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Ovarian odorant-like biomolecules in promoting chemotaxis behavior of spermatozoa olfactory receptors during migration, maturation, and fertilization

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Abstract

Background: Studies have shown that olfactory receptor genes are the largest in the human genome, which are significantly expressed in olfactory and non-olfactory tissues such as the reproductive systems where they perform many important biological functions.

Main body: There is growing evidence that bioactive metabolites from the ovary, follicular fluid, and other parts of the female reproductive tract signal the sperm through a series of signal transduction cascades that regulate sperm migration, maturation, and fertilization processes. Several studies have highlighted the role of G-protein-coupled receptors in these cellular processes. Thus, we aimed to summarize the existing evidence describing the physiological role of most prominent exogenous and endogenous biomolecules found in the female reproductive organ in enhancing the chemotaxis behavior of spermatozoa during migration, maturation, and fertilization and also to elucidate the pathological implications of its dysfunctions and the clinical significance in human fertility.

Short conclusion: In the future, drugs and molecules can be designed to activate these receptors on sperm to facilitate fertility among infertile couples and use as contraceptives.

Keywords: Olfactory receptors, Bioactive metabolites, Sperm, Chemotaxis, Ovary, Reproduction, Physiology

Background

When spermatozoa are released into the vagina near the cervical os, they have to travel through the different anatomical and biological environments of the female reproductive tract, like the cervix, uterus, utero-tubal junction, and then through the isthmus region of the fallopian tube before reaching the fertilization site. Within minutes, active sperm (morphologically healthy) reaches the final destination the isthmus region; thus, this movement seems to be facilitated by various mechanisms such as ciliary beating, muscular contraction mechanism

of the female reproductive tract, thermotaxis and chemotaxis behavior plus molecules enhancing chemoattraction that guides spermatozoa to the oocyte [1]. Chemotaxis can be defined as a guided movement with respect to the chemical concentration gradient in any environment or system. Studies have implicated the ovary, follicular fluid (FF), and the female reproductive tract as the primary sources of biochemically active biomolecules that facilitate oocyte-sperm communication during pre- and post-ovulatory period. Unfortunately, the studies aiming to find a bio-molecular predictor and their transduction signaling cascade in sperm migration, maturation, and fertilization involving chemotaxis behavior have been limited thus far. In the recent past, different multistep chemotaxis transduction pathways

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involved in sperm selection, survival, and binding of the oocyte have been identified [2, 3]. Studies have shown that FF offers an important microenvironment and nutritional status for the development of oocytes. It is known that FF constituents are products of blood plasma constituents that permeate the blood follicular barrier and of the secretory activity of thecal and granulosa cells. Therefore, it is reasonable to believe that some critical regulators in the FF secreted from the ovary and reproductive tract play a crucial role in determining oocyte-sperm interaction and communication in a dose-dependent manner [4]. Some of these important biomolecules are involved in G-protein-coupled receptors (GPCRs) chemotaxis behavior regulating sperm migration, selection, survival, maturation, and fertilization of the ovum [5].

Main text

Chemotaxis communication between sperm and ovary

The FF is separated from the ovary by the perifollicular stroma, which constitutes a “blood-follicle barrier” serving as a barrier to serum, and also capable of locally generating biomolecules moving to the serum, in relations to the metabolic activity of follicular cells [6]. The generated biomolecules change with the different developmental changes of the ovary, and it is expected that the functional and structural integrity of an oocyte is a prerequisite for its fertilization by a sperm. This is achieved through an elaborated chemotaxis control mechanism. It is quite not impossible that metabolites generated from the ovary, present in the FF and reproductive tract, influences fertility. Before focusing on the possible physiological role of some of these metabolites as regards fertilization, it is essential to identify the physiological importance and their molecular mechanism that promotes the movement of spermatozoa.

Karteris et al. [7] have shown that the critical success of fertilization involves sperm hyperactivation, which describes the physiological movement of sperm involving detachment from the oviductal wall, navigation through the narrow labyrinthine lumen, and penetration through the mucus-filled barrier plus penetrating the zona pellucida of the oocyte by cross-talk between sperm and the oocyte. This movement pattern is controlled differently according to the composition of metabolites in the fluid milieu present in the female reproductive tract. Undoubtedly, many studies have presumed the involvement of odorant-like biomolecule signaling cascade in these oviductal initiated hyperactivation processes; however, only a few have been identified so far. This is also supported by the fact that the signal transduction cascade of events regulating migration, maturation, and fertilization remains thoroughly described. It is evident that calcium ions, G-protein-coupled receptors, hormones, and other

biomolecules play a significant role in these physiological processes [8].

In human, spermatozoa encounter a different type of mucus, comprising of hyaluronic acid and other active metabolites, while passing through the cervix, uterus oviduct, and cumulus oophorus. Generally, mucus increases the elasticity and viscosity of the fluid medium in which spermatozoa swim, and only hyperactivated spermatozoa can easily penetrate this medium. Therefore, various physiological metabolites derived from the female genital tract stimulate this chemotaxis action of spermatozoa bringing about sperm-oocyte communication [9, 10]. The release of oocytes into the oviduct is accompanied by FF and cumulus oophorus that partake in motility regulation of sperm. Besides, it has been demonstrated that the ovarian follicle could also communicate with the sperm cell in the female reproductive tract before leaving the ovary [11]. Other studies like Einer-Jensen and Hunter [12] have also supported this view by giving anatomical and physiological evidence for a vascular counter-current exchange of follicular hormones and other metabolites between the veins leaving the ovary to the arteries supplying the wall of the female reproductive tract especially the isthmus. These reports justify the chemotaxis communication between sperm and ovary in regulating sperm movement. However, no specific signals or molecules were identified by them.

Migration processes

Literature by Oren-Benaroya et al. [13] has shown that little is known about the migration processes, molecular events underlining the chemoattractant signaling cascade and the different factors encountered by sperm during the migration processes. Empirical pieces of evidence by Petrunikina et al. [14] revealed that strong selective pressures and olfactory mechanisms act on sperm cells at different times and points as they travel through the female reproductive tract. Each compartment of the female tract offers the spermatozoa with diverse physiological, anatomical, ionic, fluidic, and molecular microenvironments. Hence, the process of sperm migration is a very complicated event ensuring only morphologically healthy selected sperm made its journey towards the oocyte ipsilaterally [14], by penetrating different compartments and contents in the female tract. Here, we summarized the role of various constituents and structures during spermatozoa migration in the female tract (Fig. 1).

Role of viscous mucus in the female reproductive tract

In several species especially human, different type of mucus is produced in the female reproductive tract consisting of various biomolecules such as hyaluronic acid, water, glycoprotein, immune-competent proteins, simple

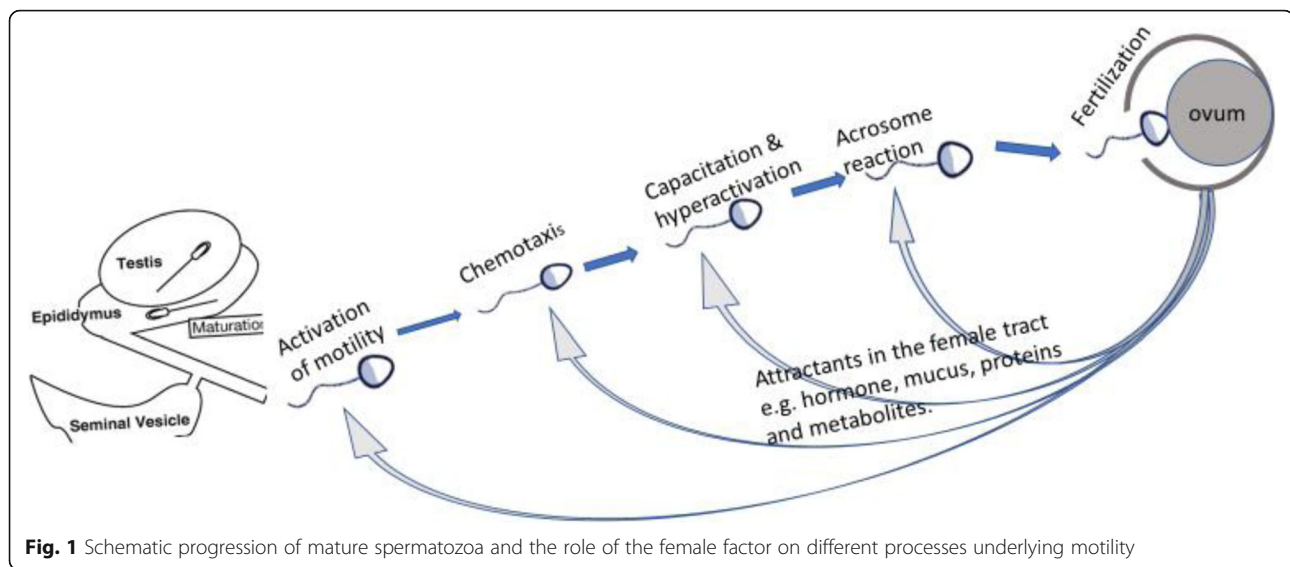


Fig. 1 Schematic progression of mature spermatozoa and the role of the female factor on different processes underlying motility

sugars, electrolytes, amino acids, Th1 and Th2 cytokines, C3 and C4 complement components, and prostaglandins of E series, with trace elements that increase the thickness and elasticity of the fluid medium [15]. Thus, only hyperactivated sperm can effectively penetrate to reach the oocyte for fertilization. Naturally, cervical mucus sub-serve enormous functions to allow smooth migration of sperm cells from a hostile vaginal environment, but may become a barrier to sperm motility acting as a “passive filter” that eliminate spermatozoa with abnormal motility in certain conditions [16]. A small change in the chemistry of cervical mucus may prevent natural conception and result in infertility by serving as a barrier to sperm migration because the extent of hydration of mucus is linked with permeability to sperm [17]. Sperm with a poor hydrodynamic profile cannot vigorously move through the mucus, which has been suggested as a means of sperm selection. Adequate secretion of cervical mucus is needed for the transport of sperm to the uterine cavity [18]; however, factors like surgeries, genetic plus infections can put a significant constraint on the adequate production of cervical mucus due to fibrosis of various degrees [19]. The quality of mucus is also a factor in some conditions (including chronic cervicitis, cystic fibrosis, hormonal insufficiency, drug contraindications, and unhealthy lifestyles, e.g., smoking), which can make the mucus hostile to sperm cells [20, 21]. In the periovulatory period, mucus serves as a selector of good sperm on a morphological basis, and the cervical mucus is highly watery. Thus sperm penetrability is highest, unlike post-ovulation, when thicker mucus is secreted, which forms a plug and inhibits sperm migration into the endometrial space [22].

Cervical mucus contains prostaglandins (such as 19-hydroxy prostaglandin PGE), which stimulates sperm

motility plus sperm penetration capacity. The prostaglandin's stimulatory effect appears to have been mediated via modulation in spermatozoa ATP. Sperm motion inside the mucus occurs majorly through the interstitial spaces in the mucin micelles, which is proportional to the size of these spaces and a substantial reduction in this space to less than the size of the head of spermatozoa may hamper the progressive movement of sperm with resultant decreased fertility [18]. Bacterial infection has mucinase activity, which may reduce the viscosity of mucus, thus favoring sperm progression but this motility is unfortunately reduced by immunological and inflammatory reaction induced by the bacterial cells [23]. Immunological infertility ensues when antibodies are formed in the cervical mucus that identifies and fight the antigens localized on the sperm cells. The presence of serological complement and complement-fixing anti-sperm antibodies in the mucus can lead to the ingestion of sperm, thereby causing a barrier to the movement of sperm towards the fertilization site. Aside from ingestion, antibodies bounded sperm are less motile, thus increasing the transition time [24].

Role of the acidic pH in the female tract

Almost all biophysics and biochemical activities in the cell depend on the pH level; thus, anything that alters the optimum pH can affect the physiology of the cell [25]. Sperm quality and movement depend greatly on the pH of the microenvironment of sperm [26]. Sperm cell transit in the female reproductive tracts varies due to the pH condition of chemical milieu and maintenance of optimal pH (acidity) has been strongly associated with migration, viability, capacitation, and hyperactivation of sperm cell [17]. Sperm cells are more viable and motile at an optimal pH range of 7–8.5 with significant

reduction when the pH is below 6.0, thereby forming a barrier to the movement [27]. However, sperm cells are endowed with an intrinsic pH regulatory mechanism [26] via the alkaline nature of semen; this necessitates the presence of a significant volume of semen to negate the vaginal acidity. Blockade in the ejaculatory ducts or hypoplastic seminal vesicles can lead to reduced semen buffering capacity against vaginal acidity and ultimately increasing the transit time to get to the site of fertilization [28]. Physiologically, vaginal acidity helps to prevent the growth of pathogenic bacteria but could inhibit fertility by reducing sperm survival and migration. Also, mild acidic pH of about 6.5 has been found to increase the potency of motility inhibitory factor (MIF II) and motility initiating protein (MIP) found to function maximally at pH of 8 causing further disturbance in forward movement of sperm cell [29, 30]. Besides maintaining a relative pH range, the protective coating on sperm cell may also offer protection for the sperm from various damages.

Role of fructose and leucocytes in the female reproductive tract

A high fructose level is essential for the survival of sperm cells and their migration through the female genital tract. Fructose and other essential sugars in the follicular fluid provide energy (ATP) for normal mitochondria function in the sperm. Therefore, a reduced amount may lower the intensity of oxidation processes resulting in lactate build-up and decreased sperm motility [31]. Physiologically, leukocytes (neutrophils and macrophages) migrate into the vaginal and cervix following introduction of the sperm cell. This does not create a barrier; instead, it serves as protection against microorganisms that might be deposited alongside with the sperm. Studies have shown that leukocyte infiltration can increase tremendously, hence overwhelming the sperm function if migration is delayed. The migration of the neutrophil has also been seen in mid-cycle through the cervical mucus. Immunoglobulins IgG and IgA are present in cervical mucus with the highest quantity in the preovulatory period to cover for defensive power lost by mucus due to hydration [17]. In a pathological state, serological complement and complement-fixing anti-sperm antibodies are formed against sperm antigen, thus destroying the sperm and creating a barrier to normal fertilization.

Role of physical stress and reactive oxygen species (ROS)

Physical stress due to migration of sperm through the tight genital tract and reactive oxygen species production is a well-known cause of damage to sperm cells. They are mostly generated from a high quantum of polyunsaturated fatty acids in their cell membrane [32]. The

detrimental effect on spermatozoa causes impaired motility, decreased acrosome reaction or damaged DNA and infertility [32]. Despite this negative profile, a balance between the reactive oxygen species (ROS) production (basically from physical, chemical stress and leucocyte presence during migration) and reduction (through scavengers and antioxidants) are essential for reproductive function. This balance is needed because a certain amount of ROS is required for sperm capacitation or acrosome reaction and hyperactivation in the female genital tract [33].

Role of allogenic factors from the immune system in the female reproductive tract

The mucosal innate immune system in the female reproductive tract (cervical mucus and vaginal washes) provides an anatomic barrier through the epithelium against microbial infections by secreting anti-microbial peptides, cytokines, plus chemokines, and also protect allogenic sperm and the immunologically distinct fetus [34]. The mediators of this innate immunity are epithelial cells barrier, mucus, expression of toll-like receptors (TLRs) on the epithelium, cytokines, chemokines, innate immune cells, and natural anti-microbial peptides. Despite exposure to various microorganisms, semen in the female genital tract are selectively given an immune privilege [35]. The survival of sperm cells in the female genital tract is related to their unusual and unique antigen-presenting molecule expression patterns [35]. In rare instances, there could be allergic reactions to the seminal plasma fluid [36]. This can impair the smooth migration of sperm if the developed immune response extends to the matured sperm cells, and failure to have this adaptive mechanism can hamper its movement and consequently, the development of allogenic immunity and infertility. The uterine immune system also mirrors the menstrual cycle and pregnancy. This could invariably offer a deferent degree of barrier to sperm movement at various points in the cycle [37].

Role of utero-tubal junction

This site forms a major reservoir and offers protection and nutrition for sperm within the isthmus of the oviduct by sperm adhesion binding to the oviductal membrane. Nevertheless, studies have also shown that only hyperactivated sperm can pull away from the epithelial wall of the oviduct to fertilize the oocyte in an upstream swimming pattern called rheotaxis [38]. The utero-tubal junction (UTJ) serves as a barrier with different relative importance according to the species and several genes (including calmeglin, calreticulin-3 or calsperin, angiotensin-converting enzyme) encoding some specific protein in the sperm cell has been indicated to be necessary for the migration of sperm cell through utero-tubal

junction [38, 39]. The very narrow and tortuous nature of the utero-tubal junction (UTJ) has been considered a barrier for spermatozoa migration to the fertilization site [40]. Also, the presence of viscous mucus at the utero-tubal junction may impede the movement of spermatozoa.

Role of the pro-ovarian myometrial contraction

de Ziegler et al. [41] showed that the peristaltic movement of the uterus controls the rapid transport of sperm in the female reproductive tract. Though, the utero-ovarian mechanism controlling sperm movement is poorly understood, endocrine-guided sperm (counter-current system) ipsilateral movement towards the dominant follicle has been suggested. Uterine cervico-fundal peristalsis ensures that spermatozoa move through the female genital tract, which is specifically confined to the stratum subvasculare of paramesonephric origin with adequate blood supply, endocrine control, and cascade of paracrine events [41].

Vascular counter-current transfer of biomolecules and hormones

In humans, Oren-Benaroya et al. [13] revealed the importance of local counter-current transfers of compounds and molecules in different parts of the reproductive system. A typical example is seen in the female reproductive tract with the surrounding peritoneal fluid, where the ovary communicates with different parts of the reproductive tracts such as ovary to ovary, ovary to the oviductal system, ovary to the uterus, ovary to the cervix, ovary to vagina, and vice versa, respectively. This communication occurs via the release of substances such as steroids, gases, hormones, local factors (endothelin), electrolytes, amino acids and heat through the interstitial fluid, lymphatic vessels, and venous system to the arterial blood, creating cross-communication, facilitating local feedback mechanisms, and modulating various functions [13, 42]. For fertilization and implantation to occur, signals originating from the ovary facilitates spermatozoa interaction and migration towards the endometrial tissues, fallopian tube, and the released oocyte during the luteal phase of the human menstrual cycle [43]. This can be described as the local transfer or exchange of information between ovary and sperm and different ovarian structures facilitating chemotaxis behavior of sperm using olfactory receptors to pick up the odorant signals generated by the ovary and uterus. The molecules and hormones (chemoattractants) from the peritoneal fluid are not derived only from the ovary, but also from other associated organs and tissues such as the mesenteries and its linked adipose tissue containing leptin and the intestines [44] (Fig. 2).

Cicinelli et al. [45] described the ipsilateral transfer and regulation of endogenous ovarian steroid and peptide molecules towards the uterus, cervix, and the vascular system around it during follicular and luteal phases in women, which facilitate the attraction of sperm cells towards the oocyte on the ipsilateral uterine wall only. In addition, degeneration and proliferation of various cells and tissue types during growth and maturation of the ovary are locally mediated by signals diffusing between neighboring cells or through an interchange of molecules in the ovarian vein and arteries. The number of sperm cells and its movement in the reproductive conduit is part of the vast communication network controlled by the ovary through odorant signals released and made available in the tube together with immunological tolerance of sperm. Thus, the ovary is believed to act as a central integrating center, programming communications with ovarian somatic cells and the reproductive tract [46]. Taken together, a significant chemotaxis stimulus in the female tract (majorly from the ovary) promotes adequate biochemical and molecular signaling cascades of an event in the mature spermatozoa with resultant migration towards the oocyte. The next paragraph gives an overview of the physiological process that occurs following an adequate migration process.

Fertilization processes

The key physiological sperm maturation processes are capacitation and hyperactivation, which are essential for adequate fertilization of the ovum.

Capacitation

Sperm capacitation can be described as a physiological alteration (including loss of proteins and cholesterol in the cell membrane) in the spermatozoa to undergo acrosome reaction. Sperm capacitation involves modifications on the surface coat of sperm, ensuing exposure of surface proteins. Capacitation consists of several processes, including sperm surface remodeling, hyperpolarization, protein phosphorylation, increased membrane fluidity, pH, and internal Ca^{2+} concentration [47]. Some messengers have been studied to initiate these biological processes such as atrial natriuretic peptide, cholesterol esters, adenosine, tyrosine-phosphorylated proteins, cholesterol sulfate, fertilization-promoting peptide (affected by female reproductive pH), desmosterol sulfate, leukocytes, calcitonin, cholesterol, angiotensin II, sialic acid-binding proteins, heparin-binding proteins, progesterone, desmosterol, and cholestadienol [48–50]. De Jonge [51] revealed that after capacitation in the female genital tract, the G-actin monomers which are primarily present in sperm are polymerized into F-actin, thereby increasing motility. As part of the final phase of

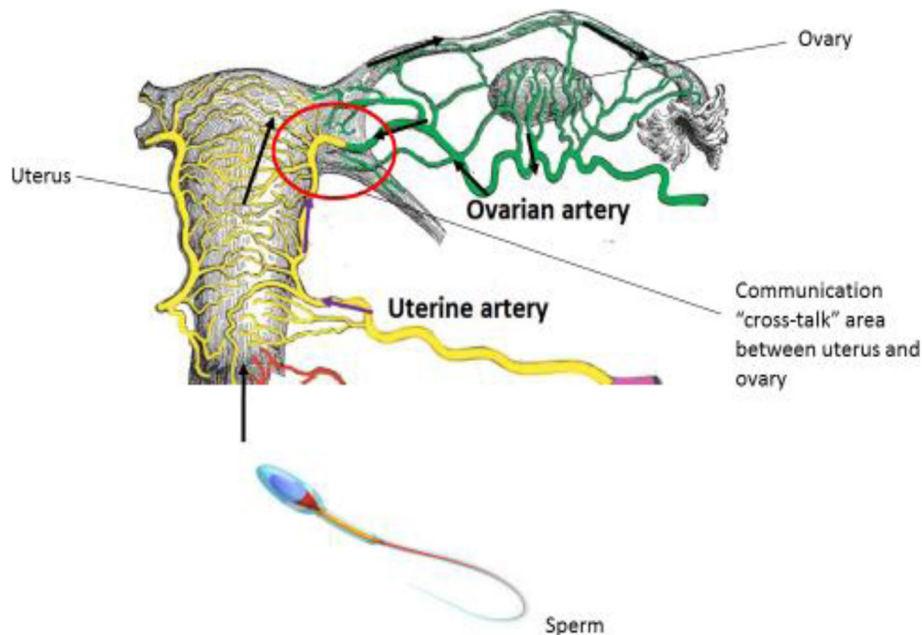


Fig. 2 Schematic diagram showing the communication area between the ovary and uterus providing evidence of vascular counter-current transfer in sperm chemotaxis behavior

acrosomal exocytosis that is activated when sperm reach the ovum, the F-actin is cleaved again to G-actin. This cleavage is necessary to enhance the proper fusion of the outer acrosomal membrane and the plasma membrane. Hence, biomolecules activation caused depolymerization of F-actin and stimulated the acrosomal exocytosis in human sperm, indicative of their role in the activation of G-protein-coupled receptors as an important mechanism sperm-oocyte communication [51].

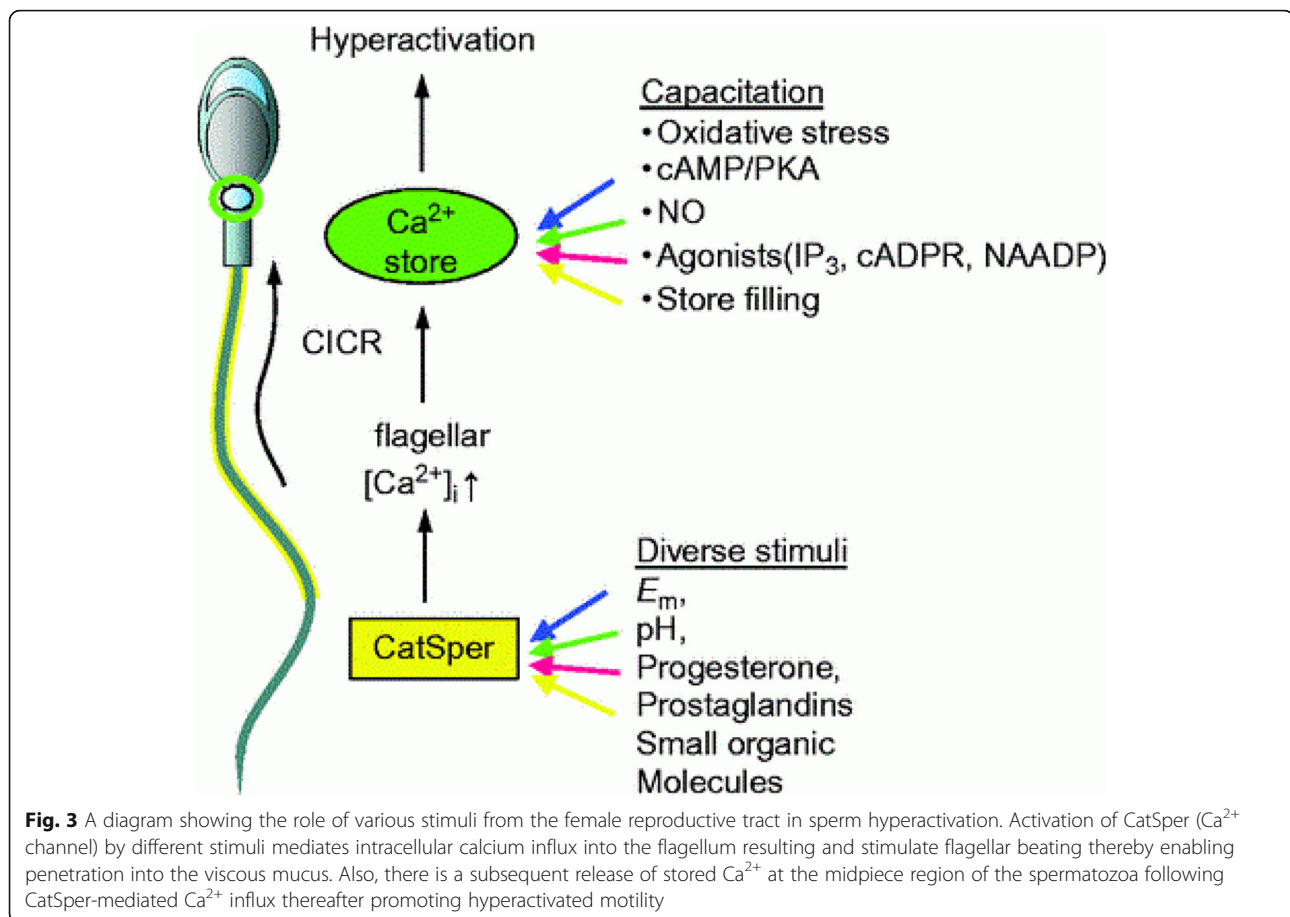
Hyperactivation

Hyperactivation can be described as a movement pattern (increased beat asymmetry plus flagellar bend amplitude, frequently changing direction, velocity, and capacitation plus the acrosome reaction) of sperm cell at the time and site of the fertilization process. This is an essential process for conception to occur, which allows the sperm cell to separate from the oviductal wall and subsequent movement in the labyrinthine lumen to penetrate the mucous substances and the zona pellucida eventually [52]. Ramírez-Reveco et al. [53] have revealed that this process involves signal or signals such as neurotransmitters, chemokines, endocannabinoids, lipids, bradykinin, platelet-activating factor, L-glutamate, metabolic substrates, ions, bicarbonate, hormones, and peptides. Secretions from the ovary and female reproductive tract such as follicular fluid that increase calcium ions concentration and intracellular cAMP are also needed for adequate interaction with the axoneme, dynein, and cytoskeleton of the flagellum as shown in (Fig. 3). These

signals initiate the hyperactivation processes by modulating phosphorylation of tyrosine regulated by Ca^{2+} -calmodulin complex, calcineurin, and phosphokinase C [53]. The sperm is known to undergo several obstacles in the female reproductive tract; hence, hyperactivation is an additional process that promotes fertilization. It is known that the follicle can interact with the sperm both before and after ovulation with the help of the accompanying follicular fluid and cumulus oophorus cells that release odorant-like substances, which signals the spermatozoa for fertilization.

Ovarian odorant-like molecules (exogenous and endogenous activators of olfactory receptors) in the follicular fluid.

The follicular fluid (FF) majorly serves as a source of nourishment to the developing oocyte. It regulates both the internal and external environment of the oocyte, thereby playing a significant role in the fertilization and development of the embryo [54]. Follicular fluid is a complex fluid that comprises of various molecules, such as hormones (luteinizing hormone, follicle stimulating hormone, oxytocin, prolactin, vasopressin, estrogen, and progesterone), proteins, enzymes, polysaccharides, and antioxidants (catalase and super-oxidase), as well as several stimulatory and inhibitory factors like methional [55]. The analysis of suitable biomarkers in the FF could help to identify normal oocyte function [56]. It has been reported that the chemical signal from the oocyte mediates the process of fertilization by ensuring that an



appropriate amount of sperm cells reach the egg [57]. Literature has shown that sperm cells are stored and undergo capacitation in the oviduct, while their motility and chemotactic behavior is enhanced by the presence of FF [58]. Although the identification of chemoattractants released from the ovary is not fully understood, however, several in vitro studies have provided significant experimental evidence in this area of research.

Progesterone, a steroid hormone released by the cumulus cells of the ovary in minute concentration, was initially reported as a chemical substance that attracts human sperm cells with significant accumulation of spermatozoa in the female genital tract [59–62]. Also, other experimental studies have revealed that several other chemoattractants, apart from progesterone, are released from the cumulus cells of the ovary into the follicular antrum [13]. While some FF chemoattractant could be species-specific, others can be common (especially progesterone) with wide distribution among species and probably responsible for the non-specific movement response of mammalian sperm cells. Thus, the non-specific movement of sperm cells observed in different species in vitro towards FF can result from the presence of chemoattractant, which is a principal

constituent of this biological fluid [63, 64]. Several ovarian chemoattractant molecules have been identified to influence the movement of sperm cells along the female genital tracts because the sperm cells undergo different steps of chemotaxis that guide them in their long journey towards the egg. These molecules are involved in the sequence of events required for their successful journey towards the egg. The FF chemoattractant possesses “odorant-like” characteristics that activate odorant receptors on the surface of sperm cell [65]. Among the established chemoattractant molecules specific for human spermatozoa are atrial natriuretic peptide (ANP), progesterone, RANTES, and peptides. At the same time, other substances (antithrombin-III, calcitonin, Bendorphin, heparin, oxytocin, substance-P, and many more) are suggested to activate the sperm olfactory receptor [48, 49].

The FF progesterone produced by the cumulus cell is a steroid hormone that plays a significant role in sperm accumulation and elicits a chemotactic response [66]. Progesterone has been identified as a chemoattractant following the expression of its receptor on the cell surface of spermatozoa, while the progressive movement of capacitated spermatozoa towards the egg has been

correlated with the presence of FF progesterone [67]. The granulosa cells in the ovaries also release ANP, a peptide hormone, into the FF and have their specific receptor site localized on the human spermatozoa [68]. The high binding affinity of ANP to its receptor, mediated by guanylate cyclase, also attracts the sperm cells towards the oocyte. Also, ANP can facilitate acrosome reaction in the spermatozoa [69]. Heparin is present in the FF and has its binding sites ubiquitously expressed on the cell membrane of spermatozoa. The presence of FF during ovulation facilitates the binding of heparin to its receptor and acts as a chemoattractant for the spermatozoa [50, 70]. In general, FF is a complex biological fluid comprising of varieties of biomolecules that mediate ovarian development and function. These constituent molecules, majorly progesterone, heparin, and ANP, possess odorant-like molecule exerting chemo-attractive properties and regulating the movement of spermatozoa in the female tract and binding of spermatozoa to the oocyte to promote fertilization.

The physiological role of odorant-like molecules in migration, maturation, and fertilization

Einer-Jensen and Hunter [12] revealed that in recent times, there has been a renewed interest and effort by scientists in understanding the physiological role or basis of physiological regulatory systems functioning as local or central control mechanisms regulating sperm migration, maturation, fertilization, and implantation of embryo in the female reproductive tract. The system of vascular counter-current transfer is beginning to gain serious recognition among reproductive physiologists and clinicians concerning the vital role played by this system. This system exhibits their primary functions via biochemical adaptations of the local blood circulatory system and lymphatic system found between paracrine and endocrine regulation [12]. These adaptations enhance the movement of regulatory biomolecules, increasing their circulating level in the female reproductive tract and releasing them by retrograde transfer or a nearby structure through destination transfer such as the ovary. This mechanism offers a functional utilization and reuse of biomolecules secreted by this tube, influences sperm behavior along the tube plus generates positive or negative feedback effects, which may be considered as a universal physiological regulatory mechanism in the female reproductive system [42].

Gabler et al. [71] showed an elaborate development plus adaptations of the circulatory system and lymphatic drainage in the mesosalpinx, mesometrium plus mesovarium to enhance the local supply of higher amounts of unbound biomolecules or hormones derived from the ovary to the female reproductive organs and vice versa. The enormously strict adhesion of the arterial wall with

associated veins plus even tunica adventitia suggested the possibility of promoting the entry of biomolecules via the adjacent blood vessels [71]. Hence, there are special conditions that promote the entry of ovarian molecules into the arterial blood supplying the oviduct, uterus, and ovary. Physiological regulators (odorants) secreted from the ovary may leave the ovarian cell by two important mechanisms: (1) in venous blood flowing into the branches of the ovarian vein, plus (2) in lymph, by several pre-collector lymphatic vessels forming near the para-ovarian lymphatic plexus then through the mesovarium to the closest local lymphatic node. Subsequently, biomolecules could be transported into the arterial blood supplying the female reproductive tract through two mechanisms: (1) by partial pressure gradient: directly, from the blood in the ovarian veins (higher concentration) to the arteries (lesser concentration). However, the precise mechanism is still not certain. Whether it is through free or passive transmembrane diffusion or an active process involving the use of energy and transporters plus (2) indirectly, it is a multi-faceted process, from the ovarian lymph as well as venous blood in the mesovarial vasculature into the arterial blood in the ovary [72].

Clinical importance

The fluid milieu of the female reproductive tract plays a vital role in cross-talk between gametes, enhances fertilization, promotes gametes/embryo transfer, stimulates nourishment, and implantation processes. The discovery and evaluation of the vital biomolecules involved in the chemotaxis behavior of sperm through the female reproductive tract as well as the molecular mechanism of their physiological interaction will help to provide useful information in the diagnosis and management of infertility and uterine deficiencies or in the formation of new methods of hormone-free contraception that inhibit the sperm cells from fusing with oocyte [73]. It is known that for many decades, the vaginal has been used for many reproductive procedures and drug administration due to effective absorption and faster nature. Various studies have indicated the rapid changes in uterine physiology after vaginal administration of progesterone, especially close to the cervix. The available information showed that these effects might be due to local counter-current transfer from the venous blood in the vaginal to the arterial blood in the uterus and lymphatic vessels, also referred to as the “first-pass metabolism” [74]. Nature does not play games; hence, there is a physiological reason for the actual chemotaxis behavior of sperm from odorant-like molecules secreted by the ovary and other parts of the female reproductive tract. The local communication between these systems is probably essential for regulating sperm and egg transport and biomolecular

aspects of tubal secretions, including transfer of early luteotrophic signals and embryo transport and development. This area is quite important in In-vitro fertilization and intra uterine insemination procedures when considering treatment options to enhance conception. It should be emphasized that great attention should be given to chemotaxis signals affecting gamete/embryo physiology, early pregnancy markers, fluid milieu of female reproductive tract in in vitro fertilization (IVF) treatment, cancer biology, and other pathophysiological conditions such as endometriosis and poly cystic ovarian syndrome. Browne et al. [75] indicated that thorough understanding of sperm migration, maturation, and fertilization in the female reproductive tract could initiate new development in assisted reproduction, which relies on supporting the sperm to reach the fertilization site or produce an embryo which is ultimately returned to the uterine cavity even though most of these techniques are well established yet success rate is still meager [75]. The biology of sperm wash, ovarian stimulation plus the behavior of sperm or embryo in the female reproductive tract can equally improve IVF procedures resulting in better clinical outcomes. Lastly, the diagnosis of infertility could also be significantly improved upon if the biology and behavior of sperm movement along the female genital tract plus the principle guiding these processes are understood.

Spermatozoa olfactory receptors

Olfactory receptors (ORs), otherwise known as odorant receptors (ORs), are usually localized on the cell membrane of the olfactory neurons and concerns with the identification of odorant molecules [76]. They have majorly comprised of G-protein-coupled receptors (GPCRs) that form the biggest genetic group within the human genome, with the body genetic make-up encoding approximately 1000 ORs [77, 78]. In mammals, ORs are expressed in the olfactory epithelium nose with a higher affinity to attract a wide range of odorants as well as utilizing the chemical properties of odorant molecules to mediate the sense of smell.

Interestingly, it has been reported that ORs are not only found in the nose. They can also be expressed in other tissues such as the cardiac cells, autonomic nervous system, spleen, prostate, and testis with wide distribution on the sperm cell [79, 80]. More than 20 members of the olfactory receptors (ORs) family have been identified in sperm cells playing different roles at various stages in the movement (e.g., speed, strength, and direction) of spermatozoa towards the egg while genomics analysis revealed that approximately 50 receptors could be expressed in the testis [81, 82]. These ORs are structurally similar to those receptors found in the olfactory epithelium mediating the sense of smell. They

are usually found in the mid-piece region and the flagellum in the mature spermatozoa [83]. Real-time PCR analysis of human testicular biopsy identified the presence of a specific receptor, human olfactory receptor 17-4 (hOR17-4) in the testis, and on the surface of a mature sperm cell, while proteomics analysis of seminal fluid shows the expression of 8 different ORs gene encoded as OR4S1, OR4C13, OR5R1, OR1I1, OR2M7, OR2T2, OR4AJ1, and OR2M3 localized on the surface of sperm cells [3, 84]. Although the exact expression status and physiological significance of the different testicular ORs are yet to be fully explained, works of literature have reported that hOR17-4 and mOR23 can influence the chemotactic movement of sperm cells towards the egg by identifying different stimuli and activating cellular transduction signals which interpret these stimuli into a coordinated movement pattern [2, 85]. The ORs, hOR17-4, and mOR23 can influence the spermatogenic process, promote epididymal growth, influence acrosome reaction, and initiate flagella movement in the mature spermatozoa to enhance sperm-oocyte interaction in addition to their significant role in chemotaxis [81]. On the other hand, ORs can facilitate cell-to-cell communication as well as identifying internal and external ligands [86].

For fertilization to occur, capacitated sperm cells must be guided towards the egg. This is usually mediated by chemotaxis in addition to oviductal contraction and thermotaxis that moves the spermatozoa from the storage site towards the fallopian tube [87]. As the sperm cells move closer to the egg, the spermatozoa ORs become activated by some chemoattractant originating from the ovary, FF, and the female reproductive tract [88, 89]. Thus, guiding sperm cells towards the egg because a larger proportion of the sperm cells become non-responsive to chemoattractant after capacitation and unable to reach the egg [83, 90]. The odorants, in the form of chemoattractants in the FF, binds to the ORs in the sperm cell to activate the G-protein-coupled receptors, thereby initiating signal transduction via adenylyl cyclase-III. This signaling pathway increases intracellular calcium ions by opening the cyclic-nucleotide-gated channel with a resultant increase in motility [91].

Molecular mechanisms of chemotaxis behavior in the spermatozoa

The process of chemotaxis has been identified as an important molecular event necessary for successful fertilization requiring adequate activation of the ORs and compelling attraction to their ligands. The detailed molecular mechanism underlying sperm chemotaxis is still an active area of research but previous experimental evidence over the years have reported significant results

that assist our understanding of this mechanism. The event is highlighted below.

In humans, the major ORs that mediate chemotaxis is OR17-4 (also called OR1D2) and its ligand has been reported to be a sperm chemoattractant. This receptor is localized on the flagellum and is structurally similar to those receptors found in the olfactory epithelium of the nose that plays a vital role in detecting smell [48, 92]. Activation of ORs, a G-protein-coupled receptors found on the flagellum by the binding of appropriate chemoattractant, causes the activation of guanylyl-cyclase in the mid-piece region [93, 94]. This results in a rapid and transient increase in cyclic guanosine monophosphate (cGMP) and increases cyclic adenosine monophosphate (cAMP) due to the activation of adenylyl-cyclase enzyme isoform on the flagella membrane. The increased cAMP opens the major Ca^{2+} -channel (CatSper) that caused an increased influx of calcium ion (Ca^{2+}) into the cell spreading from the mid-piece to the sperm head as shown in Fig. 4a and b [96, 97]. The increased Ca^{2+} ions stimulate a cascade of the event involved in contraction. In this regard, Ca^{2+} ions initiate axoneme (basic and structural unit of the flagellar) beats by promoting the sliding of the dynein (in the outer arm of the axoneme) with microtubules in the flagellum and subsequent symmetrical beating of the flagellum [85, 98]. The motor activity of the sperm flagellar eventually results in an increased flagellar beat that enables the sperm to swim towards the egg.

Resact (ligand) may include hormones, ions, metabolites, or small biomolecules from the female tract. Binding of ligands to its membrane receptor activates GC (guanylyl cyclase), which increased the production of cGMP (cyclic guanosine monophosphate) as well as soluble adenylyl cyclase (SACY) that increases cAMP (cyclic adenosine monophosphate). cGMP activates the K^+ selective-CNG (cyclic nucleotide-gated channel), causing hyperpolarization. The membrane hyperpolarization activates the HCN channel (hyperpolarization and cyclic nucleotide gate) and sperm-specific Na^+/H^+ exchanger (sNHE) that promotes depolarization and increases the intracellular pH, respectively. These two signals activate the major Ca^{2+} channel CatSper that mediates Ca^{2+} entry that enhances motility. However, Ca^{2+} efflux via NCKX ($\text{Na}^+/\text{Ca}^{2+}/\text{K}^+$ exchanger) and PMCA (plasma membrane Ca^{2+} ATPase), as well as hydrolysis of cGMP by PDE (phosphodiesterase), reduces motility. The increased intracellular Ca^{2+} promotes tyrosine phosphorylation in the flagellum and asymmetrical beat of the flagellum that enables the sperm to swim.

In addition, the presence of other ORs in the spermatozoa and their activation by binding to respective ligands (e.g., majorly ANP, progesterone in the FF) activates guanylyl-cyclase, suggesting that the

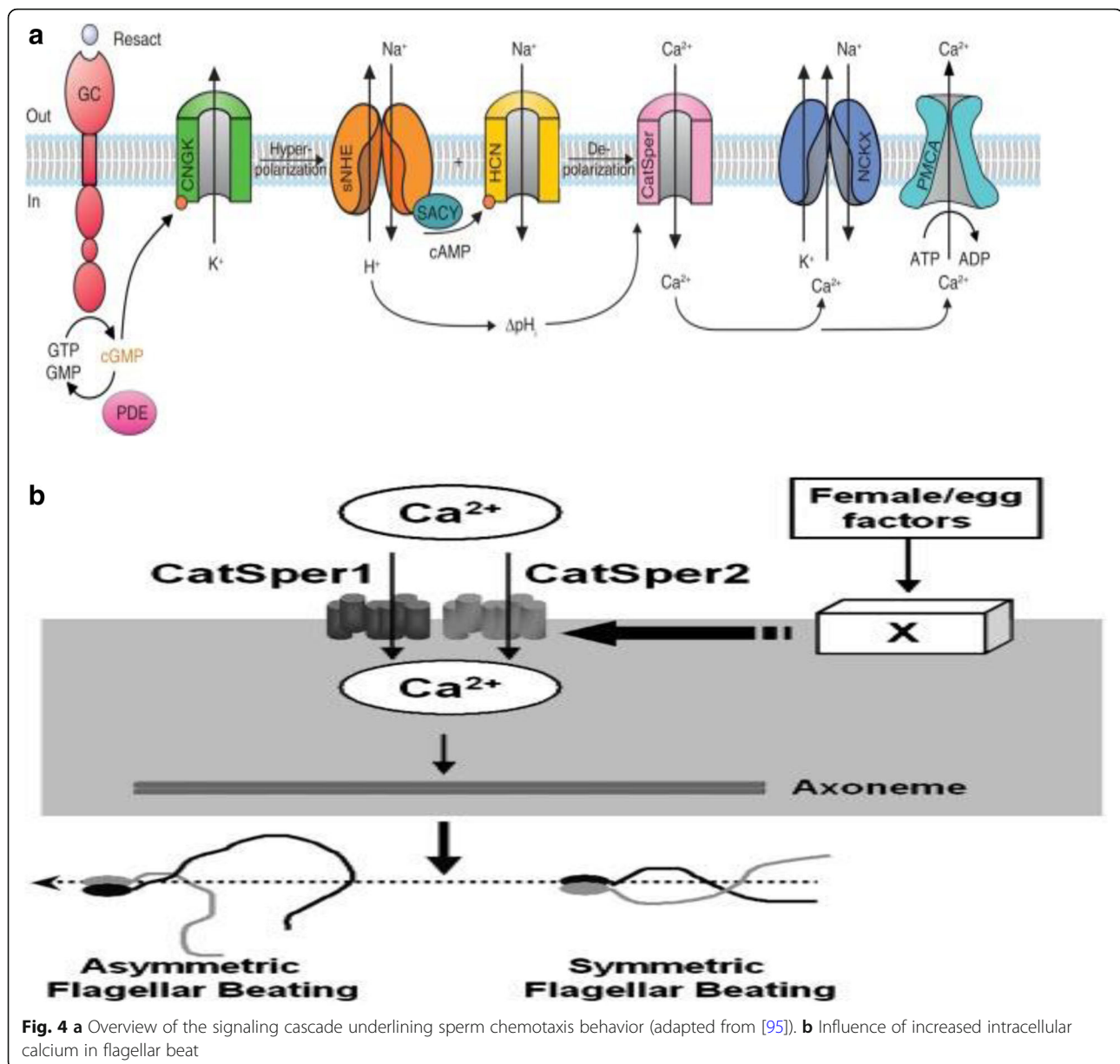
spermatozoa are endowed with numerous molecular pathways of signal transduction that complement or are stimulated differently to mediate chemotaxis in sperm cells ensuring that they cell reach the egg. In vivo experiment using sea urchins has reported that the concentration gradient of progesterone with even lower amount can lead to increase Ca^{2+} in sperm cell with increase oscillatory spikes of the flagellum [99]. This supports the evidence that progesterone is a chemoattractant that could activate the progesterone receptor localized on the head of sperm like OR17-4. In humans, other molecular activities associated with progesterone gradient include active depolarization of cell membrane and increase concentration of cAMP, as well as activation of other cellular signals involved in sperm physiology such as capacitation [100, 101]. Likewise, chemotactic response to ANP by the sperm cell has been correlated with increase guanylyl-cyclase [102].

Olfactory receptors linked with infertility and reproductive dysfunctions: potential utility as biomarkers

Studies by Ottaviano et al. [103, 104] have revealed the importance of olfactory receptor 17-4 in sperm behavior and their specific role in idiopathic infertility. Some other olfactory receptors are also involved in specific functions underlying sperm maturation and transport from the basal membrane to the seminiferous tubular lumen in which reduced expression has linked them to male infertility in azoospermic patients with spermatocyte developmental arrest. There is a need for further study to elucidate biomarkers or genetic pathways involved in this process and the physiological importance of these ORs in the male reproductive organ. Though it has been suggested that the availability of these receptors on sperm might improve acrosome activity and motility, while their localization in the testis and epididymis might suggest specific physiological functions such as in maturation and migration. Other studies have implicated the increased expression of ORs like OR51E1 and OR51E2 activation in prostate tissue, particularly in prostate cancer, suggesting their involvement in the pathogenesis and progression of prostate cancer. In breast and cervical cancer, OR1A2 and OR2A4 have been demonstrated to contribute to cytokinesis [91]. Therefore, both receptors can be promising targets for therapeutic approaches to drug development as cancer [105].

Conclusion

In conclusion, we have demonstrated so far in this review that fertilization as an important process involves ovarian odorant-like biomolecules in enhancing or stimulating chemotaxis and thermotaxis behavior of sperm towards the ovary. These processes include the



activation of olfactory receptors on the sperm to increased beat asymmetry plus flagellar bend amplitude, frequently changing direction and velocity of sperm cell at the time and site of the fertilization process. There is the localization of seven different OR proteins in diverse sections of human sperm. Ligands for these ORs expressed on the spermatozoa activate intracellular Ca²⁺ signals involving the midpiece, head, and flagellum-sensitive Ca²⁺-channels. This volatile molecule also activates the G-protein-coupled receptors found on the flagellum by the binding of appropriate chemoattractant, causing the activation of guanylyl-cyclase in the mid-piece region. The vital role of these odorant molecules in sperm chemoattraction has been discovered to play a

significant role in male and female fertility and contraception. In human sperm, progesterone stimulates a Ca²⁺ increase by a non-genomic mechanism. The Ca²⁺ signal has been suggested to control chemotaxis, thermotaxis, hyperactivation, plus capacitation of sperm. In the future, drugs and molecules can be designed to activate these receptors on sperm to facilitate fertility among infertile couples and use as contraceptives and in the treatment of different reproductive dysfunctions.

Abbreviations

RANTES: Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; ANP: Atrial natriuretic peptide; PGAP1: Post-GPI attachment to proteins 1; PDILT: Protein disulfide isomerase like, testis expressed; UTJ: Utero-tubal junction; IgG: Immunoglobulins G;

IgM: Immunoglobulins M; IgA: Immunoglobulins A; MHC: Major histocompatibility complex; TLRs: Toll-like receptors; ROS: Reactive oxygen species; DNA: Deoxyribonucleic acid; FF: Follicular fluid; GPCRs: G-protein-coupled receptors; cAMP: Cyclic adenosine monophosphate; IP₃: Inositol triphosphate; cGMP: Cyclic guanosine monophosphate; Th1: T helper type 1; Th2: T helper type 2; C3: Complement 3; C4: Complement 4; CICR: Ca²⁺-induced Ca²⁺ release; PGE: Prostaglandin E; PGF: Prostaglandin F; PGF_{1α}: Prostaglandin F_{1α}; ATP: Adenosine triphosphate; HCO₃⁻: Bicarbonate; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma; MIF II: Motility inhibitory factor II; MIP: Motility initiating protein; ORs: Olfactory receptors; IVF: In vitro fertilization

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Authors' contributions

All the authors significantly contributed to the manuscript. OTO and AD contributed to the conceptualization, design of topic, searching of literature, and write up. AD, GEO, BOI, OE, and JBD contributed to the plagiarism check and English language editing. COA and BJO contributed to the review and internal editing. All authors have read and approved the manuscript.

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