Major regulatory mechanisms involved in sperm motility

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The genetic bases and molecular mechanisms involved in the assembly and function of the flagellum components as well as in the regulation of the flagellar movement are not fully understood, especially in humans. There are several causes for sperm immotility, of which some can be avoided and corrected, whereas other are related to genetic defects and deserve full investigation to give a diagnosis to patients. This review was performed after an extensive literature search on the online databases PubMed, ScienceDirect, and Web of Science. Here, we review the involvement of regulatory pathways responsible for sperm motility, indicating possible causes for sperm immotility. These include the calcium pathway, the cAMP-dependent protein kinase pathway, the importance of kinases and phosphatases, the function of reactive oxygen species, and how the regulation of cell volume and osmolarity are also fundamental components. We then discuss main gene defects associated with specific morphological abnormalities. Finally, we slightly discuss some preventive and treatments approaches to avoid development of conditions that are associated with unspecified sperm immotility. We believe that in the near future, with the development of more powerful techniques, the genetic causes of sperm immotility and the regulatory mechanisms of sperm motility will be better understood, thus enabling to perform a full diagnosis and uncover new therapies.

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MAIN FACTORS AFFECTING SPERM MOTILITY

Sperm motility is highly dependent on several metabolic pathways and regulatory mechanisms. Besides the involvement of specific gene defects, any abnormalities of these factors could be responsible for cases of poor sperm motility and consequently infertility.

Pathways and regulatory mechanisms involved in sperm motility

The calcium (Ca²⁺) pathway and the cyclic adenosine monophosphate (cAMP)-dependent protein kinase or protein kinase A (PKA) pathway are two important metabolic pathways involved in the regulation of sperm motility. These pathways involve calcium ions, adenylyl cyclases, bicarbonate ions, different membrane channels, and phosphorylation events. All are responsible for the acquisition of competences that will enable sperm to fertilize the oocyte, namely capacitation, hyperactivity, and acrosome reaction (Figure 1).

Cellular levels of cAMP are controlled by adenylyl cyclases (ACs) that catalyze an intramolecular cyclization of ATP to cAMP under release of pyrophosphate. The mammalian ACs can be separated into two distinct types, transmembrane AC enzymes (tmACs) and soluble AC (sAC, also known as AC10). Soluble AC is directly activated by bicarbonate and Ca²⁺ and acts as a sensor for ATP, Ca²⁺, and bicarbonate/CO₂/pH at various intracellular locations. Soluble ACs are the only signaling proteins known to be directly regulated by bicarbonate. Mammalian tmACs, in contrast, are not responsive to bicarbonate. Instead, they are mainly regulated by heterotrimeric G-proteins, as part of the G-protein coupled receptor pathways. Both ACs are known to play an important role in male fertility. Transmembrane AC is involved in the basic mechanism for motility activation through cAMP-dependent protein phosphorylation and in progressive motility. Soluble AC is the predominant adenylyl cyclase responsible for the generation of most cAMP in spermatozoa and plays a critical role in cAMP signaling and is involved in the increase in beat frequency in spermatozoa. Inactivation of sAC gene leads to male sterility given the lack of forward motility. Cyclic AMP is thus essential for sperm motility regulation and fertility with reduction of cAMP levels associated with reduced sperm motility (Figure 1).

Calcium is a fundamental regulatory factor for sperm capacitation, hyperactivation, and acrosome reaction. At low intracellular Ca²⁺ concentrations, flagella beat symmetrically but when Ca²⁺ levels rise in activated sperm (Ca²⁺ of 10–40 nM), the waveform becomes more asymmetric, and sperm becomes hyperactivated (Ca²⁺ of 100–300 nM). However, high levels of Ca²⁺ (about 9 μM) suppress motility. This inhibition seems to be due to a decrease of protein phosphorylation (caused by substrate depletion or to conformational changes) induced by Ca²⁺, which prevents substrate-kinase interactions. Calcium is also involved in the regulation of dynemin-driven microtubule sliding. Calmodulin is a key axonemal...
increase in protein tyrosine phosphorylation during capacitation in vitro.

Figure 1: Schematic representation of pathways believed of being involved in the regulation of mammalian sperm motility. Activation of a Na+/HCO₃⁻ (NBC) co-transporter and the regulation of HCO₃⁻/Cl⁻ by SLC26 transporters increase HCO₃⁻ levels. The activation of the sperm Na⁺/H⁺ exchanger (sNHE) aligned with the activation of the proton channel (Hv1) leads to a raise of the pH, which activates CatSper, a cation channel of sperm that enables the entry of Ca²⁺ and thus increases the internal Ca²⁺ concentration ([Ca²⁺]). Progesterone, a steroid hormone synthesized by the cumulus/granulosa cells, activates CatSper either by binding to the channel itself or to an associated protein. Further, albumin, the main protein of human blood plasma and oocyte glycoproteins, together with alkalization of the sperm cytoplasm also, elevates the internal Ca²⁺. The overall Ca²⁺ increase may influence glycolysis and the axoneme activity promoting hyperactivation of motility. Further, HCO₃⁻ and Ca²⁺ regulate the lepithal soluble adenylyl cyclase (sAC), which generates cAMP and that by its turn activates protein kinase A (PKA). PKA induces phosphorylation of axonemal dynein, leading to consumption of ATP and thus increases the pH. PKA activates sperm tyrosine kinases (with serine and threonine residues) to trigger a cascade of protein phosphorylation involved in sperm motility.

Figure 2: The increase in protein tyrosine phosphorylation during capacitation has been shown to be regulated by a cAMP-dependent pathway involving protein kinase A (PKA), receptor tyrosine kinase pathway, and by the nonreceptor protein tyrosine kinase pathway. cAMP has been shown to activate PKA, which in turn regulates protein tyrosine phosphorylation. The binding of PKA regulatory subunit to the AKAP family of proteins promotes an increase in tyrosine phosphorylation of sperm proteins by indirect activation of Tyrosine kinases (TKs). In human sperm, AKAPs proteins, namely AKAP3 and FSP95, are the most prominent tyrosine phosphorylated proteins during capacitation. Receptors TK is transmembrane proteins having an extracellular ligand binding domain and an intracellular tyrosine kinase domain. Upon extracellular ligand binding, a receptor TK is activated and then phosphorylates it (autophosphorylation) or other proteins. By contrast, nonreceptor protein TK lacks a transmembrane domain, most are soluble intracellular proteins located in the cytoplasm, nucleus, or anchored to the inner leaflet of the plasma membrane. Tyrosine and protein phosphorylation of the sperm flagellar proteins leads to capacitation of human sperm.
phosphorylation to prepare the capacitated sperm for fertilization.22 PKA localizes at the principal piece of the flagellum, and Ctx2 null males are completely infertile.25,26

Several Ca2+-permeable-specific channels have been found in sperm based on immunostaining or on the presence of transcripts in spermatogenic cells, such as high voltage-gated Ca2+ channels, cyclic nucleotide-gated channels, cation channels of sperm (CatSper), and transient receptor potential channels (Figure 1). These are a family of alkalization-activated cation channels (CATSPER-1-4) that are highly conserved in humans. They are the principal Ca2+ channels activated by progesterone in human sperm.27 Mutations in these channels were associated with human infertility and also suggested as a target for development of a male contraceptive.28–31 Thus, it is likely that Ca2+ plays different roles in distinct stages of the sperm journey.

Phosphorylation is essential in almost every aspect of the cell life, and protein kinases are known to regulate important signaling pathways and cellular processes such as transcription, cell-cycle progression, cell movement, apoptosis, and immunological functions. Protein kinases share a conserved catalytic domain that transfers a phosphate group from ATP and covalently attaches it to specific amino acids with a free hydroxyl group, frequently on both serine and threonine amino acids (serine/threonine kinases). Calcium is important to activate the kinase through limited proteolysis by Ca2+-dependent protease.32 Phosphorylation (Figures 1 and 2) substantially contributes to proper functioning of sperm proteins,33,34 and it seems to be a necessary prerequisite for a sperm to fertilize an oocyte.35–38 During capacitation, it was detected an increase in the phosphorytosine content of human FS proteins,39 which makes evident involvement of protein tyrosine phosphorylation in the control of sperm motility.

In human sperm, the A-kinase anchoring proteins (AKAPs) (AKAP3 was formerly called FSP95), Ca2+-binding and tyrosine phosphorylation-regulated protein (CABYR), which is localized in the FS, are the most prominent tyrosine phosphorylated proteins during capacitation.40–42 Immotile sperm with deficiency in tyrosine phosphorylation do not capacitate properly, and this has been related to altered sperm membrane lipid composition, particularly due to high cholesterol content, which would impair the ability of this sperm to respond to capacitation-inducing stimuli.43–46 Sperm protein phosphorylation is highly regulated, and there are several pathways involved.44,45,67

The cAMP-dependent pathway (Figures 1 and 2) can also regulate protein tyrosine phosphorylation by stimulation of PKA activity, because PKA activates some intermediate tyrosine kinases involved in sperm motility.20,68 It was demonstrated that the presence and activity of a kinase (PI 3-kinase) in human sperm and its inhibition results in an increase in intracellular CAMP levels and in tyrosine phosphorylation of the protein AKAP3. This results in the binding of PKA to AKAP3, which is important for motility. These results provide a confirmation that PKA can be targeted to sperm tails by interaction with tyrosine phosphorylated form of AKAP3.49 AKAP scaffolding proteins are thus very important in regulating sperm motility as they sequester enzymes, such as protein kinases and phosphatases with the appropriate substrates to coordinate phosphorylation and dephosphorylation events.50 In humans, AKAP3 and AKAP4 are the most abundant structural FS proteins that anchor cAMP-dependent PKA.41

The role of reactive oxygen species in the acquisition and control of sperm motility
Reactive oxygen species (ROS), such as the superoxide anion (O2−), hydrogen peroxide (H2O2), and nitric oxide (NO−), are chemically reactive molecules resulting from oxygen consumption. At certain concentrations, ROS are of extreme importance to sperm function.51,52 It was shown that O2− triggers hyperactivation and capacitation, since the presence of superoxide dismutase (enzyme that catalyzes the dismutation of O2− into oxygen and H2O2) blocks both events.53,54 Other studies also gave evidence of the involvement of ROS on sperm function by demonstrating that low levels of NO− induce capacitation and that at higher levels, it blocks sperm motility.55,56 Thus, low levels of O2− are required to the capacitation process with H2O2 acting as an inducer of the acrosome reaction with high O2− levels being deleterious for sperm function57 and higher H2O2 levels adversely affect sperm motility parameters.58

The cAMP/PKA pathway is also dependent of ROS.59,69 ROS are naturally originated in the human ejaculate: (a) sperm by themselves from spontaneous production through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system at the level of the sperm plasma membrane,60–63 or by the natural production of ROS by mitochondria, which is considered the main source of ROS in spermatozoa;64,65 (b) from leukocytes infiltrated into semen.66 When ROS production is heightened or a compelling reduction in the effectiveness of antioxidant defenses arises, an imbalance between ROS production and the biological system’s aptitude to withdraw or repair the ROS damage occurs, which is known as oxidative stress (Figure 3). This can be caused by several factors.67 Cytoplasmic droplets (excess of residual cytoplasm) are a result of defective spermiogenesis and a considerable source of ROS.68

Leukocytospermia is also positively correlated with an increase in ROS production.69,70 Genitourinary tract infections,71 chronic inflammation,72 and pathologies such as varicocele73 induce ROS production and contribute to sperm immotility. The lifestyle, including smoking,74 dietary deficiencies,75 excessive alcohol consumption,76 psychological stress,77 the contact with environmental pollutants,78 and age,79 are all positively correlated with oxidative stress and linked with sperm immotility. Thus, increased ROS levels have been correlated with decreased sperm motility and with the proportion of various sperm head and tail anomalies,80,81 and some hypotheses have been proposed for this correlation (Figure 3).

One hypothesis is that ROS inhibit the activity of some enzymes such as glucose-6-phosphate dehydrogenase (G6PD), which through the hexose monophosphate pathway controls the intracellular availability of NADPH. Inhibition of G6PD leads to a decrease in the availability of NADPH and a parallel accumulation of oxidized glutathione and reduced glutathione. This leads to a reduction in the antioxidant defenses of the sperm and peroxidation of membrane phospholipids.52,82 Another way of injury may be due to the fact that high ROS levels induce a cascade of events that result in a decrease in axoneme protein phosphorylation and sperm immobilization.83 Advantages of this effect of ROS in sperm function are being used to develop contraceptives. Besides the direct influence on sperm motility, the increase of ROS is also related with an increase of DNA damage.84,85

The control of cell volume and osmolarity is fundamental for sperm motility
The maintenance of a correct cell volume and osmolarity is vital. During maturation and at ejaculation, sperm experiences great changes in its environment, namely rapid changes in the osmotic environment, once the osmolarity of cauda epididymal fluid (osmol: 342 mmol kg−1) is higher than the contents of uterus (osmol: 284 mmol kg−1).80,85 When sperm encounters hypo or hypertonic environments, they tend to swell or shrink.
owing to the influx or efflux of water during reestablishment of the osmotic equilibrium. To maintain cell functionality in face of these osmotic changes, sperm possesses volume regulatory abilities, particularly regulatory volume decrease in response to hypotonic challenge (Figure 4). Defects in the mechanisms of volume regulation and in the epididymal osmolyte uptake cause an abnormal increase in sperm head volume and angulation of sperm tail that leads to an alteration of movement patterns, compromising forward progression resulting in defects in sperm motility and fertility.

The cytoplasmic droplet found at the midpiece of some sperm is a portion of excessive residual cytoplasm that is normally lost during the final maturation phase of spermiogenesis. The normal connecting piece and upper midpiece contain a small portion of cytoplasm with a few endoplasmic reticulum vesicles. The midpiece is the major site of water influx and cell volume regulation, and these vesicles are important when sperm face hypo-osmotic challenges. The cytoplasmic droplet is indeed, really important for sperm function given that spermatozoa without it were immotile due to a defective spermatogenesis. In addition to cytoplasmic droplet, it has been reported that sperm osmolytes, namely glutamate and K+ channels are involved in mechanisms of sperm regulatory volume decrease.

Calcium is also known to be involved in the regulation of cell volume, namely by the activation of Ca2+-dependent K+ channels (Figure 4).

Ejaculated sperm is immersed in the seminal plasma, a medium composed of aliquots of the fluid of the testis, epididymal tail, and the secretions of the accessory sexual glands. It also contains a wide variety of factors that influence the functionality of sperm. Sperm motility is also negatively influenced by seminal osmolarity, as patients with normal motility exhibit a mean value of semen osmolarity significantly lower (Ca2+: 3.36 mmol l−1; osmol: 318 mmol kg−1) than that of patients with low sperm motility (Ca2+: 3.10 mmol l−1; osmol: 345 mmol kg−1). Seminal plasma...
proteins are also considered modulators of sperm function and several important biological roles have been attributed to them.  

The striking reduction of cell volume is one of the most distinct morphological changes during the differentiation of spermatids into sperm and is largely due to osmotically driven fluid efflux. Aquaporins (AQP) may be involved in the rapid reduction of spermatid volume during spermiogenesis, the final step of spermatogenesis. In humans, it was detected the presence of the water transport protein AQP3 in the principal piece of ejaculated sperm, and of AQP7 in the tail of spermatids and testicular spermatozoa, as well as at the midpiece and the anterior flagellum portion of ejaculated sperm.

The AQP3 was shown to be essential for sperm volume regulation, which is important for the balance between sperm motility and swelling in response to physiological hypotonicity, since AQP3-deficient sperm exhibited hampered migration in the oviduct, resulting in reduced male fertility. Regarding the AQP7 expression, it was observed that its absence in ejaculated sperm of some infertile patients was directly correlated with motility rate.

Molecular abnormalities and associated flagellar sperm structure
Normal sperm morphology is one of the most informative semen parameters used for infertility diagnosis. It is correlated with poor sperm motility, as an isolated event was not associated with a decreased probability of pregnancy. Abnormalities in the sperm structure can occur as a single defect or attain different sperm components. In the large majority of the cases, the ultrastructural analysis of immotile sperm reveals nonspecific flagellar anomalies that include disruption of the normal axoneme pattern in association with other components of the sperm tail. Specific defects are however found in dysplasia of FS (DFS) and primary ciliary dyskinesia (PCD).

DFS is characterized by a marked hypertrophy and hyperplasia of the FS. Typically, the annulus is not formed, and the abnormal FS invades the midpiece. It is also frequent to observe absence of the central pair complex and dynein arms (DA) (Figure 5). It has been estimated that about 20% of DFS cases have a familiar incidence and family tree analysis seems to indicate an autosomic recessive inheritance. However, there are no consensus if DFS is a genetic disorder. Indeed, no association between DFS and defects in genes that code for AKAP3 and AKAP4 proteins were found.

Regarding PCD, it is a genetic, heterogeneous, and autosomal recessive disease that is characterized by cilia immotility due to absence of DA (Figure 5), resulting in recurrent infections of the upper respiratory tract. Absence or dislocation of the central pair complex, defects of radial spokes, and doublet abnormalities are also common. In about 50% of PCD cases, patients present Kartagener syndrome, which is characterized by the combination of situs inversus and therefore, investigations into the genetic basis of PCD have started by analysis of DA proteins. It is a genetic disease that is characterized by cilia immotility due to absence of DA (Figure 5), resulting in recurrent infections of the upper respiratory tract. Absence or dislocation of the central pair complex, defects of radial spokes, and doublet abnormalities are also common. In about 50% of PCD cases, patients present Kartagener syndrome, which is characterized by the combination of situs inversus and protists. As motor of sperm, the axoneme is one of the most studied structures. Due to the high complexity of sperm, any alteration in external and/or internal factors regulating sperm motion as well as in the cellular structure and metabolism involved in generating flagellar beat may result in defects in sperm motility, which consequently results in male infertility. In humans, a strict association between mutations in some genes and alteration in sperm motility is not simple to...
Dyneins are motor proteins that convert the chemical energy contained in ATP into the mechanical energy of movement. The outer and inner DA are composed of heavy chains (HCs), intermediate chains (ICs), and light chains (LCs).\(^{116,117}\) The HC contains the motor machinery that is responsible for transducing chemical energy into directed mechanical force applied to the microtubule surface as it possesses the sites of both ATP hydrolysis and ATP-sensitive microtubule binding; the IC participates in the structural attachment of the DA to flagellar microtubules; and the LC participates in several functions, such as redox-sensitive vicinal dithiols, Ca\(^{2+}\)-binding, and intraflagellar transport. The variety of structure and function of these chains indicates that many regulatory mechanisms are present and needed for the proper sperm motility.\(^{118,119}\) Multiple dynein genes are found in the genomes of organisms with motile cilia and flagella.\(^{120}\)

At least, five human genes are known to encode for outer DA HC genes such as DNAH5 (dynein, axonemal, and heavy chain 5), DNAH8, DNAH9, DNAH11, and DNAH17. Relative to the inner DA, there are eight human genes such as DNAH1, DNAH2, DNAH3, DNAH6, DNAH7, DNAH10, DNAH12, and DNAH14. The intermediate and light chains are thought to contain at least five genes, including DNAI1 (dynein, axonemal, and intermediate chain 1), DNAI2, DNAI3 (dynein, axonemal, and light chain 1), DNAL1, DNAL11, and NME8 (NME/NM23 family member 8) (National Center for Biotechnology Information-NCBI-database-accessed in October 2014). As these chains regulate DA activity, mutations may result in abnormal ciliary ultrastructure and function and were already associated with syndromes such as PCD.\(^{114,117}\)

Another essential structure for sperm function is the dynein regulatory complex (DRC), which functions for dynein regulation and limitation of doublet sliding.\(^{121}\) Some components of the DRC serve primarily to regulate DA activity while others play a role in mediating structural interactions between the DA and the radial spokes.\(^{122,123}\) Four genes were identified as components of the DRC in humans such as DRC1 (dynein regulatory complex subunit 1), DRC7, CCDC39 (coiled-coil domain containing 39), and CCDC40.

The radial spokes and central pair complex are also essential for sperm function since they are important regulators of DA. Mutations that disrupt assembly of the central pair complex generally result in abnormal motility.\(^{124,125}\) Radial spokes and central pair complex are involved in converting simple symmetric bends into the asymmetric waveforms required for forward swimming and in the release of ATP inhibition in a controlled manner.\(^{126,127}\) In addition, the central pair may function as a distributor to provide a local signal to the radial spokes that selectively activates subsets of DA.\(^{128}\) In humans, it has been already described at least seven radial spokes proteins and its encoding genes are RSPH1 (radial spoke-head 1 homolog), RSPH3, RSPH4A, RSPH5, RSPH9, RSPH10B, and RSPH10B2 (NCBI and UniProt databases, accessed July 2014). One of the most known radial spokes genes is the RSPH1 gene that encodes a radial spoke-head protein that is mainly expressed in respiratory and testis cells. It is important for the proper building of the central pair complex and radial spokes, since mutations in RSPH1 lead to an abnormal axoneme configuration with central pair complex and radial spokes defects.\(^{129,130}\) Whereas mutations in RSPH4A and RSPH9 were associated with anomalies in central pair complex.\(^{120}\) Using next generation sequencing, mutations in CCDC39 and CCDC40 genes were also found among individuals with PCD with IDA and central pair complex defects.\(^{131}\)

As mitochondria provide part of the energy for motility, dysfunctions of the human mitochondrial sheath as well as of mitochondrial membrane integrity represent the main feature of sperm immotility.\(^{65,132}\) Mitochondrial DNA (mtDNA) mutations/deletions might have several implications to male fertility.\(^{133-136}\) The integrity and copy number of mtDNA were significantly correlated with sperm count and motility, as they were related to an increase of excessive ROS
formulation through increased lipid peroxidation in men presenting large-scale mtDNA deletions.135–139

In humans, the lack of the annulus causes a disorganization of the midpiece–principal piece junction with associated sperm immotility, altogether with mitochondrial structural and functional disability.140 Septins (SEPT) are essential structural components of the human annulus.141 It was shown that SEPT4 an SEPT12 are essential for the structural and mechanical integrity of sperm, including proper mitochondrial architecture and establishment of the annulus,141,142 and SEPT7 was shown to be involved in the regulation of sperm morphology and maturation.143 In patients with sperm immotility and annulus defects, a defective labeling for SEPT4 and/or SEPT7 was observed, and these proteins were suggested as biomarkers for monitoring the status of spermiogenesis and sperm quality.144

PREVENTIVE AND THERAPEUTIC APPROACHES TO IMPROVE SPERM MOTILITY

There is no present treatment to sperm immotility due to genetic causes. However, the quality of sperm, which includes sperm motility, can be protected. As discussed above, unhealthy lifestyle habits (recreational toxins, physical inactivity, and excessive use of personal technologies), specific toxic environmental exposures, and several pathologies related to endocrine and cardiovascular diseases are correlated with sperm oxidative stress and can be totally avoided.145–150

Other conditions that also increase sperm oxidative stress can be treated by surgery (varicocele)77 by the use of corticosteroids (presence of anti-sperm antibodies following chronic genital tract inflammations)151–153 and the correct and timely use of antibiotics for genital tract infections.154–156

Based on the knowledge that the human body developed an antioxidant system to keep ROS at an optimum level, several antioxidants have been used to improve sperm motility both in healthy157–158 and infertile men.159–160

For instance, Vitamin E is a potent peroxyl radical scavenger that functions as a chain-breaking antioxidant. This prevents the propagation of free radicals in membranes and plasma lipoproteins (prevents lipid peroxidation), and decreases the levels of malondialdehyde (an organic compound that is used as a marker for oxidative stress),160 thus improving sperm motility.159,160 Vitamin C (L-ascorbic acid) acts as a reducing agent by donating electrons to various enzymatic reactions. It protects against oxidative stress behaving as a scavenger of ROS (prevents lipid peroxidation). In addition, by recycling Vitamin E, it protects against DNA damage induced by the $H_2O_2$ radical. This molecule is also widely used in preventive treatments.159 Another example is Coenzyme Q10 (ubiquinone), which is a component of the electron transport chain in the mitochondrial respiratory chain. The energy generated is dependent on its availability in the human body. It is also an antioxidant that acts by stabilizing membranes and recycling Vitamin E. It is currently used for treatment of sperm immotility, especially in idiopathic asthenozoospermia.161

Hormonal agents and sperm vitalizers can also be used to improve sperm motility.162 For instance, pentoxifylline, a phosphodiesterase inhibitor, was shown to increase sperm motility163,164 by interfering with the metabolism of cAMP.165

However, although the use of these agents has been positively correlated with sperm motility,166 they can cause adverse effects.155 Consequently, more studies are needed to determine the optimal doses for each compound and establish a solid link with the desired effects.

CONCLUSIONS

This review has explored a little of the complex process underlying sperm motility, which has several pathways and genes involved. In a well-designed process, a minimal alteration may lead to male infertility. Besides preventive measures and some empirical therapies, there is the urgent need for developing a safe and directed therapy based on the genetic causes of sperm immotility and on the pathways that govern sperm motility.

AUTHOR CONTRIBUTIONS

RP Literature search; data analysis and interpretation; text writing. RS Critical discussion; manuscript critical review. AB Patient samples; critical review of the manuscript. MS Study conception and design; data analysis and interpretation; final text writing. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing financial interests.

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