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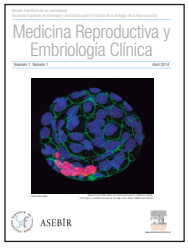

REVISIÓN

A molecular approach to sperm immotility in humans: A review

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Abstract
Reduced sperm motility represents one of the major male causes of infertility. Ultrastructural defects in the sperm flagellum caused by genetically inherited and congenital defects are one of the main causes to reduced sperm immotility. Several molecular components have been already associated to reduced sperm motility and more are expected to be discovered, especially with the application of Next-Generation Sequencing technology. In this review we will give emphasis to the main molecular components of the sperm flagellum associated to sperm motility. We will also discuss some of ultrastructural defects in structures of sperm flagellum and the two main genetic disorders that are associated with poor sperm motility: Primary Ciliary Dyskinesia and Dysplasia of the Fibrous Sheath, with reference to genes that are known to be involved in these disorders.

PALABRAS CLAVE
Inmovilidad espermática;
Flagelo espermático;
Disquinesia ciliar primaria;
Displasia de la vaina fibrosa

El enfoque molecular en la inmovilidad espermática humana: una revisión

Resumen
La reducción de la movilidad espermática constituye una de las principales causas de infertilidad masculina. Los defectos ultraestructurales en el flagelo, derivados de defectos genéticos y congénitos, son una de las principales causas de la inmovilidad espermática. Son varios los componentes moleculares asociados a una menor movilidad espermática y es de esperar que se descubran otros con la aplicación de nuevas técnicas de secuenciación. En esta revisión nos centraremos en los principales componentes moleculares del flagelo asociados a la movilidad. También analizamos algunos de los defectos ultraestructurales en la estructura del flagelo y los dos principales trastornos genéticos que se asocian a la movilidad espermática deficiente: la discinesia ciliar primaria y la displasia de la vaina fibrosa, con referencia a los genes involucrados en dichos trastornos.

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Introduction

The spermatozoon (Figs. 1A-1C) is divided into two fundamental parts, the sperm head and the sperm tail or flagellum. The main components of the sperm head are the nucleus, which contains the genetically material, and the acrosomal vesicle, which covers the anterior half of the head and contains crucial enzymes for the acrosomal reaction and is of great importance for fertilization. The flagellum is responsible for sperm motility and contains both the energy production site and the propulsive apparatus of the cell. The flagellum consists of four distinct segments: the neck piece (NP), the midpiece (MP), the principal piece (PP) and the end piece (EP). The NP contains the basal plate (BP), the proximal centriole (PC) and the striated/segmented columns (SC). The MP contains the axoneme (Ax), the outer dense fibers (ODF) and the mitochondria sheath. The PP contains the Ax, the ODF (proximal PP) and the fibrous sheath (FS: proximal and distal PP). The PP is separated from the MP by the annulus (An) that is a ring of dense material found at the end of the mitochondrial sheath. The EP contains only the Ax.[1,2]

The Axoneme

The Ax (Figs. 1D-1F) is the flagellar motor. Its basic structure is represented by a 9d+2s microtubule pattern, with a pair of central microtubules (MT), C1 and C2, which are surrounded by nine peripheral MT doublets. The Ax is surrounded by the ODF and then by mitochondria in the MP, by the ODF and then by the FS in the proximal PP, whereas in the distal PP it is only surrounded by the FS.[2]

The nine peripheral doublets are numbered 1 to 9 in a clockwise direction (number one is the one perpendicular to the central pair of MT). Each doublet consists of an internal complete MT, A, onto which is attached a second external and incomplete MT, B. Microtubule A has two dynein arms, outer (ODA) and inner (IDA). Doublets are linked to each other by nexin bridges and to the central pair of MT by the radial spokes. Nexin bridges act as a regulator of the dynein complex and structurally limits doublet sliding.[3] The two MT of the central pair are linked by a series of regularly spaced linkages (central bridge) and are surrounded by a fibrilar central sheath that are formed by a pair of spiral fibres attached to the central MT at the level of the connecting links. These constitute the central apparatus of the Ax.[1,4] Each MT doublet is externally anchored to 9 corresponding asymmetric ODF[1,4] that protect the tail against shearing forces encountered during epididymis transport and especially during ejaculation, but also during transit through the female genital tract.[5]

The molecular composition of flagellum components has been studied mainly in sperm from marine invertebrates and the biflagellate green algae *Chlamydomonas*. These showed that the molecular composition of the flagellum components is composed of approximately 250 proteins. The Ax is a sophisticated structure with a cytoskeleton, protein motors, molecular chaperones, regulatory elements such as Ca^{2+} binding proteins and protein kinases/phosphatases.[6,7].

Tubulins α and β are the main constituents of MT. These globular proteins of 50–55 kDa constitute 70% of the protein mass of the Ax.[8,9] Tubulins are often subjected to post-translational modifications, such as acetylation, palmitoylation, phosphorylation, polyglutamylation and polyglycation,[10] which are important for proper binding and assembly of the axoneme MT and motility.[11] For instance, polyglutamylation of α-tubulin plays a dynamic role in the dynein-based motility process.[12]

Another essential class of Ax proteins are dyneins. Dyneins are ATPases from a family of motor proteins that drive microtubule sliding in cilia and flagella.[13] These motor proteins convert the chemical energy contained in ATP into the mechanical energy of movement. Dyneins can be divided into two groups: cytoplasmic dyneins and axonemal dyneins. The axonemal dyneins are key elements to motility of eukaryotic cilia and flagella and comprise the ODA and the IDA. The ODA is composed of two heavy chains (HC), α and β; three to five intermediate chains (IC) and six light chains[6] (LC). It produces most of the force for flagellar movement.[14] The IDA are more complex, with eight distinct HC, which are organized with various IC and LC into seven different molecular complexes, one two-headed isoform and six single-headed isoforms.[15] The HC contain the motor machinery that is responsible for transducing chemical energy into directed mechanical force applied to the microtubule surface, possessing the sites of both ATP hydrolysis and ATP-sensitive microtubule binding.[16,17] The IC and LC are thought to be involved in binding dynein to MT-A.[16] They also help to specify the intracellular location of the dynein and regulate its motor activity.[17,18] In response to changes in motility they are also regulated through phosphorylation/dephosphorylation through a kinase/phosphatase system present in the radial spoke and central pair.[6]

The ODA Docking Complex (ODA-DC) is a structure that interacts directly with the ODA and is responsible for its assembly at regular intervals of 24 nm. It is also important as an intermediate in the binding of ODA to its unique attachment site within MT-A.[14] The ODA-DC contains three polypeptides (DC1-DC3). The DC1 and DC2 polypeptides potentially determines the 24-nm longitudinal spacing of the ODA.[14] The DC3 polypeptide has some important roles in the regulation of the ODA, playing a role in calcium-regulated ODA activity.[19]

The Dynein Regulatory Complex (DRC) is composed of six Ax proteins.[20] Studies using DRC mutants showed that some components of the DRC serve primarily to regulate activity, while others play a role in mediating structural interactions between dynein arms, the A-tubule of the outer doublet, and the radial spokes.[13,20] Recent studies using cryo-electron tomography, revealed that DRC forms a continuous connection from the A-tubule to the B-tubule of the neighbouring microtubule doublet.[3] This continuous connection and the finding that the DRC is the only structure besides the dynein arms that connects with adjacent outer doublets led the authors to suggest that the DRC is the nexin link and to propose the term nexin-DRC (N-DRC) to the DRC.[3]

The radial spokes and central pair are essential structures for the regulation of dynein arms.[21,22] Among other important roles, it was proposed that radial spokes and central apparatus may be involved in converting simple symmetric bends into the asymmetric waveforms required