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Review

Tales From the Tail: What Do We Really Know About Sperm Motility?

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Male factor infertility is a significant problem in humans and domestic animals (Lunenfeld and Insler, 1993). In humans, it is estimated that 20% of couples are infertile and that, in 50% of these cases, the infertility can be attributed, at least in part, to the male partner (World Health Organization, 1990). Similarly, in animals, it is likely that infertility in the male is at least as common as in the female. Economic losses due to reproductive inefficiency in male animals can be substantial, particularly when infertility affects a genetically superior individual (Roberts, 1986). Although some instances of male factor infertility can be explained by readily identifiable pathologies of the reproductive tract or deficiencies in reproductive hormones, many others remain idiopathic. Common problems in subfertile and infertile human and animal patients include low sperm numbers, low numbers of morphologically normal sperm, and low numbers of motile sperm (Linford et al, 1976; Boyle et al, 1992; Pickett, 1992; Wallace, 1992). Although the correlations between sperm numbers and fertility as well as sperm morphology and fertility are not always strong, it is generally accepted that immotile or poorly motile sperm are incapable of fertilization without extensive laboratory assistance.

Yet in spite of the importance of sperm motility to reproduction, reduced sperm motility remains only a clinical sign of infertility, and we actually understand very little about the signaling pathways and molecular mechanisms that control the assembly and function of the normal mammalian sperm flagellum. Modern assisted reproductive techniques such as intracytoplasmic sperm injection (ICSI) now allow us to minimize and even bypass the requirement for sperm motility in male fertility. However, the success of these techniques only increases our need to better understand the genes and proteins that are not functioning normally in these subfertile populations of sperm. Without this knowledge, we may inadvertently pass on genetic defects to future generations. A more complete understanding of the molecular processes that go into the creation of a motile sperm will enable us to address the issue of reduced motility and associated subfertility more effectively in the clinic. Eventually, poor sperm motility might be able to be treated or even cured through

genetic therapy rather than simply being bypassed by ICSI. Viewed from a different angle, knowledge of the molecules that are required to assemble a functional flagellum may allow us to eventually intentionally disrupt the normal function of crucial, sperm-specific proteins, which could result in the development of a safe, effective male contraceptive. The purpose of the present article is to review the current understanding of the molecular mechanisms that contribute to normal mammalian flagellar function and sperm motility. Much of the information summarized here was gained through the study of model systems, including mice, rats, hamsters, and other species. However, the ultrastructure of mammalian sperm is highly conserved, and it is likely that many of the genes, proteins, and protein functions identified in laboratory animal species also are conserved in humans and domestic animals. Nonetheless, this may not always be the case, and I have attempted to point out those incidences in which functionally relevant species differences have been identified.

Activated and Hyperactivated Sperm Motility

Most mammalian sperm display two types of physiological motility: activated motility, as is seen in freshly ejaculated sperm, and hyperactivated motility, as is seen in most sperm recovered from the site of fertilization (Katz and Yanagimachi, 1980; Suarez and Osman, 1987). The flagellum of an activated sperm generates a symmetrical, lower amplitude waveform that drives the sperm in a relatively straight line. In contrast, once sperm from most species become hyperactivated, the flagellar beat becomes asymmetrical and higher amplitude, which results in circular or figure-eight trajectories (Yanagimachi, 1970, 1994; Ishijima et al, 2002). Current evidence suggests that the role of activated motility is to aid in propelling the sperm through the female reproductive tract to the oviduct, whereas the role of hyperactivated motility is to help sperm detach from the oviductal epithelium, reach the site of fertilization, and penetrate the cumulus and zona pellucida of the oocyte (Suarez et al, 1991; Stauss et al, 1995; Ho and Suarez, 2001).

There is good evidence that both activated and hyperactivated motility are important for normal fertility. In the case of activated motility, immotile sperm generally are unable to reach the uterotubal junction. This has been clearly demonstrated in rats (Gaddum-Rosse, 1981). Additionally, in a number of species, including humans, there is strong clinical evidence suggesting that decreases in activated sperm motility decrease male fertility. Hyperactivated motility has been shown to enhance the ability of a sperm to reach the site of fertilization and to penetrate the egg vestments. In rodents, and probably in other species as well, hyperactivated motility is also correlated with the ability of a sperm to fertilize an oocyte in vitro (Fraser and Quinn, 1981; Boatman and Robbins, 1991). The majority of the present review will discuss the molecular mechanisms involved with the regulation of activated sperm motility (also referred to as "sperm motility" or "motility"). Items that are specifically relevant to hyperactivated sperm motility will be pointed out throughout the text.

Ultrastructure of the Sperm Flagellum

One of the earlier approaches to studying the mechanisms involved in sperm motility was to study the ultrastructure of the sperm tail. As a result, although our understanding of the molecular components of the sperm flagellum is incomplete, the flagellar ultrastructure has been well characterized and provides a starting point from which to study the function of the individual protein components of the tail.

The ultrastructure of the mammalian flagellum is highly conserved and is composed of a number of cytoskeletal elements whose proper assembly is critical for sperm motility. The flagellum is structurally divided into four major parts: the connecting piece, the midpiece, the principal piece, and the end piece (Figure 1; Fawcett, 1975). The connecting piece is the portion of the flagellum

that attaches to the implantation fossa of the nucleus in the sperm head. From the remnant of the centriole at this point, the axoneme extends throughout the length of the flagellum. The axoneme is a cytoskeletal structure composed of a ring of 9 microtubule doublets surrounding a central pair. Inner and outer dynein arms project from each of the outer 9 doublets, and these arms are responsible for generating the motive force of the flagellum. Additionally, 9 radial spokes, each of which originates from 1 of the 9 outer microtubular doublet pairs, project inward toward the central pair in a helical fashion. The midpiece also begins at the connecting piece and is characterized by the presence of 9 outer dense fibers (ODFs) that lie outside each of the 9 outer axonemal microtubule doublets and by a sheath of mitochondria that encloses the ODFs and the axoneme. The midpiece terminates about one-fourth of the way down the sperm flagellum at the annulus, which marks the beginning of the principal piece.

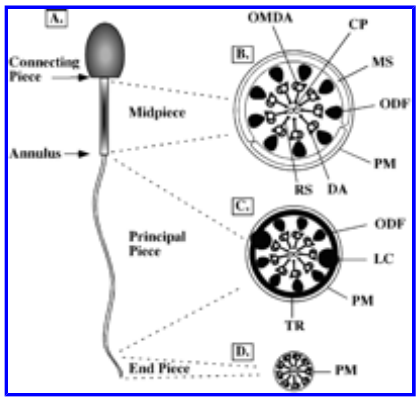

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Figure 1. Schematic representation of a mammalian sperm and the ultrastructure of the flagellum. **(A)** Mammalian sperm flagella are structurally divided into 4 areas: the connecting piece, midpiece, principal piece, and end piece. The end of the midpiece and start of the principal piece are demarcated by the annulus. **(B)** Schematic cross-section through a representative segment of the midpiece showing the plasma membrane (PM) and mitochondrial sheath (MS) surrounding the 9 outer dense fibers (ODFs). Within the ODFs are the components of the axoneme: the 9 outer microtubule doublets of the axoneme (OMDA) with associated dynein arms (DA) and radial spokes (RS) and the central pair of microtubule doublets (CP). In an actual sperm, several projections are present on the CP. These are not shown in this figure. **(C)** Schematic cross-section through a representative segment of the principal piece showing the PM surrounding 7 ODFs. ODFs 3 and 8 have been replaced by the two longitudinal columns of the fibrous sheath (LC). The two columns are connected by transverse ribs (TR). The axonemal components are unchanged. **(D)** Schematic cross-section through a representative segment of the end piece. The ODFs and FS tapered at the termination of the principal piece and are no longer present in the end piece, thus leaving only the PM to surround the axoneme.

At this point, the mitochondrial sheath (MS) ends and the ODFs associated with outer axonemal doublets 3 and 8 are replaced by the 2 longitudinal columns of the fibrous sheath (FS). The columns of the FS run the length of the principal piece and are stabilized by circumferential ribs. The presence of the FS and of only 7 (rather than 9) ODFs surrounding the axoneme define the principal piece. The principal piece makes up approximately two-thirds of the length of the flagellum. Near the distal end of the principal piece, the FS and the ODFs taper and then terminate. The short remaining region of the flagellum, which contains only the axoneme surrounded by the plasma membrane, is the end piece.

The presence and structure of the axoneme are highly conserved in all ciliated and flagellated eukaryotic cells. However, only mammalian sperm flagella contain all three additional accessory structures: the MS, ODFs, and FS.

The Axoneme is the Flagellar Motor

Eukaryotic axonemal assembly and function has been studied most extensively in the unicellular green algae *Chlamydomonas reinhardtii.* In this species, more than 200 axonemal and axoneme-associated proteins have been identified. Out of these 200 proteins, more than 25 loci have been identified by

mutations that affect the assembly of the axoneme, and more than 52 loci have been identified by mutations that result in altered motility (Luck et al, 1977; Dutcher, 1995). These mutations involve structural, motor, targeting, and stabilizing proteins, to name a few (Luck et al, 1977; Dutcher, 1995; Yagi and Kamiya, 1995; Piperno et al, 1996; Smith and Lefebvre, 1996).

In mammals, as in *Chlamydomonas,* the axoneme extends throughout the flagellum and generates the flagellar motive force. The axoneme is a complex structure that is composed of a highly stable, characteristic 9 + 2 array of microtubules and associated proteins (Fawcett, 1975; Clermont et al, 1990). Although the α and ß tubulins are by far the most prominent proteins in the axoneme, it is likely that mammals possess at least as many axonemal and axoneme-associated proteins as does *Chlamydomonas* (Luck et al, 1977). In spite of their relevance to sperm motility, few of these mammalian proteins have been well characterized.

Dyneins are the "motor" proteins located in the arms of the outer microtubular doublets and are members of a multigene family of proteins (Porter and Johnson, 1989; Holzbaur and Vallee, 1994; Milisav, 1998). Activation of the axonemal dynein ATPase causes the sliding of adjacent outer doublet microtubules, which results in flagellar bending (Gibbons and Rowe, 1965; Tash and Means, 1982). In *Chlamydomonas,* the central pair of microtubules, together with radial spokes emanating from the outer 9 microtubule doublets, transmit regulatory signals to the dynein arms (Porter and Sale, 2000). Additionally, the central pair and radial spokes regulate the size and shape of axonemal bending in a calcium-dependent fashion (Wargo and Smith, 2003). The high degree of structural conservation between *Chlamydomonas* and mammalian axonemes makes it likely that a very similar regulatory mechanism is also present in mammals.

Axonemes are not unique to sperm cells; rather, they are found in all flagellated and ciliated cells, from *Chlamydomonas* flagella to the inner-ear hair cells of mammals. Thus, disorders of the axoneme in mammals can result in such varied phenotypes as infertility, deafness, blindness, chronic respiratory disease, or some combination of these problems.

The Mitochondrial Sheath—A Source of Adenosine Triphosphate for the Sperm

Sperm mitochondria are located only in the MS of the midpiece and produce adenosine triphosphate (ATP) for the cell through aerobic respiration. Although these functions are similar to those of somatic mitochondria, sperm mitochondria have been associated with several unique proteins or protein isoforms that are not found in the mitochondria of somatic cells. In mice, these include sperm-specific isoforms of lactate dehydrogenase and hexokinase (Burgos et al, 1995; Travis et al, 1998).

The sperm axonemal dyneins have a high requirement for ATP as an energy source for flagellar motility. Because sperm mitochondria are restricted to the midpiece of the flagellum, the ATP generated by these mitochondria would need to travel some distance to supply the needs of the axonemal dyneins located in the more distal segments of the flagellum. It has long been suspected that this distance is too great and that ATP originating in the midpiece could not diffuse adequately to meet these needs in a timely fashion (Storey and Kayne, 1975). On the basis of these observations, it has been suggested that either other regions of the sperm flagellum must be able to produce ATP to supply the more distal parts of the tail or that there must be some mechanism by which ATP can be shuttled from the MS to the rest of the flagellum.

Also of interest, it has been shown that species-specific differences in the metabolic capabilities of mitochondria exist. This results in variations in the ability of sperm from different species to metabolize different substrates (Storey and Kayne, 1980). It is possible that this variation has

evolved as a result of species-specific differences in the substrate composition of oviductal fluids of the female.

The ODFs Provide Structural Support

Historically, it has been suggested that the role of the ODFs is to provide passive elasticity to the motile flagellum (Fawcett, 1975). More recently, several ODF proteins have been isolated and characterized in a variety of species, including humans (Gastmann et al, 1993; Morales et al, 1994; Hoyer-Fender et al, 1995; Kim et al, 1995; Burmester and Hoyt-Fender, 1996, 1998; Kierszenbaum et al, 1996; Tres and Kierszenbaum, 1996; Brohmann et al, 1997; Shao et al, 1997; Schalles et al, 1998; Zarsky et al, 2003). Some of these have proved to be keratin-like intermediate filament proteins (eg, Sak57), which thus supports the idea that the ODFs provide structural support to the flagellum. Currently, there are no reports on targeted mutations in any of the ODF-specific genes. In part because of this, the functions of ODFs in sperm motility (other than the putative structural role) remain largely speculative.

The FS—Structural Support and More

The FS is another sperm cytoskeletal structure that traditionally was thought to play a mechanical role in sperm motility by providing a rigid support for the flagellum and determining its planar beat (Fawcett, 1975; Lindemann et al, 1992). Outer microtubule doublets 3 and 8 are the only doublets in direct proximity to the FS (the other doublets are separated from the FS by the persistence of the ODFs in the principal piece). It has been suggested that, by supporting outer doublets 3 and 8 and the central pair of microtubules, the FS creates an "I-beam"-like structure along which the other microtubules can slide. In support of this hypothesis, and in support of the hypothesis that doublets 3 and 8 directly participate in FS sliding, it has been shown in mice that, in demembranated sperm in which axonemal sliding is activated with ATP, the FS slides proximally toward the connecting piece while doublets 1, 2, 4-7, and 9 (but not 3 and 8) are asynchronously extruded distally. Also of note, this FS sliding is cyclic adenosine monophosphate (cAMP)-dependent, which suggests that cAMP-dependent kinase, protein kinase A (PK-A), is involved (Si and Okuno, 1993, 1995).

The role of the FS as a supporting structure for the flagellum is likely to be real; however, more recent evidence demonstrates an additional, more active role for the FS in sperm motility. In a wide variety of mammalian species, including humans, a growing number of proteins involved in motility signaling pathways and metabolism have been localized to the FS (Carrera et al, 1994; Bradley et al, 1996; Westhoff and Kamp, 1997; Bunch et al, 1998; Miki and Eddy, 1998; Mori et al, 1998; Travis et al, 1998; Turner et al, 1998, 1999; Nakamura et al, 1999; Fujita et al, 2000; Carr et al, 2001). On the basis of increasing evidence that multiple members of both motility and metabolism-related pathways localize to the FS, it is likely that this accessory structure serves as a scaffold and organizing center for multiple signaling and metabolic cascades that are critical for normal flagellar function (Turner et al, 1999; Miki et al, 2002; Eddy et al, 2003).

Other FS proteins, including, for example, a mu-class glutathione-s-transferase, have also been identified and raise the possibility that another function of the FS is to protect sperm from oxidative stress that could interfere with sperm motility or cause DNA damage (Fulcher et al, 1995).

Assembly of the Flagellum

Early microscopic studies have provided extensive information on the morphological development of mammalian flagellar components. The flagellum can first be seen projecting from the surface of a round spermatid during early spermiogenesis. The axoneme is the first flagellar structure to appear;

it originates from the distal centriole located at the caudal pole of the nucleus and elongates in a proximal to distal direction (Fawcett and Phillips, 1969).

During midspermiogenesis, the ODFs develop in close association with the 9 outer doublets of the axoneme (Fawcett and Phillips, 1969). They originate as thin, electron-dense filaments in the most proximal portion of the future midpiece and then elongate in a distal to proximal direction and increase in thickness (Irons and Clermont, 1982; Oko and Clermont, 1989; Clermont et al, 1990). They persist throughout the midpiece and the principal piece, tapering gradually and eventually terminating distally at the end piece (Fawcett, 1965).

The formation of the FS occurs throughout most of spermiogenesis, but, unlike the axoneme and the ODFs, the FS is assembled distally to proximally along the length of the flagellum (Irons and Clermont, 1982; Oko and Clermont, 1989; Clermont et al, 1990). Thin longitudinal columns, connected to outer doublets 3 and 8 of the axoneme, appear at the distal end of the flagellum. The columns increase in diameter, elongate proximally along the axoneme, and only later become connected by circumferential transverse ribs. This unusual distal to proximal assembly of the FS implies that there must be some mechanism by which FS proteins are shuttled down the length of the developing flagellum in an assembly-incompetent form before they are be pieced together distally to proximally into the FS (Johnson et al, 1997).

The midpiece also develops during spermiogenesis, originating when the annulus, a ring-shaped structure that forms at the connecting piece, migrates distally to meet the most proximal extent of the FS. The MS forms in the midpiece when mitochondria assemble in a helical arrangement around the proximal flagellum, behind the migrating annulus. The mitochondria divide and elongate, eventually assembling end-to-end to form two helices that wind around the outside of the ODFs (Woolley, 1971).

Generation of the Flagellar Beat

The flagellar waveform is created by the motor activities of the axonemal dynein arms working against the stable microtubule doublets. Phosphorylation of the axonemal dynein appears to be a critical regulatory point in the initiation of flagellar motility (Tash, 1989). After phosphorylation, the dynein ATPase is activated. This results in the generation of the flagellar beat as the hydrolysis of ATP is converted into force, thus causing the microtubules to slide past one another. Dephosphorylation of dynein by the calmodulin-dependent protein phosphatase calcineurin then reverses this process.

Recall that the dynein arms are attached to each of the outer 9 microtubule doublet pairs. These arms project outward in the direction of the adjacent outer microtubule doublet. Microtubule sliding occurs as the result of a transient, ATP-dependent interaction of a dynein arm with its adjacent microtubular doublet. During this interaction, the dynein arms generate force between doublets, resulting in the adjacent microtubules sliding past one another (Satir, 1968; Summers and Gibbons, 1971; Brokaw, 1972, 1989; Shingyoji et al, 1977). Because the axoneme is anchored to the base of the sperm head, this sliding force is translated into a bend in the flagellum (Figure 2). Because dynein produces force in only a single direction (Sale and Satir, 1977), the generation of a normal flagellar waveform requires that phosphorylation/dephosphorylation and the associated activation and inactivation of the dynein arms occur in an asynchronous manner around the circumference and along the length of the axoneme. In *Chlamydomonas,* it has been shown that this asynchronous activation occurs through the interactions of the central pair microtubules and the radial spokes (Wargo and Smith, 2003).

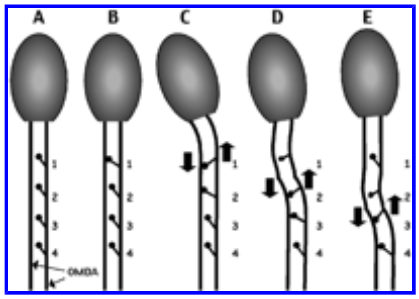

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Figure 2. Simplified schematic representation of the mechanism by which axonemal dynein arms generate the flagellar beat. The parallel lines in the region of the flagellum represent adjacent outer microtubule doublets of the axoneme (OMDA). To simplify the figure, only 2 outer microtubule doublets are represented (rather than the actual 9). The central pair of microtubule doublets is not shown, nor are the any of the accessory structures. Dynein arms between the pair of OMDAs are numbered. Each symbol represents a pair of inner and outer dynein arms originating from the microtubule on the right and extending toward the microtubule on the left. **(A)** None of the dynein arms are active; as such, the adjacent microtubule doublets are straight and there is no flagellar bend. **(B)** The first dynein arm has engaged the adjacent microtubule doublet. **(C)** The first dynein arm has generated a downward stroke, resulting in the adjacent microtubules sliding past one another (large arrows). Because both microtubule doublets are anchored to the sperm head, this sliding force is translated into a bend in the axoneme—the start of a flagellar beat. Also, the second dynein arm has engaged the adjacent microtubule doublet. **(D)** The first dynein arm has released the adjacent microtubule doublet, whereas the second dynein arm has generated a downward stroke. This results in the propagation of the flagellar bend down the length of the microtubules. The third dynein arm has engaged the adjacent microtubule. **(E)** The flagellar beat is being propagated by the downward stroke of the third dynein arm, whereas the second dynein arm has released the adjacent microtubule. The first dynein arm has returned to its original position in preparation for another stroke. This sequence will be repeated by the fourth dynein arm, and so on along the length of the microtubules. One must imagine a similar sequence occurring for all 9 dynein arm pairs and their associated 9 outer microtubule doublets. Additionally, one must imagine this sequence occurring in an asynchronous but coordinated fashion around the circumference and along the entire length of the flagellum (ie, in 3 dimensions). It is this coordinated use of dynein arms and the associated bending of the outer microtubule doublets that result in a normal flagellar beat. The ODFs and the FS add structural support. In Chlamydomonas, it has been shown that the central pair of microtubules, together with the radial spokes emanating from the 9 outer microtubule doublets, coordinate and regulate the actions of the dynein arms and so control the size and shape of the axonemal bend.

Compartmentalization of Signaling Pathways

Sperm are highly polarized cells in which specialized functions are compartmentalized within specific subcellular regions. Of relevance to the present review, sperm motility is compartmentalized to the flagellum. Therefore, many of the proteins directly involved in the regulation and maintenance of mammalian sperm motility must localize to the sperm tail. One example of how compartmentalization is achieved in sperm is the use of A-kinase anchor proteins (AKAPs) to tether PK-A to the FS of the flagellum, thus restricting the scope of action of the kinase to within close proximity of motility-related targets in the axoneme (Carrera et al, 1994; Mei et al, 1997; Miki and Eddy, 1998; Mandal et al, 1999; Vijayaraghavan et al, 1999). In addition to tethering PK-A to the FS, anchoring proteins also may target other signaling and metabolic proteins to the sperm tail. In this regard, the major protein of the mouse sperm FS is an AKAP called AKAP4 (Carrera et al, 1994). It has been shown that sperm from mice lacking the AKAP4 protein have severely reduced sperm motility and are infertile. In addition, the absence of this anchoring protein results in a reduction or loss of other proteins (ie, those proteins that normally are anchored or targeted to the FS by AKAP4) from the FS, thus further adversely affecting sperm function and adding evidence to

the hypothesis that the FS functions as more than simply a structural support for the tail (Miki et al, 2002). Recently, AKAP4 has been shown to interact with a second FS AKAP, AKAP3. This finding suggests that anchoring proteins like AKAP4 have both functional and structural roles in the FS (Brown et al, 2003). AKAPs now have been shown to be major components of the FS in a variety of species, including rodents, bulls, and humans (Turner et al, 1998; Mandal et al, 1999; Moss et al, 1999; Jha and Shivaji, 2002). In all cases, they are believed to function in anchoring PK-A to the flagellum.

Regulation of Flagellar Motility

Two signaling pathways have emerged as central to normal mammalian motility: the cAMP/PK-A pathway and calcium signaling (Suarez et al, 1987; Tash and Means, 1987; Lindemann and Goltz, 1988; White and Aitken, 1989; Brokaw, 1991; Yanagimachi, 1994; Ho et al, 2002). Other signaling cascades also are likely to play roles. For example, both heterotrimeric and small G-protein-mediated pathways recently have been implicated in sperm motility (Hinsch et al, 1993; Nakamura et al, 1999; Fujita et al 2000; Carr et al 2001). Similar to PK-A, there is evidence that some of these proteins are compartmentalized to the flagellum, and specifically to the FS, via the actions of anchoring proteins (Carr et al, 2001). Changes in pH also affect sperm motility (Yanagimachi, 1994). However, there have been relatively few studies on these signaling pathways.

Protein Phosphorylation

In mammals, activated sperm motility is, at least in part, initiated and maintained by the cAMP-dependent phosphorylation of flagellar proteins (Tash and Means, 1982, 1983; San Augustin and Witman, 1994). A major downstream target of cAMP in sperm is the serine/threonine kinase PK-A, thus making it likely that this enzyme plays a central role in these phosphorylation events (Visconti et al, 1997). PK-A activity may work through multiple pathways to control flagellar function. One likely mechanism of action of PK-A is that the resulting protein serine/threonine phosphorylation activates a downstream, as yet unidentified, tyrosine kinase or kinases whose targets are primarily located in the flagellum (Leclerc et al, 1996; Si and Olds-Clarke, 2000).

Direct evidence supporting a role for the catalytic activity of PK-A and its associated serine/threonine phosphorylation in sperm motility has come from gene "knockout" studies in mice. Although most mice with a targeted deletion of the gene encoding the alpha isoform of the catalytic subunit of PK-A die during the postnatal period, a few survive to adulthood. These adults have stunted growth and lack progressively motile sperm (Skalhegg et al, 2002). To date, only a few of the protein targets for PK-A phosphorylation in sperm have been identified (Tash and Bracho, 1998). One known target is axonemal dynein, and phosphorylation of this protein appears to be a critical regulatory point in the initiation of flagellar motility, as was discussed above (Tash, 1989).

It is likely that anchoring PK-A to the fibrous sheath of the flagellum via AKAPs is important in directing the activity of the kinase to motility-related targets in the tail. Inhibition of the anchoring of the type-II regulatory subunit of PK-A in sperm resulted in an arrest of bovine sperm motility in one study (Vijayaraghavan et al, 1997). However, targeted deletion of the type II regulatory subunit of PK-A, and the associated loss of anchoring of the catalytic subunit of PK-A, had no obvious effect on murine sperm motility or fertility (Burton et al, 1999). It is likely that, in the absence of proper targeting of the type II regulatory subunit, the type I regulatory subunit of PK-A is able to compensate.

Serine/threonine phosphatases appear to provide a balance for serine/threonine kinases, and the resulting net phosphorylation of the relevant target proteins is one factor that influences the

status of sperm motility (Tash, 1989; Tash and Bracho, 1994). Specifically, immotile primate sperm contain higher levels of the protein phosphatase PP1 gamma 2 than do motile sperm, and motility can be initiated in bovine caput epididymal sperm by the inhibition of phosphatase activity (Smith et al, 1996; Vijayaraghavan et al, 1996). In this regard, in somatic cells, members of the AKAP family scaffold both kinases and phosphatases to a single place within the cell (Coghlan et al, 1995; Klauck et al, 1996). If these anchoring proteins play similar roles in sperm, then they may serve as master organizers of the phosphorylation/dephosphorylation pathways that are so critical for the regulation of motility.

Cyclic AMP also may work through pathways independent of PK-A. It was hypothesized that a cyclic nucleotide-gated ion channel in sperm and/or cAMP-mediated guanine nucleotide exchange factors in testes also might be activated by cAMP and thus may provide alternative pathways for the PK-A-mediated regulation of flagellar motility (Burton et al, 1999).

In addition to serine/threonine phosphorylation, protein tyrosine phosphorylation is also associated with the onset of sperm motility (Tash and Bracho, 1998). In this regard, tyrosine phosphorylation of glycogen synthase kinase-3 alpha has been closely linked to the onset of motility in bovine sperm (Vijayaraghavan et al, 1997, 2000), making it likely that phosphorylation of this protein is involved in the control of the onset of sperm motility.

Several investigators have identified an association between the onset and end of hyperactivated sperm motility in primates and rodents and the tyrosine phosphorylation and dephosphorylation (respectively) of flagellar proteins (Chan et al, 1998; Mahony and Gwathmey, 1999; Si and Okuno, 1999), and it has been suggested that one of these phosphotyrosine-containing proteins is an AKAP, AKAP4 (Si, 1999). This implies that changes in some aspect of AKAP4 activity are linked to the onset of hyperactivation.

Calcium Signaling

Calcium has long been implicated as a regulator of activated sperm motility (Tash and Means, 1987), and it may be the primary mechanism by which the onset of hyperactivated motility is achieved (Suarez et al, 1987; Lindemann and Goltz, 1988; White and Aitken, 1989; Brokaw, 1991; Yanagimachi, 1994; Ho et al, 2002). In mammals, the majority of work on sperm calcium channels has been conducted in rodents and, to a lesser extent, in humans. Indirect evidence for a role of calcium in mammalian sperm motility is found in the fact that several calcium channel alpha-1 (ie, pore-forming) subunits have been identified in sperm (Lievano et al, 1996; Westenbroek and Babcock, 1999; Wennemuth et al, 2000). Arnoult et al (1996, 1998, 1999) identified only a T-type channel activity in mature sperm. However, the results of other studies have suggested that a wide range of voltage-gated calcium channels—including L-, N-, and R-type channels—may be present (Benoff, 1998; Wennemuth et al, 2000). Some calcium-channel subunits have been localized to the flagellar principal piece, which is consistent with these channels having roles in the regulation of sperm motility (Westenbroek and Babcock, 1999; Ren et al, 2001). Additionally, cyclic nucleotide gated (CNG) channels are present on the sperm flagellum and developing spermatogenic cells. Different subunits of these channels are present in different temporal and spatial patterns in sperm (Wiesner et al, 1998). These CNG channels are ports of calcium entry in sperm and may give rise to different patterns of calcium influx in different microdomains of the flagellum. Current evidence suggests that sperm CNG channels are sensitive to both cGMP and cAMP, although they seem to be most sensitive to cyclic guanosine monophosphate (cGMP) (Wiesner et al, 1998).

The results of several studies have provided more direct evidence for a role for calcium in mammalian sperm motility. Calcium increases flagellar wave asymmetry in permeabilized sperm and,

eventually, if calcium levels increase sufficiently, results in the inhibition of sperm motility (Tash and Means, 1982). This inhibition of motility is associated with a decline in protein phosphorylation mediated by CaM and by the calcium/calmodulin dependent phosphatase, calcineurin (Tash and Means, 1987; Tash et al, 1988). In this regard, exposing sperm to a CaM inhibitor reduced the percentages of activated and hyperactivated sperm (Si and Olds-Clarke, 2000). In addition to other functions in sperm (Carrera et al, 1996), calcium/calmodulin may act at the membrane to pump calcium out of the flagellum, and/or it may regulate dynein ATPase and myosin light-chain kinase activities and thus be directly involved in the control of axoneme function (Tash and Means, 1982). The effects of cAMP (resulting in phosphorylation of target proteins) and calcium signaling (resulting in dephosphorylation of target proteins) oppose one another in sperm and so serve to regulate flagellar function (Tash and Means, 1983; Tash and Bracho, 1994).

Of particular interest, CatSper1, a gated cation channel that localizes specifically to the principal piece of mature sperm, is required for cAMP-induced calcium influx into sperm. The cAMP-stimulated rise in intracellular sperm calcium is abolished in mice with a targeted deletion of the gene that encodes the CatSper1 protein. Sperm from these mice are poorly motile and are unable to fertilize zona-intact eggs, which thus suggests that calcium influx via CatSper1 is critical for normal sperm motility (Ren et al, 2001). A related, voltage-gated putative calcium channel (CatSper2) also has been described in the sperm flagellum, and the messenger RNA for this protein has been identified in rodents and humans (Quill et al, 2001). Additionally, mice with a targeted deletion of an unrelated voltage-dependent calcium channel, $Ca_V2.3$ ($alpha_{1E}$), although fertile, demonstrated abnormalities in intracellular calcium transients in sperm. Sperm from these animals demonstrated increased linearity compared with wild-type sperm, which thus suggests that the $Ca_V2.3$ channel also may play a role in the control of flagellar movement (Sakata et al, 2002).

Because of the fundamental importance of calcium to sperm function, it is necessary that we understand its downstream targets. In *Chlamydomonas,* calcium regulates flagellar motility through the regulation of dynein-driven microtubule sliding. This regulation may be mediated by calmodulin (CaM) and calmodulin-dependent kinase II (CaMKII), two classical downstream elements of calcium signaling pathways (Smith, 2002). CaM (Weinman et al, 1986; Bendahmane et al, 2001) and at least one form of CaMK (author's unpublished data) are present in mammalian sperm as well. There is convincing evidence that calcium works through calmodulin to influence capacitation, the acrosome reaction, and activated and hyperactivated motility in mammalian sperm (Si and Olds-Clarke, 2000; Bendahmane et al, 2001). Other studies have identified a link between calmodulin and the regulation of T-type calcium currents in sperm (Lopez-Gonzalez et al, 2001). Further down the pathway lies calcineurin, a calcium/calmodulin-dependent serine/threonine phosphatase that has been implicated in the regulation of flagellar motility in rodents and humans (Tash et al, 1988; Carrera et al, 1996).

Fuel for the Tail

Because mitochondria are found only in the midpiece, oxidative phosphorylation also is restricted to this region of the cell. However, large amounts of ATP are required along the full length of the motile flagellum. Specifically, flagellar kinases need ATP to phosphorylate motility-related downstream targets. Additionally, the dynein ATPases, the motors of the axoneme, require ATP as an energy source. Mathematical models based on the diffusion constant of ATP and a morphometric estimate of the volume of the mouse sperm flagellum (Du et al, 1994) have predicted that ATP produced by the midpiece mitochondria would not be able to diffuse sufficiently along the length of the FS to supply the entire flagellum with enough energy to support the axonemal dynein ATPase (B. T. Storey, personal communication). Additionally, it has been shown in mice that, if mitochondrial oxidative phosphorylation is defective, fertilization can still occur, sperm still produce ATP (at

lower levels than in wild-type sperm), and sperm motility is still present although reduced (Narisawa et al, 2002). These data support the idea that sperm have evolved alternative methods of energy production that are independent of mitochondrial oxidative phosphorylation.

In this regard, several glycolytic enzymes (some in spermatogenic cell-specific forms) have been identified in the FS/principal piece of a growing number of mammalian species. These include hexokinase, lactate dehydrogenase, and glyceraldehyde 3-phosphate dehydrogenase (GAPD-S) (Bradley et al, 1996; Westhoff and Kamp, 1997; Bunch et al, 1998; Mori et al, 1998; Travis et al, 1998). Additionally, all of the glycolytic enzymes downstream of GAPD-S remain attached to the cytoskeleton even after membrane removal, which thus suggests that they are components either of the FS or the ODFs (Storey and Kayne, 1975). This strongly supports the possibility that mammals may have solved the problem of ATP diffusion in the flagellum by developing a system in which ATP is produced by glycolysis compartmentalized within the FS. Consistent with this hypothesis, mammalian sperm produce lactate from glucose under aerobic conditions (Storey and Kayne, 1975). Additionally, ATP production through glycolysis is required for hyperactivated sperm motility (Hoshi et al, 1991; Urner and Sakkas, 1996), and the inhibition of oxidative phosphorylation does not block fertilization (Fraser and Quinn, 1981). Thus, glycolysis in the principal piece, but not necessarily oxidative phosphorylation in the midpiece, seems to be critical for normal mammalian sperm function.

There are several known differences in the ability of sperm from different species to carry out glycolysis and oxidative phosphorylation. These differences are of profound importance when handling gametes in vitro. For example, glucose will inhibit capacitation in bull sperm but is required for this process in mouse sperm. The role of glucose in human sperm metabolism and fertilization remains somewhat controversial (Quinn et al, 1995; Mahadevan et al, 1997; Barak et al, 1998; Williams and Ford, 2001).

Genetic Defects and Sperm Motility in Humans

Many genetic mutations are known to cause male infertility in mice (Matzuk and Lamb, 2002), and it is likely that many cases of male infertility in humans and other species also will prove to have genetic components. In the mouse, infertility has been associated with mutations in genes coding for such varied products as flagellar transport proteins, structural proteins, motor proteins, transcription factors, and signaling proteins, just to name a few. Unfortunately, our knowledge of the genetic basis for human and domestic animal infertility lags far behind. On a positive note, the high degree of conservation of many of these genes among mice, humans, and domestic animal species will allow for the efficient application of the broad body of information on mouse genetic infertility to an understanding of male infertility in other mammalian species. In a few instances, single gene defects already have been proved to be responsible or are suspected of being responsible for some cases of infertility associated with poor sperm motility in men. These will be briefly reviewed here.

Primary ciliary dyskinesia (PCD; also called immotile cilia syndrome or Kartagener syndrome) is a genetically heterogeneous, autosomal recessive disease that is characterized by a generalized paralysis of ciliated cells, including sperm and respiratory cilia (Blouin et al, 2000). Clinical signs include bronchiectasis, chronic sinusitis, and male infertility. In approximately 50% of patients with PCD, embryonic cilia also are apparently affected, which results in situs inversus (Kartagener syndrome) (Afzelius, 1976; Eliasson et al, 1977; Narayan et al, 1994). In most cases, the results of electron microscopic analysis of sperm and ciliated cells reveal that the outer microtubule doublets of the axoneme lack inner and/or outer dynein arms (Waite et al, 1978; Afzelius and Eliasson, 1979; Rossman et al, 1980; Aitken et al, 1983). As such, mutations in a component or components of axonemal dynein have been suspected as the cause. To date, mutations in three human

genes have been implicated in a minority of patients with PCD/Kartagener syndrome. Each of these genes codes for a different component of the axonemal dynein arms (Pennarun et al, 1999; Guichard et al, 2001; Zariwala et al, 2001; Bartoloni et al, 2002; Olbrich et al, 2002). However, it is likely that several additional genes remain to be discovered as causes of this heterogeneous disorder.

Dysplasia of the fibrous sheath (DFS) in humans is characterized by male sterility associated with severe or complete asthenozoospermia (Chemes et al, 1987). Under light microscopy, the majority of sperm from affected individuals possess short, thick, irregular flagella with no clear distinctions among the midpiece, principal piece, and end piece. The results of electron microscopic examination of sperm from patients with DFS reveals that the most striking feature of the sperm is a disorganized, thickened FS that fails to form its trademark longitudinal columns and transverse ribs. In many cases, DFS is familial, which strongly suggests a genetic component. Because of the abundance and likely structural roles of AKAPs in the sperm FS, mutations in one or both of the two most abundant FS AKAPs, AKAP3 and AKAP4, are suspected to be the possible causes of the DFS phenotype. However, studies to date have failed to identify problems with either of these genes or proteins in affected men (Turner et al, 2001).

Retinitis pigmentosa (RP) is a heritable, heterogeneous group of human disorders characterized by the progressive degeneration of the modified ciliated cells (photoreceptor cells) of the retina. Although blindness is the most significant clinical sign in patients with RP, the axonemal abnormalities in RP also appear to affect ciliated cells of the respiratory tract as well as sperm flagella (Arden and Fox, 1979). In sperm cells from patients with RP, the predominant abnormalities include the presence of extra microtubules and the absence of a subset of outer microtubule doublets (Hunter et al, 1986, 1988). Usher syndrome is an autosomally inherited subtype of RP that is characterized by infertility, retinal degeneration, a congenital hearing impairment, and a vestibular deficit. It is the most common cause of congenital deafness and blindness in humans, and it is likely that several different genetic loci are involved (Boughman et al, 1983; Smith et al, 1994). Researchers have begun to identify and map some of the genes involved in RP, but many more have not yet been identified (Humphries et al, 1992). An unconventional myosin molecule (VIIa) has been shown to play a role in Usher syndrome type IB (Gibson et al, 1995; Hasson et al, 1995; Weil et al, 1995). The role of this gene in male fertility and sperm motility has not been well characterized.

Conclusions and Perspectives

Our improved understanding of the molecular basis for sperm motility allows us to begin to imagine the number of genes and resulting proteins that must function normally to generate a "fertile" sperm. Proteins involved in sperm structure, protein assembly, calcium signaling, protein phosphorylation, metabolism, and protein targeting all are crucial to proper sperm function, so mutations in any of these genes could theoretically adversely affect fertility. Additionally, these considerations do not even begin to address the genes involved in spermatogenesis (eg, DAZ) or in the development of a normal reproductive tract (eg, the cystic fibrosis transmembrane conductance regulator gene).

Our current technology and understanding limits most of our work in humans and domestic animals to the study of single-gene defects, like those described above. These single-gene defects typically result in severe but rare phenotypes. Thus, in the short term, studies focusing on these isolated genes result in potential benefits to a limited number of individuals. The full value of understanding these genes is realized when one uses the new information to refine and redefine our current understanding of basic physiology. The information also serves as a well-defined starting point from which to examine and identify other genes linked to multifactorial or multigenic

diseases. The majority of cases of clinical male subfertility and infertility present with wide variations in clinical signs and severity, thus making it very likely that many or most of these cases are multifactorial and/or multigenic in origin. This greatly complicates the problem of identifying their genetic origins. Nonetheless, recent progress in molecular biology, as well as the establishment of detailed genetic databases, will greatly facilitate the study of multigenic diseases.

An understanding of the genetics of sperm motility has become even more critical with the advent of assisted reproductive technologies such as ICSI. In the past, oligospermic men or those with severely impaired sperm motility have been largely unable to reproduce, thus naturally limiting the propagation of any underlying genetic mutations. However techniques such as gamete intrafallopian transfer, in vitro fertilization, and ICSI now allow us to minimize or even bypass the requirement for sperm motility. The very real likelihood that genetic defects may be the underlying causes of some cases of severe aberrations of sperm numbers or sperm function raises the concern that these defects now will be passed on to future generations through the use of these techniques. Additionally, disorders such as PCD, Kartagener syndrome, RP, and Usher syndrome illustrate that the effects of genetic mutations that result in male infertility are not necessarily limited to the reproductive tract. Studies on the molecular composition of normal sperm will provide new information on the underlying causes of the genetic disorders of germ cells. This information will allow clinicians to be more informed about potential genetic defects and may eventually result in improved diagnostics and even genetic therapy for patients seeking treatment for infertility.

Footnotes

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