-EGF) and diphtheria toxin receptor-associated protein (DRAP27)/CD9 form a complex with integrin α3β1 at cell-cell contact sites. J. Cell Biol. **129**, 1691–1705

Nickles M. W., Atkinson J. P. (1990): Characetization of CR1 and membrane cofactor proteins of two primates. J. Immunol. **144**, 4262–4268

Okabe M., Magira M., Kawai Y., Matzno S., Mimura T., Mayumi T. (1990): A human sperm antigen possibly involved in binding and/or fusion with zona-free hamster eggs. Fertil. Steril. **63**, 625–630

Ramarao C. S., Myles D. G., White J. M., Primakoff P. (1996): Initial evaluation of fertilin as an immunocontraceptive antigen and molecular cloning of the cynomologus monkey fertilin β subunit. Mol. Reprod. Dev. **43,** 70–75

Sengoku K., Takuma N., Miyamoto T., Horikawa M., Ishokawa M. (2004): Integrins are not involved in the process of human sperm-oolemmal fusion. Hum. Reprod. **19**, 639–644

Springer T. A. (1990): Adhesion receptors of the immune system. Nature **346**, 425–434

Sundstrom S. A., Komm B. S., Ponce-De-Leon H., Yi Z., Teuscher C., Lyttle C. R. (1989): Estrogen regulation of tissue-specific expression of complement C3. J. Biol. Chem. **264**, 16941–16947

Talbot P., Shur B. D., Myles D. G. (2003): Cell adhesion and fertilization: steps in oocyte transport, sperm-zona

pellucida interactions, and sperm-egg fusion. Biol. Reprod. **68,** 1–9

Taylor C. T., Biljan M. M., Kingsland C. R., Johnson P. M. (1994): Inhibition of human spermatozoon-oocyte interaction *in vitro* by monoclonal antibodies to CD46 (membrane cofactor protein). Hum. Reprod. **9**, 907–911

Taylor C. T., Johnson P. M. (1996): Complement-binding proteins are strongly expressed by human preimplantation blastocysts and cumulus cells as well as gametes. Mol. Hum. Reprod. **2**, 52–59

Tsujimura A., Shida K., Kitamura K., Nomura M., Takeda J., Tanaka H., Matsumoto M., Matsumiyja K., Ukuyama A., Nishimune Y., Okabe M., Seya T. (1998): Molecular cloning of murine homologue of membrane cofactor protein (MCP, CD46): preferential expression in testicular germ cells. Biochem. J. **330**, 163–168

Valentovičová J., Simon M., Antalíková J. (2005): Function of complement regulatory proteins in imunity of reproduction: a review. Czech J. Anim. Sci. **50**, 135–141

Vidaeus C. M., von Kapp-Herr C., Golden W. L., Eddy R. L., Shows T. B., Herr J. C. (1997): Human fertlin β: identification, characterization, and chromosomal mapping of an ADAM gene family member. Mol. Reprod. Dev. **46,** 363–369

Vinatier D. (1995): Integrins and reproduction. Eur. J. Obstet. Gynecol. Reprod. Biol. **59**, 71–81

Willett B., Hosie M., Shaw A., Neil J. (1997): Inhibition of feline immunodeficiency virus infection by CD9 antibody operates after virus entry and is independent of virus tropism. J. Gen. Virol. **78**, 611–618

Ziyyat, A., Rubinstein E., Monier-Gavelle F., Barraud V., Kulski O., Prenant M., Boucheix C., Bomsel M., Wolf J.-P. (2006): CD9 controls the formation of clusters that contain tetraspanins and the integrin α6β1, which are involved in human and mouse gamete fusion. J. Cell Sci. **119**, 416–424

Received: September 9, 2008
Final version accepted: October 16, 2008