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# ROLE OF INTEGRINS IN HUMAN SPERM CELLS ON THE REPRODUCTION PROCESS

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## ABSTRACT
Ovum and spermatozoa cells, namely male and female reproductive cells that unite at the time of fertilization, are synchronized molecular events that occur sequentially. Apart from being present in the egg cell, adhesion molecules called integrins are also involved in this molecular process. However, recently, these integrins have also been found in spermatozoa cells, especially in the head and tail areas. Because this problem is intended as an introduction to the laboratory which is part of the thesis research, the method used in this research is a literature review whose publication age is not more than 10 years. Research findings indicate that integrins play a crucial role in egg-sperm recognition, their interaction, and fusion, potentially addressing infertility issues in couples of reproductive age.

**Keywords:** cells; fertilization; molecular; reproduction; sperm.

## INTRODUCTION

Fertilization is a series of coordinated molecular events in which the fusion of the female gamete cell (egg cell) and the male gamete cell (sperm) occurs (Georgadaki et al., 2016). Fertilization will produce a single cell called a zygote. Fertilization in humans occurs in a woman's fallopian tube or oviduct, which is the ampulla of the fallopian tube.

In humans, fertilization is called internal fertilization because the process occurs in a woman's body. Human fertilization, therefore, gives birth to fewer children but is safer (Ariki & Ulandari, 2018) (Prihyugiarto & Setyonaluri, 2018).

Fertilization occurs by fulfilling several conditions and goes through several preceded stages or processes (Georgadaki et al., 2016). The process aims to produce mature egg and sperm cells to have quality fertilization. The important thing is the occurrence of metabolic activation of the egg and sperm to be able to start the fusion of sperm cells into the egg, which marks the occurrence of fertilization (Machaty et al., 2017).

The process of egg maturation occurs in the ovary. Young egg cells (follicles) found in the ovaries will undergo a maturation process with the help of stimulation from FSH (follicle stimulating hormone) so that the eggs can grow and become mature. Furthermore, this mature follicle will stimulate the hormone estrogen so that it can form the endometrial lining. The hormone estrogen will additionally send a message to the pituitary gland to cease producing FSH and commence producing the hormone LH (luteinizing hormone). LH stimulates ovulation, which is the discharge of an ovum from the ovary.

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The same thing applies to sperm cells; only mature sperm can carry out fertilization (Suherman & Siregar, 2017). Maturation of sperm cells occurs in the epididymis (James et al., 2020). Of all the mature sperm, there is only one superior sperm that can fertilize the egg. A new thing from this research is the molecular events involving adhesion molecules, namely integrins. So far, it is known that integrins are only found in female egg cells, but it turns out that this molecule is also found in spermatozoa cells, specifically in the head and tail.

The next process is the process of ejaculation, namely the discharge of semen containing sperm into the vagina. Hundreds of thousands of sperm are placed in the vagina. If they are in an acidic environment, some of them will die. However, many will live because the fluid's defensive components are there. Soon after, sperm must travel through the mucus in the cervical area, in the direction of the uterus, and finally into the tubes known as the fallopian tubes. They move this way when swimming, their numbers decrease to penetrate the slime. Uterine contractions help the sperm on their way to the egg inside the uterus. The oviduct's ampulla serves as the location of fertilization. The oocyte slowly moves through the uterus without being fertilized, where it degrades and is absorbed. In each ejaculation, there are approximately 120 million sperm cells in 1 ml of seminal fluid. During the journey of sperm cells in the female reproductive tract, sperm will experience capacitation for sperm cell activation.

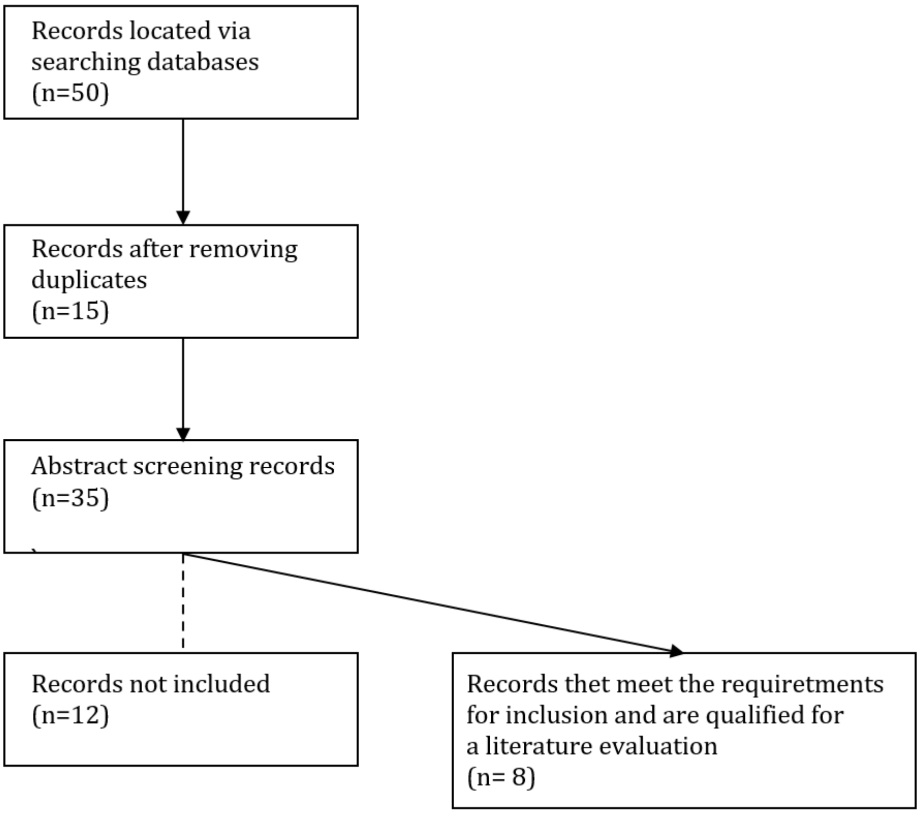
Activation also occurs in the egg cell, and because of this activation, the egg cell wall will be strengthened against other sperm cells. Later, a male pronucleus will be formed in the head of the sperm cell and a female pronucleus, where there will be singami or fusion of the two cells. In the process of activation of spermatozoa cells, several components are involved, one of which is integrin. Many of the integrins and tetraspanins discovered in ova are likewise presented in sperm, where they play a role in the development, stimulation, and communication of sperm with the neighboring epithelium and ultimately with the ovum. The role of integrins in the reproductive process is very important, considering that integrin expression determines the success of spermatozoa fusion with the oocyte; in other words, fertilization can occur if there is integrin expression. In this article, we will elucidate the function of integrins in the activation of sperm cells during the process of fertilization (Merc et al., 2021). Many families face difficulty in having children (Sari et al., 2020) so the role of BKKBN is not only to regulate the number of children a family has but also help to find solutions for those who have difficulty getting children (Aziza & Hantono, 2023). It is expected that this research may help the government, especially the BKKBN, in finding a formula to increase male fertility.

Integrin has only been identified in the oocyte, but recently it has also been found in the sperm. However, the role of integrin in the process of maturation, activation, and interaction of sperm with the surrounding epithelium and eventually with the oocyte is still unknown. Thus, the main objective of this current study is to review the latest developments in knowledge about integrins in reproduction and their role in the process of sperm activation through sperm migration process which is through the female reproductive tract; the formation of oviductal reservoirs; sperm maturation processes occurring capacitation and acrosomal reactions, and their direct and indirect involvement in the adhesion and fusion of gamet membranes leading to fertilization.

## METHOD

This current study used a literature review. Several databases were employed, including PubMed, Science Direct, Google Scholar, and other databases containing research findings or scientific articles. The search term strategy used keywords “cells”, “fertilization”, “molecular”, “reproduction”, and “sperm”. This study only included the publications conducted within the last 10 years (2014-2024). Around 50 articles were gathered using the keywords. After selection, 8 articles were retained and used as literature review material (Figure 1).

Figure 1 The PRISMA diagram of study selection




**RESULTS AND DISCUSSION**

The extent of the role of this integrin is still unknown in reproduction, especially in the human reproductive system, both in men and women. For this reason, this research limits the role of integrins in the male reproductive system, namely the system that works on sperm. The review included eight articles that are presented in Table 1.

Table 1 Matrix of articles included in the study

| No | Authors, year, title | Aims Of Study | Study Setting | Method | Results | Strengths and limitations |
|---|---|---|---|---|---|---|
| 1 | Tourmente et al., 2022, Capacitation promotes a shift in energy metabolism in murine sperm | To find out The process of metabolic change that occurs at the time of capacitation of sperm | mouse | Animals, sperm collection, and incubation, sperm capacitation, Assessment of sperm metabolic rates | performed sperm incubation in capacitation media resulting in a significant increase in the percentage of sperm capacity in the sample | The process of capacitation of mouse sperm on capacitative media, limited to mouse sperms |

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| | | | | | incubation sperm in capacitating medium promoted a significant increase in the percentage of capacitated sperm in the samples | |
| 2 | Yuniarifa et al., 2022, Perbedaan Efek Pemberian Secara Kombinasi dan Tunggal Ekstrak Biji Anggur (Vitis Vinifera l.) dan Glutation terhadap Motilitas, Jumlah, dan Morfologi Sperma Tikus Wistar yang Diberi Paparan Asap Rokok | To determine the motility, quantity and morphology of the sperm of mice that have been exposed to cigarette smoke, by giving: 1. Combination of Grain Extract (Vitis Vinifera l.) and Glutation 2. single Grain Extracts (Vites Vanifera l) and 3. single Glutathione | white mouse male wistar gallur | experimental laboratory with post test only control group design approach | Giving a combination of Grain Extract (Vitis Vinifera l.) and glutathione has the best effect on the motility and morphology of sperm, as well as giving a single glutathione has the greatest effect on sperm count in male white wister mice exposed to cigarette smoke. | Effects of the administration of Grain Extract (Vitis Vinifera l.) and glutathione on the motility, morphology and number of sperm, limited to male white wistar mice |
| 3 | Merc et al., 2021, Role of Integrins in Sperm Activation and Fertilization | to summarizet he current knowledge on integrins in reproduction and deliver novel perspectives and graphical interpretations presenting integrin subunits localization and their dynamic relocation during sperm maturation | None | This current study used a literature review | This review delivers a comprehensive overview of existing literature on integrin | The role of integrin in the reproductive process, its limitation on human sperm |

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| | | in comparison to the oocyte | | | | |
| 4 | Reid et al., 2011, Cellular mechanisms regulating sperm–zona pellucida interaction | 1. Defining the molecular mechanisms that underlie the species-specific interaction(s) between a fertilizing spermatozoon and the zona pellucida (ZP) 2. Gaining a thorough understanding of these mechanisms would aid in tackling the dual problems of explosive population growth in developing countries, and the increasing incidence of infertility throughout many developed countries. | None | This current study used a literature review | specific expression and localization in mammalian gametes including known species-specific | the molecular mechanisms a fertilizing, its limited on regulating sperm-zona pellucida interaction |
| 5 | Harjunpää et al., 2019, Cell Adhesion Molecules and Their Roles and Regulation in the Immune and Tumor Microenvironment | describe the molecular mechanisms regulating integrin function and the role of integrins and other cell adhesion molecules in | None | This current study used a literature review | Tumor cells also recruit regulatory cells such as Tregs and MDSCs which express high levels of integrins enabling them | the molecular mechanisms regulating integrin function in a immune responses, its limited in the tumor |

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|---|---|---|---|---|---|---|
| | | immune responses and in the tumor microenvironment. | | | to reach the tumor site | microenvironment. |
| 6 | Frolikova et al., 2019, Addressing the Compartmentalization of Specific Integrin Heterodimers in Mouse Sperm | To evidence that the β4 integrin subunit is expressed in mouse sperm and that it pairs with subunit α6; additionally, there is a detailed identification of integrin heterodimer pairs across individual membranes in an intact mouse sperm head. | Mice, Laboratory of Reproductive Biology | Real Time Quantitative PCR (q-RT-PCR), SDS-PAGE Electrophoresis and Western Blotting | identified sperm-specific localization for heterodimers α6β4, α3β1 and α6β1, and their membrane compartmentalization and the presented data show a complexity of membranes overlaying specialized microdomain structures in the sperm head. | The role of integrin in the reproductive process, its limitation on rat sperm |
| 7 | Fontenete et al., 2017, Heterocellular cadherin connections: coordinating adhesive cues in homeostasis and cancer | to understand the physical basis of these heterotypic interactions and their influence on the behavior of heterogeneous cellular populations as well as their roles in mediating phenotypic and genetic changes as cells evolve through complex environments during morphogenesis and cancer. | tumor cells | | E-cadherin is expressed by alternatively activated M2 macrophages 65, 66, which are tightly associated with fostering tumor-promoting microenvironments | therapeutic strategies directed towards the eradication of tumors. Its limited the role of heterotypic cadherin interactions in regulating chronic inflammation, cell growth, and survival and the malignant characteristics of clonal populations of tumor cells |

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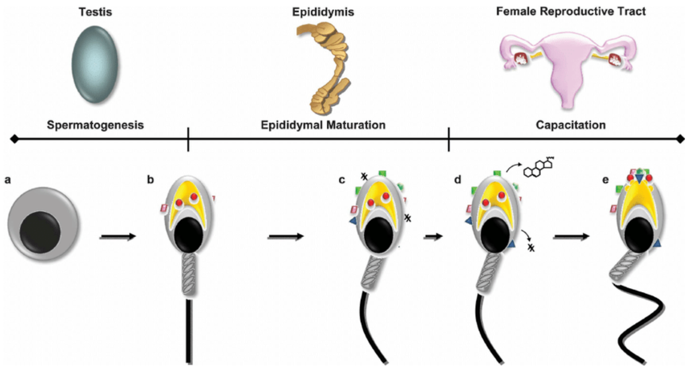
| 8 | Vernaz et al., 2022, Evaluation of Sperm Integrin α5β1 as a Potential Marker of Fertility in Humans. | To investigated the correlation between the subcellular localization of sperm integrin α5β1 and early embryo development outcome after in vitro fertilization (IVF) procedures in human. | Twenty-four semen samples from normozoos permic men and metaphase II (MII) oocytes from healthy women aged under 38 years, from couples who underwent IVF cycles | Analysis of immunofluore scence using antibodies against the integrin α5 subunit. | Evaluating integrin α5β1 immunolocaliz ation in sperm can be a useful tool for selecting sperm with fertilization potential from human sperm samples before IVF procedures. | The role of integrin in the IVF procedures, its limitation on human sperm |

**Spermatozoa capacitation**

The development stage of sperm is referred to as sperm capacitation, takes place in the female reproductive system, and serves as the first step towards entering the acrosome reaction phase and hyperactivation of spermatozoa. Capacitation does not involve any changes in shape and is succeeded by sperm hyperactivation, which is characterized by vigorous, unpredictable movement (Tourmente et al., 2022).

Proteolytic enzymes are essential to this process because they transform cervical mucus into a more watery fluid. Activation may occur after removal of inhibitory factors, such as surface-attached glycoproteins, seminal plasma proteins, and membrane cholesterol depletion (Yuniarifa et al., 2022). Hyperactivation, the final stage of sperm being activated, is the highly energetic phase of the spermatozoa's robust flagellar motility and capacity to move toward the ampulla of the fallopian tube. Some processes are involved in capacitation, including the functional integration of the signal transduction pathway that controls ZP3's induction of the acrosome reaction, flagellar motility changes that may be necessary to penetrate the zona pellucida and an increase in the ability to bond with the egg. Following these occurrences, the metabolism, the membrane's physical properties, the status of protein phosphorylation, and the pH and calcium concentrations inside cells rise along with the membrane potential's hyperpolarization. Numerous elements may help sperm activate in vivo. High-density lipoproteins, one sterol-binding protein found in the fallopian tube, have been shown to hasten the removal of cholesterol from sperm, including the role of adhesion molecule proteins, namely integrins (Merc et al., 2021). Moreover, progesterone can control various components of sperm activation. It is produced by the fluid in the ovarian follicle and the cells around the egg, and it is located in the area around the fallopian tube. Glucose is recognized as vital for the achievement of capacitation. Its role is not only as a source of energy that enables sperm cells to move but also enables them to successfully fertilize eggs.

Figure 2 Schematic of spermatozoa changes during the maturation stage.




Source: (Reid et al., 2011)

**Integrins and their role in spermatozoa activation integrins**

Integrins are transmembrane heterodimer glycoprotein receptor adhesion molecules, consisting of two subunits that are not covalently linked, *Figure* (Reid et al., 2011). Regulate various cell functions. Integrins bind to various extracellular matrices, including collagen and laminin. Each integrin molecular heterodimer consists of a large extracellular domain that binds to other extracellular proteins and a short intracytoplasmic domain that is associated with the cytoskeleton via various cytoplasmic adapter proteins.

The cells attach to and interact with each other via cell-adhesion molecules (CAM). Adhesion molecules in cells and cell-ECM are extremely diverse in terms of structure as well as their expression in different cells and tissues. As a result, the resulting interactions are very specific.

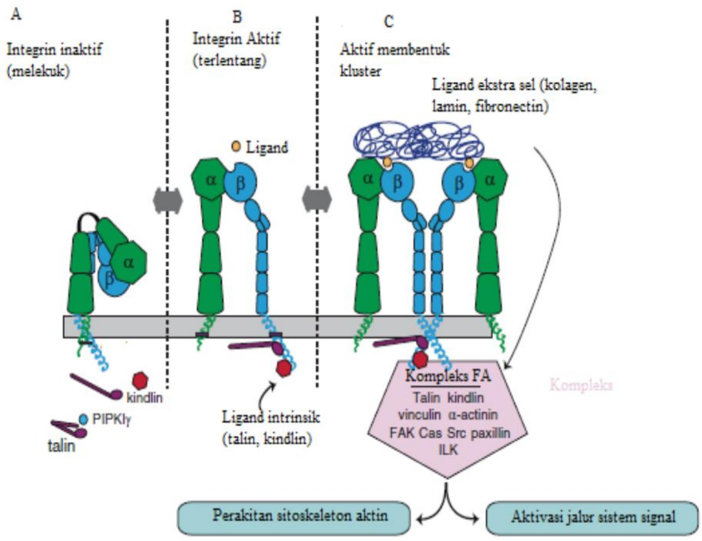
**The division of the adhesion molecule**

Adhesion molecules can be divided into four categories as follows:

1. Cadherin superfamily.
2. Immunoglobulin superfamily.
3. Integrins.
4. Selectin.

Adhesion molecules can behave as adhesion molecules as well as adhesion receptors, namely the integrins and the Ig superfamily (Harjunpää et al., 2019). Adhesion molecules have various domains, which play a role in binding to neighboring cells or within the cell itself. The domain may even be found on other adhesion molecules (they share the same domain) (Frolikova et al., 2019).

Figure 3 Integrin structure and function




Source: (Jia, 2016)

The interaction between the same cell type is called homotypic adhesion, or between different cell types, it is called heterotypic adhesion. Adhesion molecules can bind to the same adhesion molecule (homophilic binding) or different adhesion molecules (heterophilic binding) (Fontenete et al., 2017).

**Role of integrins in sperm activation**

When it comes to the reproduction of humans, integrin-mediated attachment is involved in a number of physiological and pathological processes, including fertilization, embryo implantation, and placentation (Merc et al., 2021). The outer layer of mammalian eggs has been revealed to have integrin receptors, and after capacitation, spermatozoa display fibronectin and vitronectin, which are chemicals that bind to these receptors, on their surface. Human spermatozoa have also been found to include integrins, and the amount of these proteins fluctuates according to the spermatozoa's level of functionality.

Integrins are recognized to play a crucial role in complex physiological processes that are unique to gametes, and they have been found in germ cells, leading to the fusion of sperm and eggs. Integrins are involved in sperm development, including capacitation and interaction with gametes, resulting in successful fertilization.

Expression of α6β1 integrin has been reported in human spermatozoa. Using flow cytometry, integrin subunits α4, α5, and α6 have also been found in healthy human sperm. Their expression is decreased in sperm with aberrant morphology or poor motility. In the basement membrane of human spermatozoa, spermatocytes, spermatids, and seminiferous tubules, the integrin 1 subunit has been identified histochemically. Additionally, the positive correlation between β1 integrin expression in human spermatozoa and their ability to fertilize suggests that sperm integrin may play a role in the identification and interaction of egg-sperm (Merc et al., 2021).

Therefore, α6β1 Integrin has been proposed by Reddy et al. as a clinical marker for assessing the quality of sperm. Several other studies on human sperm have shown a relationship between integrin expression levels and their ability to fertilize.

**Integrins in the fallopian tubes**

During migration from the womb to the fallopian tube, particularly to the proximal part known as the ampulla, sperm must overcome significant obstacles in the uterotubal junctions (UTJ) in the female reproductive system. It is known that different proteins play a role in this selection, which is carried out by reproductive epithelial cells (REEs), which operate as active selective filters for the transportation of sperm. In this instance, integrins expressed on REE epithelial cells have the potential to become partners that bind to sperm proteins from the ADAM family. Sperm cannot go through the REEs because they are unable to connect to the integrin on the fallopian tube's epithelial cells. Sperm that pass through the UTJ connect to the epithelial cells in the isthmus of the fallopian tube (FT) via receptors on the sperm head, forming a reservoir in the oviduct. The molecular mechanism underlying this action is not yet apparent, though. Additionally, it has been hypothesized that integrins may be important for sperm adhesion to oviductal epithelial cells. The interaction between integrin 5β1, which is present on the surface of sperm, and fibronectin, which is present on the surface of ciliated cells of the human oviduct, is one potential method. Through its RGD domain, fibronectin connects with integrins. Oviductal ciliated cells have also been found to have integrins on their surfaces, including types αV, β3, and β1, indicating their potential involvement in these interactions. These integrins specific to the oviduct have the potential to connect with sperm-specific fibronectin. According to studies, sperm attachment to oviductal epithelial cells extends sperm longevity by controlling sperm motility and capacitation, ensuring that sperm maturation is timed with ovulation. This binding process is believed to also allow for the gradual release of sperm that can fertilize and the selection of sperm with the best quality. The binding procedure lowers the possibility of more than one sperm fertilizing the same egg while increasing the likelihood of successful fertilization.

It is interesting to note that sperm are released at a faster pace during ovulation. Capacitation starts as a result of sperm interacting with the oviduct's fluid components, and sperm's capacity to bind to fallopian tube epithelial cells eventually declines. Elevated levels of fibronectin in the oviductal.

**Integrins in the interaction of oviduct fluid and sperm**

Integrins and tetraspanins, such as CD9 and CD81, are essential for sperm to interact with the fluid in the fallopian tube. In humans, fallopian tube integrins have been implicated in the process of sperm-endosalpingeal interaction. Integrins probably contribute to sperm motility within the female reproductive canal, sperm fallopian tube development, sperm capacitation, and fertilization. Extracellular microvesicles and exosomes are known to be present in the reproductive fluids of the male and female genital tracts. These membrane-coated vesicles carry the essential proteins to the sperm surface as they develop in the epididymis and later in the female reproductive system.

After attaching to the fallopian tube reservoir, the sperm interacts with protein-rich viductosomes, which are vesicles of fallopian tube fluid. Because sperm cannot endocytose, unlike somatic cells, fusion serves as the main method for the transfer of proteins between sperm and microvesicles.

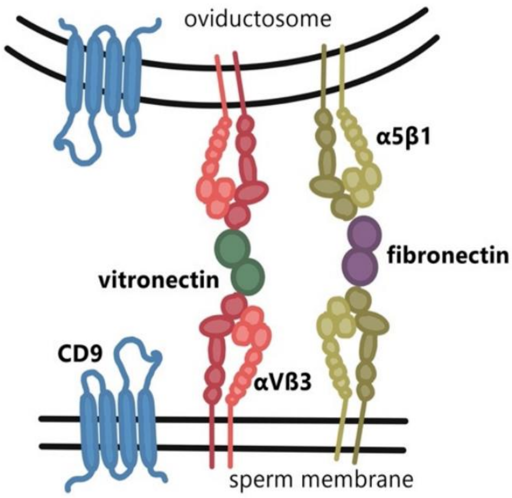
Integrins play a crucial part in this fusion process, according to research by Al-dossary & Martin-deleon (2016) who looked at the presence, localization, and activity of the CD9 protein and the αV subunit of the αVβ3 integrin in a mouse model. Both compounds were discovered in the sperm's viductosome and the area involved in Gamete membrane fusion primarily occurs in the head and neck.

According to studies, the presence of RGD motifs or antibodies against subunit V can prevent the viductosome from fusing with the sperm membrane (mediated by fibronectin and vitronectin ligands that bind integrins α5β1 and αVβ3) (Vernaz et al., 2022). This proves integrins are necessary for this mechanism. Al-Dossary et al.'s hypothesis states that the CD9 protein generates fuse sites on the membranes of sperm and viductosomes, wherever other sticky proteins such integrins α5β1 and αVβ3 are also present.

The proper integrin ligands, fibronectin and vitronectin, link to their active receptors and close the gap between the sperm and oviductosome membranes to less than 0.5 nm to ensure electrstatic opposition on the head of the polar lipid. This causes the plasma membrane's outer layer to crack open, which causes hydrophilic fusion holes to develop between the sperm and the oviductosome and eventually fuse.

In addition to mouse sperm, human sperm also included the V integrin, which was found in the PM covering the acrosome cap (AC) and inner acrosome membrane (IAM). This suggests that the same mechanism proposed by Al-dossary & Martin-deleon (2016). for mice may be used to mediate the fusion of human sperm membranes with viductosomes in the female reproductive canal.

Figure 4 Sperm interaction with the oviduct tosome membrane through the integration of heterodimers




Source: (Merc et al., 2021)

### Role of integrin rearrangement and membrane stability

The outer acrosome membrane (OAM) and plasma membrane (PM) are fused during the acrosome reaction, which causes the acrosome to exocytose and results in a major rearrangement of the sperm membrane.

Since the ejected contents have damaged the zona pellucida, sperm can now enter the perivitelline region and come into direct contact with the oolemma oocyte. During the acrosome reaction, proteins from the apical acrosome (AA), including Izumo1, CD9, CD81, CD46, and integrins, travel to various compartments of the sperm head, particularly to the primary sperm melting location known as the equatorial segment (ES), which is generated by IAM and the remainder of the PM.

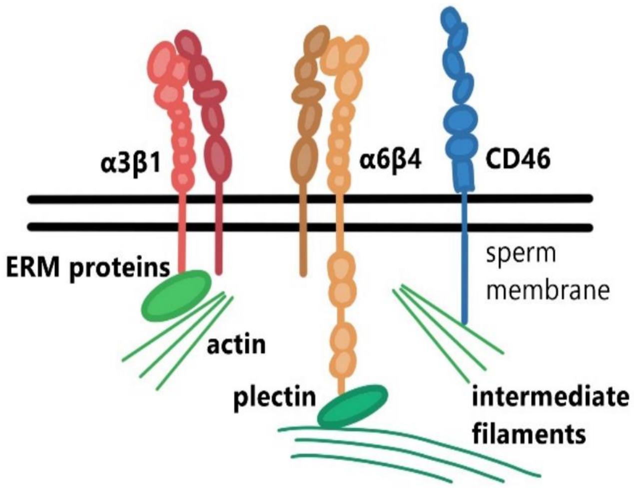
These transported proteins then take the role of the fusion and contacts of the gamete membrane. According to their dynamic translocation during the last stages of sperm maturation, integrins might be involved in the actions that take place after the acrosome reaction. The release of hybrid vesicles during the fusion of the PM and OAM, followed by fusion with the remaining PM surrounding the sperm, is thought to be the mechanism by which protein transportation occurs. These vesicles are known to include other substances, including as the protein CD46, in addition to integrins. In many responses, the actin network is crucial for signaling events and pathways. It is yet unclear which specific proteins, including actin, may be involved in the reorganization and stabilization of this protein network. Due to their capacity to control and regulate the reorganization of the actin cytoskeleton through direct or indirect interactions, integrins are thought to play a significant role.

Through their binding partners in a web of membrane proteins including CD46, CD81, and CD9, actin and integrin interact indirectly. It can be deduced that the same process also operates in sperm based on recent studies that deepened our understanding of the tetraspanin network's presence in sperm. It has been shown that the integrin 1 binding partner in sperm is the transmembrane protein CD46 and that these two proteins move in tandem during the acrosome response. Additionally, through the actin cytoskeleton, CD46 is in charge of maintaining the acrosome membrane and hence the entire acrosome.

This acrosome stability is mediated either directly by binding to actin filaments in the presence of ERM proteins (ezrin, radixin, and moesin) or indirectly through interactions with β1 integrins. An experiment supports the idea that the CD46 protein, maybe in conjunction with the β1 integrin, contributes to the stability of acrosomes. The β4 integrin possesses a cytoplasmic tail that is noticeably longer than those of other integrin subunits and can take part in cytoskeletal remodeling.

This affects the activation of one of the proteins Rac1 (botulinum toxin substrate 1 protein C3-related Ras), which is essential for acrosome capping and responses, specifically actin remodeling in the upper part of the acrosome. In contrast to other integrins, integrin β4 associates with intermediate filaments like keratin 5 via its partner plectin, which, together with actin and tubulin, encircles the sperm nucleus. The cytoplasmic domain 4's structural uniqueness is what gives it this binding capacity, which may help maintain the cell's structural and mechanical integrity. B4 integrins probably similarly interact with tetraspanins to β β1 integrins. In a recent study, Jankovicova et al. showed that the CD151 protein is expressed in sperm ES and that it interacts with the β6 integrin subunit. This protein assembly should result in the formation of a stabilizing complex of proteins at this central fusogenic site during the acrosome process.

Figure 5 Integrins heterodimers and CD46 attached to the sperm membrane that enable interaction with the cytoskeleton through ERM proteins (ezrin, radixin, moesin) or lectins.




Source: (Merc et al., 2021)

**Integrins in the arrangement of protein complexes**

In reproductive cells, integrins' main binding partners are tetraspanins. Tetraspanins have been found in abundance in sperm, especially CD9, CD81, and CD151. Their major job is to control the complex assortment of membrane proteins (including receptors, signaling proteins, and fusogens), which are proteins with four transmembrane domains and two extracellular regions. Tetraspanins help to restructure the membrane, move proteins, and stabilize individual sperm compartments. They can also change how other proteins in the protein network function, especially by interacting with integrins like 3β1 and 6β1 or Vβ3.

Binding can take place directly (CD151) or indirectly (CD9 and CD81). CD9 is a crucial protein in egg cells. When the CD9 gene was eliminated, female mice almost completely lost their ability to conceive, but the male mice retained their ability to conceive. Antibodies against CD9 dramatically decreased in vitro fertilization. The interaction between the CD9 protein and other proteins, such as integrins, within the oolemma, also referred to as cis interactions (lateral bonds between proteins or subunits in the membrane of one cell) and trans interactions (antiparallel interactions between proteins or subunits between the membranes of two cells to facilitate cell-cell adhesion), is the primary function of the CD9 protein in egg cells.

The high degree of curvature of the egg microvilli is where CD9 is concentrated, according to the crystal structure of this molecule, It is also the location where CD9 produces the egg microvilli. Trans-protein interactions have been suggested to be involved in CD9's potential role in promoting gamete adherence. In addition, Miyado et al. (2019) proposed that CD9 may play a critical role in the creation of microvesicles that are released from the egg into the environment prior to fertilization. Because exosomes transfer CD9 from CD9-positive oocytes to sperm, these sperm can attach to oocytes that lack CD9. These results, however, can also be understood in light of the eventual finding of CD9 expression.

Exosomes may also be used to transfer other proteins, like integrins, between gametes. The CD81/mouse model was used to examine CD81 tetraspanin's function in addition to CD9's (Barraud-Lange et al., 2007). Compared to Cd9/ animals, the fertility of Cd81-deficient mice did not significantly decline, but the CD9//CD81/ double mouse model completely rendered females infertile. Importantly, evidence suggests that, like integrins, tetraspanins may have a species-specific function. It is also notable that anti-CD81 antibodies severely restrict mouse fertilizing yet have no effect on successful human egg fertilization. Anti-CD151 antibodies, on the other hand, prevent the membrane union of sperm and oocyte, notably in humans.

**CONCLUSION**

Fertilization, embryo implantation, and placentation are just a few of the physiological and pathological processes in human reproduction that are aided by the action of integrin-mediated adhesion molecules. Based on developments in the laboratory, it has been observed that the plasma membrane of mammalian eggs contains integrin receptors, after capacitation, spermatozoa have adhesion molecules like fibronectin and vitronectin on their surface that bind to these receptors. Additionally, integrin β1 expression in human spermatozoa and fertilization success are positively correlated, indicating a potential role for integrin in sperm detection and interaction with eggs. It is well known that several proteins from structurally sound and usually motile sperm contribute to this selection process in reproductive epithelial cells (REEs), which function as active selective filters for sperm transport. One potential method is the attachment of fibronectin, which is situated at the apex of the ciliated cells in the human oviduct and is present on the surface of sperm, to integrin β51. Tetraspanins (such CD9 and CD81) and integrins in the oviduct fluid interact with sperm integrins, and collectively they play a critical role in the contact between sperm and oviduct components.

In a mouse model, the CD9 molecule and the V subunit of the αVβ3 integrin were studied by Al Dossary et al. to determine whether they existed, where they were located, and what they did, has confirmed the important role that integrins play in the merging process. Both molecules were found in the oviductosome and the head and neck region of the sperm, which is the main location where the gametic membranes merge. According to studies, antibodies against subunit V or Arg-Gly-Asp peptide chains (RGD motifs) can stop the oviductosome from merging with the sperm membrane, which is assisted by fibronectin and vitronectin ligands that bind integrins α5β1 and αVβ3. This demonstrates that integrins play a significant role in fertilization.

And the end, knowing the role of integrin in the human fertilization process, where integrin is decisive in the identification of the egg-sperm and its interaction and fusion of both, can help deal with cases of infertility in fertile-age couples.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