Do human eggs attract spermatozoa?

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Summary

A key process in human fertilization is bringing the two gametes together, so that the complex molecular events involved in sperm and egg interaction can begin. Does nature allow fertilization to occur only as a consequence of a chance collision, or is there a precontact sperm-egg communication? This review summarizes the bioassays used in testing human spermatozoa for chemotaxis, emphasizing the necessity to distinguish between chemotaxis and other accumulation-causing processes, and the results obtained. It demonstrates that human sperm chemotaxis to a follicular factor(s) does occur, at least in vitro, and that only capacitated spermatozoa are chemotactically responsive. Substances that have been proposed as attractants for human spermatozoa are reassessed. The potential role of sperm chemotaxis in vivo is discussed. Faulty precontact sperm-egg communication may be one of the causes of male infertility, female infertility, or both. On the other hand, interfering with human sperm chemotaxis may represent an exciting new approach to contraception. *BioEssays* 21:203–210, 1999. © 1999 John Wiley & Sons, Inc.

Introduction

Human spermatozoa travel a tortuous path toward the egg after its deposition in the vagina. Spermatozoa, with an average length of 60 µm, cross through the uterine cervix and cavity (70–80 mm in length), find the opening of the fallopian tube (0.2–0.5 mm in diameter), enter the tube, and, after an additional way of 50–80 mm down the road,(1) find one egg (0.1 mm in diameter; 0.2 mm with the cumulus cells around it) and fertilize it. Is it a ''blind date'' or an oriented migration toward an attractant source, i.e., sperm chemotaxis? It was believed that, in species with internal fertilization, for which very large numbers of spermatozoa ($4–40 \times 10^7$ in humans)(2) are ejaculated directly into the female reproductive tract and a sufficient number may reach the egg coincidentally, there is no apparent need for sperm chemotaxis. However, human spermatozoa are present within the fallopian tubes in numbers that are orders of magnitude less than those inseminated(3–5) (Fig. 1). The total number of human spermatozoa present within both fallopian tubes is ~250 (range, 80–1,400 spermatozoa).(5) This number represents only ~0.004% of the total motile sperm inseminated (1 of every 25,000 spermatozoa!). Although there is no significant difference between the number of spermatozoa found within the ovulatory tube compared with the nonovulatory tube, there is a significant difference between the sperm distribution within the tubes: the ovulatory tubal ampulla, where fertilization occurs, contains a significantly larger percentage of spermatozoa than the ampulla of the contralateral tube.(5) Because the chance of a chaotic successful collision between a spermatozoon and the egg within the tubal ampulla is statistically very low, one of the mechanisms that may bring the two gametes together is sperm chemotaxis.

Sperm chemotaxis is defined as modulation of the direction of travel by a chemical gradient of a stimulus, resulting in approach to an attractant or retreat from a repellent. (Attractants and repellents are collectively called chemotactic stimuli.) Attraction between gametes of the opposite sex by chemotaxis is a common phenomenon in marine metazoa, including sea urchin, coral, algae, and fish.(6–8) In mammals,

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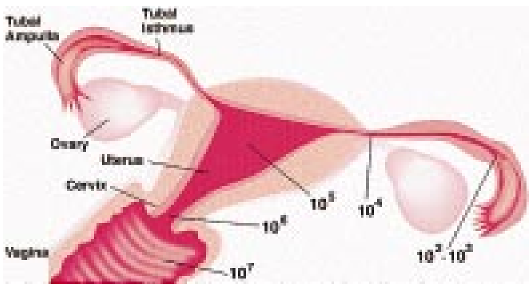

Figure 1. Sperm distribution in woman's genital tract subsequent to insemination. (Based on data reviewed in references 3–5.)

TABLE 1. Assays Used for Determining Human Sperm Chemotaxis

Assay	Distinction between chemotaxis and chemokinesis	Distinction between chemotaxis and trapping	References
A. Sperm accumulation—ascending gradient	−	−	10, 11, 13
B. Sperm accumulation—descending gradient	+	+	13
C. Choice assays	+	−	14–16, 18
D. Track analysis of swimming spermatozoa	+	+	13

the occurrence of sperm chemotaxis was established only in recent years.[8] This review focuses on human sperm chemotaxis and brings forth the state of the art of this field. It describes and assesses bioassays used for testing human sperm chemotaxis, and it reviews and evaluates substances studied as potential attractants. The possible in vivo physiologic significance of this process is discussed, including future clinical implications for diagnosis and treatment of male and female infertility. On the other hand, interference with sperm chemotaxis has a potential to develop into an exiting new modality for contraception.

Bioassays for human sperm chemotaxis

Bioassays used for measuring sperm chemotaxis in humans (for obvious reasons, all of them in vitro assays) may or may not have the ability to distinguish between chemotaxis and other processes that may cause sperm accumulation, e.g., speed enhancement (chemokinesis) or trapping of any kind. Table 1 lists the published assays and indicates whether or not they can make this distinction.

Sperm accumulation—ascending gradient

This technique is a macroscopic assay in which spermatozoa sense an ascending gradient of the attractant and accumulate near or at its source. The principle is that spermatozoa from one reservoir accumulate in another reservoir that contains the attractant. The two reservoirs are connected and the attractant gradient is established by diffusion. A number of variations of this type of assay, which use different apparatuses, have been published: (1) a modification of a technique that was initially developed for studying neutrophil chemotaxis[9] in which the spermatozoa- and attractant-containing wells are separated from each other by a thin (10-μm-thick) polycarbonate membrane;[10] (2) an apparatus in which the spermatozoa- and attractant-containing wells are connected by means of a tube;[11] and (3) a modification of the capillary assay developed by Adler[12] for the study of bacterial chemotaxis, in which a capillary filled with an attractant is immersed in a well containing sperm suspension.[13] The main disadvantage of this kind of assays is that they cannot distinguish between chemotaxis and other causes of sperm accumulation (Table 1).

Sperm accumulation—descending gradient

This technique is an inverted capillary assay. The spermatozoa in the well are suspended in a solution that already contains the presumed attractant, and the capillary contains either a control buffer or the attractant.[13] When the capillary contains just buffer, the spermatozoa sense a descending gradient of the attractant as they move from the well to the capillary. When the attractant is in both the capillary and the well, they sense no gradient at all. This assay, thus, measures the sperm tendency to leave the attractant rather than to accumulate in it. By counting the spermatozoa accumulated in the capillaries in these settings, it is possible to distinguish between chemotaxis, speed enhancement, and trapping.[13] This ability is because only chemotaxis, unlike the chemokinetic and trapping effects, is dependent on the presence of a chemical gradient.

Choice Assays

In this class of assays, spermatozoa choose between two wells (or two chambers), one containing the attractant and the other containing buffer as a control. A number of designs of this sort have been published: a sealed chamber for microscopic measurements,[14] and—for macroscopic measurements—apparatuses with two,[15] three,[16] or five[17,18] wells or chambers, connected with a tube or a groove. Such assays can distinguish between chemotaxis and chemokinesis, but they cannot distinguish between chemotaxis and trapping.

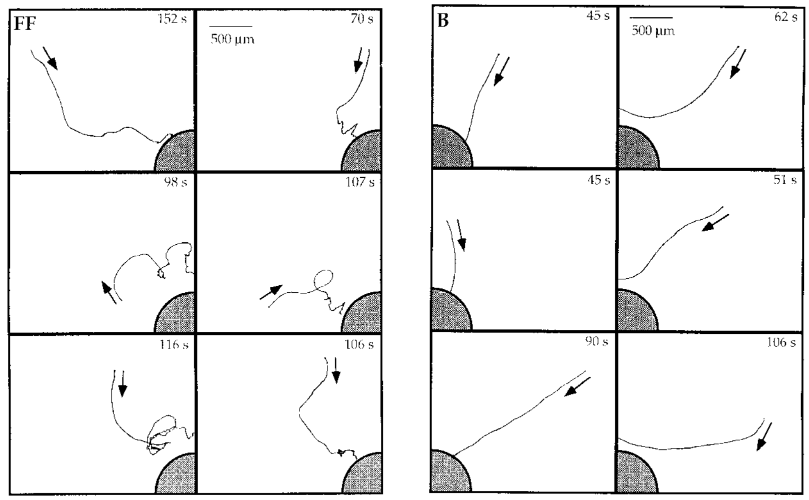

Figure 2. Representative tracks of spermatozoa in a choice assay (by using a sealed chamber) toward a well containing a 10-fold diluted chemotactically active fraction of follicular fluid (FF) and a control well containing buffer (B). The duration of each track is indicated at the top right corner of each panel. The arrows indicate the direction of progression of each trajectory.

Track analysis of swimming spermatozoa

Chemotaxis, unlike chemokinesis and trapping, involves typical directional changes of the spermatozoa toward the source of the attractant (Fig. 2). Therefore, an essential assay to distinguish between chemotaxis and other processes that may cause sperm accumulation is to study the tracks made by the spermatozoa in a gradient of the attractant. This tracking is done by tracing video-recorded tracks either manually or by a computerized motion analysis system.(13)

To conclude, not every assay used for measuring sperm chemotaxis can actually distinguish chemotaxis from other causes of sperm accumulation (Table 1). This conclusion should be taken into account when evaluating results of studies of human sperm chemotaxis.

Sperm chemotaxis in humans

Human sperm chemotaxis has been reported to occur, or not to occur, to a number of chemicals:

Chemotaxis to follicular fluid

The first implication that human spermatozoa might be attracted to female-originated stimuli came from a study published over 40 years ago.(19) In that study, ovarian cyst fluids, the outer liquid of egg white, and a single follicular fluid caused, among other effects, sperm accumulation. These early observations were no more than suggestive, because of the very small number of determinations carried out with each fluid and because no controls for other accumulation-causing processes were performed.

Follicular fluid contains secretions of the egg and its surrounding cells and it is available from women undergoing in vitro fertilization (IVF) treatment. This fluid is thought to provide the oocyte with an environment favorable for fertilization and to stimulate sperm processes required for reaching and penetrating the egg.(20) Therefore, many of the subsequent studies in humans (the next one performed 26 years after the first study) used follicular fluid. It should be noted, however, that follicular fluid per se may have no physiologic role after ovulation because, in mammals, only small quantities of this fluid are transported into the fallopian tube.(21)

Although the large majority of the studies of human sperm chemotaxis concluded that chemotaxis to follicular fluid occurs (Table 2), different groups had sometimes different results. It would be helpful to indicate already at this stage that one of the main reasons for the differences is the use of nondiluted follicular fluids in some studies. This could lead to both false-negative and false-positive results.(22) False-negative results may be obtained when the concentration of the attractant in the chemotaxis assay is too high; in such a concentration, the attractant saturates the chemotaxis receptors on the sperm surface and prevents them from sensing the gradient. False-positive results may be obtained because less than 10-fold diluted follicular fluids (or even human or bovine serum) may cause nonspecific sperm accumulation.(13,23) For example, Arnal et al. (Table 2) used nondiluted or 1:1 diluted follicular fluid and found that higher number of spermatozoa accumulate in follicular fluid than in a control buffer. However, this finding was not used as evidence for chemotaxis because they found that, under the conditions of the experiment, the spermatozoa within the follicular fluid lost their motility, suggesting that trapping by motility loss was a dominant factor in that study.(24,25)

More recent studies that used accumulation assays with all the variations listed above [in Table 2—the studies of Ralt et al. (a & b), Villanueva-Díaz et al. (b), and Cohen-Dayag et al.] found, without exception, sperm accumulation in follicular

TABLE 2. Human Sperm Chemotaxis to Follicular Fluid

Study[a]	Assay type[b]	≥10-fold dilution of FF[c]	Apparent chemotaxis observed	Comments
Schwartz et al.[19]	C	+	+	Only one follicular fluid was tested
Arnal et al.[24,25]	A	−	+?	The accumulation was apparently trapping caused by motility loss
Villanueva-Díaz et al. (a)[17]	C	−	+	The assay was carried out under agarose. Such assays are strongly dependent on the agarose manipulation[23]
Ralt et al. (a)[26]	A	+	+	
Makler et al.[14,54]	C	−	−	
Villanueva-Díaz et al. (b)[15]	A	−	+	
Ralt et al. (b)[13]	A B C D	+	+	
Cohen-Dayag et al.[11]	A	+	+	

[a]Chronological order.
[b]According to Table 1.
[c]Plus and minus signs indicate that the follicular fluid (FF) was or was not, respectively, ≥10-fold diluted for the assay.

fluid.[11,13,15,26] Regretfully, not all of them used diluted follicular fluid (Table 2), and not all of them distinguished, by different assays, between chemotaxis and other accumulation-causing processes. One of these studies [in Table 2—the study of Ralt et al. (a)] further revealed that not all the follicular fluids are active in causing sperm accumulation and that all the active ones are from follicles whose eggs can be fertilized.[26] Two other studies that used choice assays [in Table 2—the studies of Villanueva-Díaz et al. (a) and Makler et al.] reached conflicting results, possibly because of using nondiluted follicular fluids. The only thorough study that used all the assays listed in Table 1 [in Table 2—the study of Ralt et al. (b)] obtained consistent results in all of the assays and clearly demonstrated chemotaxis of human spermatozoa to follicular fluid: spermatozoa accumulated in capillaries containing 10^3- to 10^4-fold diluted follicular fluid, they sensed a descending gradient of follicular fluid and avoided moving down the gradient, and they moved toward a follicular fluid-containing well (but not toward a control well) with directional changes of their swimming path, typical of chemotaxis (Fig. 2). The chemotactic response was accompanied by chemokinesis.[13]

It was further demonstrated that, in a given sperm population, there are chemotactic and nonchemotactic spermatozoa, and that the fraction of chemotactic spermatozoa in the total sperm population is 2% to 12%.[11] This small fraction of responsive spermatozoa was probably another reason for the lack of response found in the studies of Makler et al. (Table 2). Most interestingly, the chemotactic responsiveness was demonstrated to be temporary, and the identity of the responsive spermatozoa was found to change with time, resulting in a continuous process of replacement of chemotactic spermatozoa within a sperm population.[11] Finally, it was demonstrated that only capacitated spermatozoa, i.e., spermatozoa that possess the potential to undergo the acrosome reaction (a release of proteolytic enzymes enabling sperm penetration through the egg coat) and to fertilize the egg,[27] are chemotactic.[28] (See reference 29 for a review of how capacitated spermatozoa are measured.) The significance of this finding is discussed below.

It, thus, is clear that human capacitated spermatozoa (unlike noncapacitated spermatozoa) are chemotactically responsive, and they are attracted to follicular fluids retrieved from follicles whose eggs can be fertilized.

Possible attractants in follicular fluid

The identity of the attractant(s) in follicular fluid is not known. An active fraction of follicular fluid which contains the attractant(s)—probably heat-stable peptide(s)[30]—has been identified.[13] On the other hand, other constituents of follicular fluid, listed in Table 3, have been examined for being attractants:

Progesterone. Villanueva-Díaz et al.[31] demonstrated in a choice assay that progesterone causes human sperm accumulation, that preincubation of spermatozoa with a progesterone receptor antagonist eliminates the accumulation, that dialysis of follicular fluid causes loss of this activity, that a lipid extract of follicular fluid causes sperm accumulation as does crude follicular fluid, and that heat or trypsin treatment does not affect the accumulation in follicular fluid. On the basis of these observations, they suggested that progesterone is the attractant in follicular fluid. However, this suggestion appeared to be in conflict with earlier results, demonstrating lack of correlation between sperm accumulation in follicular fluid and the level of progesterone in the fluid,[26] as well as lack of correlation between the characteristics of the active fractions of follicular fluid and those of progesterone.[30] Recently, Jaiswal et al.[16] apparently resolved the conflict by demonstrating that progesterone indeed causes sperm accumulation, but that this accumulation

TABLE 3. Additional Substances Examined as Attractants

Substance examined	Assay type[a]	Apparent attraction observed	Comments
Progesterone[16,31]	C	+	The observed accumulation was apparently the consequence of trapping by hyperactivation[16]
Progesterone[16]	D	−	
ANP[43,44]	A B C	+	
Heparin[18]	C	+	A distinction between chemotaxis and trapping was not made
Synthetic *N* formylated peptides[10]	A	+	No distinction was made between chemotaxis and other processes
Synthetic *N* formylated peptides[14]	C	−	

[a]According to Table 1.

is caused primarily by physiologic trapping, not by chemotaxis. Chemotaxis was eliminated by track analysis and finding that most of the spermatozoa present near the progesterone-containing well apparently reached there by coincidence, not by changing their swimming path toward the well. Physiologic trapping was apparently caused by acquiring motility patterns resembling hyperactivation (e.g., wide amplitude and marked lateral displacement of the head).[32,33] Progesterone is well known to cause sperm hyperactivation.[34–36] Accordingly, Jaiswal et al. found that, upon approaching a progesterone-containing well, about half of the spermatozoa acquired hyperactivation-like motility.[16] Because one of the characteristics of hyperactivation is very small progressive motility despite the vigorous motion,[37] the hyperactivated spermatozoa remained in the vicinity of the well. In this manner, some of the spermatozoa that happened to reach the vicinity of the progesterone-containing well by coincidence were essentially trapped there. Further evidence that progesterone is at least not the major attractant in follicular fluid was provided by demonstrating that removal of progesterone from follicular fluid does not eliminate the chemotactic activity of the fluid (but does eliminate its hyperactivation-causing activity).[16]

Atrial natriuretic peptide. Atrial natriuretic peptide (ANP) is a polypeptide hormone that is synthesized, stored, and secreted from a variety of cell types in mammals. It is secreted in large quantities by the atrial portion of the heart. It exerts many of its actions by means of activation of particulate guanylate cyclase.[38,39] ANP is present in human follicular fluids[40,41] and specific ANP receptors have been identified on human spermatozoa.[42] As shown in Table 3, sperm chemotaxis to ANP was demonstrated by sperm accumulation in capillaries with ascending[43] and descending[44] gradients and by choice assays.[44] Furthermore, the chemotaxis process was accompanied by chemokinesis,[44] as had been found earlier for follicular fluid.[13] Nevertheless, ANP does not seem to be the attractant in follicular fluid. This is because, at physiologic concentrations, chemotaxis to ANP can be observed only in the presence of neutral endopeptidase inhibitor such as phosphoramidon, which is probably absent in vivo,[44] and because no correlation was found between the chemotactic activities of follicular fluids and their ANP content.[43] It, therefore, was proposed that ANP may directly affect guanylate cyclase in vitro in a manner similar to that caused by the physiologic attractant in vivo.[44]

Heparin. The fact that heparin is one of the constituents of follicular fluid, at least in mice,[45] prompted a study of its potential as an attractant.[18] Human spermatozoa were found to accumulate in heparin (Table 3). However, because only a single assay was used—a choice assay that does not distinguish between chemotaxis and trapping—and because heparin can induce capacitation (at least in bull spermatozoa)[46] and acrosome reaction,[47] it is possible that heparin, like progesterone, induces hyperactivation and, thereby, trapping.

Other substances examined for being chemotactic stimuli

Small synthetic *N*-formylated peptides such as *N*-formyl-Met-Leu-Phe (fMLP) are attractants for neutrophils and macrophages.[48] Such peptides were reported to bind to specific sites on human spermatozoa[49,50] and—by using the accumulation assay with an ascending gradient through a filter—to be attractants.[10] However, studies that used the choice assay did not confirm human sperm chemotaxis.[14] For comparison, bull spermatozoa were initially reported to be attracted to synthetic peptides,[51,52] but later the ''attraction'' was demonstrated to be trapping.[53] This finding demonstrates how important it is to carry out assays that distinguish chemotaxis from other accumulation-causing processes (Table 1). Furthermore, the physiologic significance of sperm chemotaxis to these peptides, if it occurred, is not at all clear, because such peptides are derived from bacteria.[48] Had chemotaxis to these peptides had any physiologic role, it would more likely be in pathologic states, not in normal fertilization.

By using the choice assay, Makler et al.[54] studied a number of substances for being chemotactic stimuli for human spermatozoa. They examined cervical mucus, wash fluid from the uterus, supernatant of follicular fluid, a suspension of cumulus cells, and human ova as potential attractants. They also examined hydrochloride acid, sodium hydroxide, ethanol, and glutaraldehyde as potential repellents. They did not find any sperm response to these substances.[54] However, these results should be taken with great caution. Because the fraction of capacitated/chemotactically responsive spermatozoa in a sperm population is usually very low and varies from sample to sample, sometimes chemotaxis can hardly be detected. Therefore, it is essential to carry out, for each sperm sample, a positive control with a known attractant or, at least, to determine the level of capacitated cells in the sample and make sure that it is sufficiently high. Regretfully, such controls have not been carried out by Makler et al. Furthermore, chemotaxis is a process that has a bell-shaped dependence on the attractant concentration.[12,13] Therefore, no response may be observed at high attractant concentrations. No attention has apparently been paid to this fact by Makler et al.[54]

Physiologic significance

The remarkable correlation found in humans between the chemotactic activity of a follicular fluid and the ability of the egg from the same follicle to become fertilized[26] strongly suggests that sperm chemotaxis may have an important role in humans in vivo. What is this role? Unlike the case of species with external fertilization in which most, if not the whole, of the sperm population is chemotactically responsive,[6,7,55] in humans only a small fraction of the sperm population (2% to 12%) is chemotactically responsive at any given time.[11] The identity of the responsive spermatozoa in humans changes with time: chemotactic spermatozoa lose their activity, whereas others acquire it.[11] This finding raised the possibility that spermatozoa are selectively chemotactic only at a certain physiologic stage. The capacitated stage, i.e., the stage at which spermatozoa possess the potential to undergo the acrosome reaction (a release of proteolytic enzymes enabling sperm penetration through the egg coat) and to fertilize the egg,[27] seemed a reasonable possibility.[23]

The sperm capacitated state in humans is transient with a life span of 50–240 minutes (at least in vitro), and there is a continuous process of replacement of capacitated spermatozoa within a sperm population.[28] Spermatozoa acquire their chemotactic responsiveness as part of the capacitation process and lose this responsiveness when the capacitated state is terminated. This conclusion is based on the following observations: (1) The percentage of capacitated cells in the total sperm population (2% to 14%) is similar to the percentage of chemotactic spermatozoa (2% to 12%). (2) A subpopulation enriched with chemotactic spermatozoa is also enriched with capacitated spermatozoa, and vice versa, a subpopulation depleted of chemotactic spermatozoa is depleted of capacitated spermatozoa. (3) Chemotactic responsiveness of a total sperm population is lost upon intentional depletion of capacitated spermatozoa; such responsiveness is regained after further incubation under capacitating conditions. (4) Both the capacitated state and the chemotactic responsiveness are temporary, appear only once in the sperm lifetime, and there is synchrony between them.[28] In other words, the linkage between capacitation and chemotaxis relies on the similar percentages, kinetics, and continuous replacement of capacitated and chemotactic spermatozoa in a sperm population, and on the fact that deliberate depletion of capacitated spermatozoa results in total loss of chemotaxis and, vice versa, depletion of chemotactic spermatozoa results in depletion of capacitated spermatozoa.

The observations which suggest that only capacitated spermatozoa respond chemotactically to an attractant secreted from the egg or its surrounding cells, suggest that, in vivo, the role of human sperm chemotaxis is not to direct as many spermatozoa as possible to the egg, but rather to recruit a selective population of spermatozoa, i.e., capacitated spermatozoa, for fertilizing the egg. The role of the observed continuous replacement of capacitated spermatozoa is possibly to ensure availability of capacitated spermatozoa for an extended period of time, despite the short life span of the capacitated state.

The timing and location of sperm chemotaxis in vivo is not known. As shown in Figure 3, it is known that, at least in mammals other than humans, a considerable fraction of the spermatozoa ejaculated into the female reproductive tract are retained with reduced motility in storage sites (usually the oviductal isthmus); when ovulation occurs, some of them resume high motility and travel the distance between the storage and fertilization sites within minutes (see references 4, 56, 57 for reviews). Because these spermatozoa appear to be capacitated,[58,59] one possibility is that the role of sperm chemotaxis is to bring the spermatozoa, released from the storage site, to the egg. In view of the relatively small number of spermatozoa released from the storage site (Fig. 2), chemotaxis may be required to increase the prospects that an egg will meet capacitated spermatozoa as soon as it ovulates. However, the observation that a dye injected into the lowermost region of the oviductal isthmus of pigs or hamsters is rapidly transported to the upper ampulla shortly before, during, and within a few hours after ovulation[60,61] makes this possibility less likely. If the same holds true for humans, it seems that a gradient of an attractant cannot be established over long distances in the fallopian tube, suggesting that the range of sperm attraction to the egg and, thereby, sperm selection may be relatively short (Fig. 3). It is possible, however, that the cumulus oophorus surrounding the egg provides viscoelastic milieu that resists the stirring action of the contractions and of the oviductal cilia.[11]

On the basis of the finding that, in mammals, the few first spermatozoa that enter the cumulus find the egg very effectively,[62] another possibility for the location of sperm chemotaxis is the cumulus. However, if the finding—that the cumulus oophorus secretes a substance that alters the pattern of sperm movement[63]—holds true also in humans and represents a chemotactic response, then the chemotaxis process should occur before the cumulus. Also, the finding

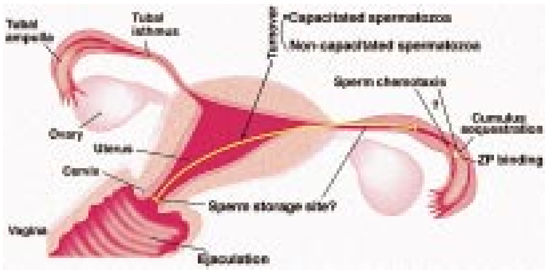

Figure 3. A proposed sequence of events in the mammalian female genital tract. The yellow curved bar indicates the region in which turnover of capacitated spermatozoa may occur. The dimensions of the egg and the cumulus oophorus surrounding it (together seen as a yellow circle in the ampulla) are exaggerated to make the egg-cumulus visible. ZP, zona pellucida.

that only capacitated spermatozoa can penetrate the cumulus oophorus,[64] makes the possibility of chemotaxis within the cumulus less likely. It is also possible that the cumulus cells are not homogeneous and that those closer to the egg are the ones that secrete the attractant. Such a situation, if correct, can form an attractant gradient within the cumulus even if the egg is not the organelle that secretes the attractant. Yet another possibility is that there are two sequential steps of chemotaxis, each to a different attractant.[65] Determination of the cellular origin of the attractant(s) for human spermatozoa may distinguish between some of these open possibilities.

In view of the notion that chemotaxis is required for the selection of ripe spermatozoa, faulty precontact sperm-egg communication may be one of the causes of male infertility, female infertility, or both. It is reasonable that, in the future, chemotaxis may be exploited as a diagnostic tool for sperm quality and male infertility and may be used as a biological sperm-selection procedure before IVF, especially before IVF with micromanipulation (intracytoplasmic single sperm insertion) or for intrauterine insemination. Moreover, the chemotactic activity of a follicular fluid may be an effective way to monitor the possible effect of different ovulation induction protocols on the maturational status of oocytes aspirated for IVF.[66] On the other hand, this may represent an exciting new approach to contraception.

Conclusions

Human sperm chemotaxis to follicular fluid has been well established in vitro. It seems that, in vivo, the role of sperm chemotaxis in humans is not to direct as many spermatozoa as possible to the egg but rather to recruit capacitated spermatozoa, constituting only 2% to 14% of the sperm population at any given moment, for fertilizing the egg. The observed turnover of capacitated/chemotactically responsive spermatozoa may ensure the availability of ripe spermatozoa for an extended period of time. We have proposed a sequence of events, preceding fertilization, in which sperm chemotaxis may serve as a key process in bringing the two human gametes together.

Future experiments should reveal the identity and the physiologic origin of the attractant(s) secreted by the egg or its surrounding cells, and the identity of their respective receptors on the sperm. Advanced techniques such as optical[67] and electrical[68] trapping may allow the investigation of individual spermatozoa. This, in turn, will assist in trying to determine the chemotactic/capacitated state of a spermatozoon and to explore the mechanism of human sperm chemotaxis.

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