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ЦИЛИОПАТИЙ: ЗАРАЖДАЮЩИЙСЯ КЛАСС ГЕНЕТИЧЕСКИХ РАССТРОЙСТВ ЧЕЛОВЕКА

THE CILIOPATHIES: AN EMERGING CLASS OF HUMAN GENETIC DISORDERS

АННОТАЦИЯ. Реснички и жгутики – древние, эволюционно консервативные органеллы, которые выступают из клеточных поверхностей, выполняют разнообразные биологические функции, в том числе передвижение всей клетки в соответствии строгого эволюционного порядка. Дефекты ресничек связаны с рядом заболеваний человека, таких как первичный цилиарный дискинезий, гидроцефалий, поликистоз почек и печени, и некоторые формы дегенерации сетчатки. Подобные дефекты могут привести к более широкому набору развития взрослых фенотипов, связанных с туберкулёзом почек, синдромом Барде - Бидля, синдромом Алстрёма и синдромом Меккеля-Грубера. Молекулярные данные, связывающие, по-видимому, несвязные клинические заболевания начинают выделять общую тему, где дефекты в

структуре и функциях ресничек могут привести к предсказуемому фенотипическому образцу, который имеет потенциально интеллектуальное и терапевтическое значение.

ABSTRACT. Cilia and flagella are ancient, evolutionarily conserved organelles that project from cell surfaces to perform diverse biological roles, including whole-cell locomotion; movement of fluid; chemo-, mechano-, and photosensation; and sexual reproduction. Consistent with their stringent evolutionary conservation, defects in cilia are associated with a range of human diseases, such as primary ciliary dyskinesia, hydrocephalus, polycystic liver and kidney disease, and some forms of retinal degeneration. Ciliary defects can lead to a broader set of developmental and adult phenotypes, with mutations in ciliary proteins now associated with nephronophthisis, Bardet-Biedl syndrome, Alstrom syndrome, and Meckel-Gruber syndrome. The molecular data linking seemingly unrelated clinical entities are beginning to highlight a common theme, where defects in ciliary structure and function can lead to a predictable phenotypic pattern that has potentially predictive and therapeutic value.

КЛЮЧЕВЫЕ СЛОВА: реснички, жгутики, биологические функции, дефекты, клетки.

KEY WORDS: cilia, flagella, biological roles, defects, cells.

Cilia in human disease

Although the architecture of cilia is much more complex than initially thought, a broad distinction can be made between motile and sensory functions. In some organisms, such as Chlamydomonas, cilia serve a dual role; in addition to motile functions, the alga's flagella are required for sensory transduction after flagellar adhesion during the mating process. When mating-type plus and minus gametes of algae mate, interactions between specific adhesion molecules localized to the flagella trigger a signaling cascade that results in an increase in cAMP and the formation of a zygote. In the fla10-1 mutant, which is defective in kinesin-II at the restrictive temperature of 32◦C, flagellar adhesion is normal but zygotes are not formed due to

the inability to increase the levels of cAMP as a response to the stimuli. Additionally, the UV-A/bluelight receptor phototropin, which controls the mating behavior of Chlamydomonas, localizes to the cell body but also the flagellum. In mammals, however, there appears to be a more discrete compartmentalization of motile and sensory functions, where balance has been achieved by the mixing of dedicated cilia within the same anatomical structure, such as the node presenting both types of cilia. Likewise, in the olfactory epithelium of most vertebrates sensory and motile cilia are present in discrete regions whereas in humans the two populations are interspersed. Phenotypically, there are some immediate distinctions and predictions that result from defects in each ciliary type.

Motile Cilia Dysfunction

The role of motile cilia in a number of physiological processes has been long recognized and thus the consequences of motile cilia dysfunction are perhaps more tractable and specific, with four major manifestations in mammals: early embryonic death due to failure of embryonic turning, respiratory dysfunction, reproductive sterility, and hydrocephalus. In the embryonic node, a group of motile primary cilia generates a leftward flow of extraembryonic fluid that is thought to generate the first cues to establish the left-right axis of symmetry. Furthermore, there appear to be two populations of cilia in this region of the embryo, one motile group generating the flow and a second, nonmotile group sensing it. Consequently, defects in ciliary motility can lead to left-right symmetry defects. This has now been shown in several mouse mutants. In the inversus viscerum (iv/iv) mouse, disruption of left-right dynein, an axonemal dynein heavy chain important for ciliary motility, results in immotile cilia and randomization of the left-right axis of symmetry, with 50% of embryos being normal and 50% presenting situs inversus. Complete absence of cilia in the node occurs when members of the heterotrimeric kinesin complex, fundamental in IFT, are compromised. Targeting of KIF3A and B in the mouse results in left-right defects, embryonic lethality, and developmental problems. Primary ciliary dyskinesia (PCD) (OMIM: 24,2650) is a group of heterogeneous disorders characterized by bronchiectasis, sinusitis, and infertility, with defects in

body situs being present in Kartagener syndrome (OMIM: 24,4400). As first described by Afzelius (1976) while studying individuals with immotile sperm, cilia in PCD patients lack dynein arms, as shown by electron microscopy, but can also present with other ultrastructural defects that result in impaired or inefficient motility. To date, mutations in a number of genes encoding components of the machinery required for ciliary motility have been reported in PCD and Kartagener syndrome. First, by filtering a candidate gene list with Chlamydomonas mutants that result in immotile animals with axonemal defects reminiscent of PCD (absence of outer dynein arms), Pennarun and colleagues identified mutations in DNAI1, a gene encoding a dynein intermediate chain. Mutations in DNAH5 and DNAH11 encoding two axonemal dynein heavy chains also cause PCD. Ciliary motility is also required for brain development and function. Cilia in the ependymal cell layer surrounding the ventricles maintain a flow of cerebrospinal fluid, the so-called "ependymal flow," necessary to maintain an open aqueduct. In Mdnah5 mouse mutants, the murine ortholog of DNAH5, a defect in the axonemal dynein heavy chain that is expressed in ependymal cells, leads to a deficiency in outer dynein arms and results in impaired ciliary beating . In the ependymal cell layer, this defective ciliary function translates into failure to produce "ependymal flow" resulting in closure of the cerebral aqueduct and the development of hydrocephalus, a condition associated with PCD in humans. The autosomal recessive mouse model of hydrocephalus (hy3) is caused by disruption of the gene Hydin, which encodes a protein expressed in the ciliated ependymal cell layer lining the ventricles, the ciliated epithelial cells in the respiratory tract and oviduct, and spermatocytes in the testis. Hydin is a novel protein that, based on its expression pattern and mouse phenotype, is a potential candidate for the pathogenesis of some human ciliopathies.

Sensory Cilia Defects

In contrast to the disorders of motile cilia, defects in sensory cilia appear to underlie a broad range of phenotypes, probably due to their nearly ubiquitous presence in almost every cell type of the human body and their emerging role in morphogenetic signal transduction.

Ciliary dysfunction in the retina.

Vertebrate photoreceptors are polarized sensory neurons composed of an inner and an outer segment connected by a highly specialized 9+0 cilium, the connecting cilium. Like other types of cilia, the synthesis of materials required for the formation, maintenance, and function of the outer segment occurs in the inner segment. Consequently, IFT is responsible for moving cargo across the connecting cilium, is critical for the survival of photoreceptor cells, and underlies the pathogenesis of at least some forms of retinal degeneration. For example, specific disruption of kinesin-II in photoreceptors leads to the accumulation of opsin and arrestin in the inner segment, resulting in an increased incidence of apoptotic cell death, a hallmark of RP. The requirement of delivering as many as 2000 photopigment molecules per minute to the mammalian outer segment might explain the sensitivity of photoreceptors to IFT defects. RP is a genetically heterogeneous group of retinal dystrophies that result in night blindness and progressive visual loss. The role of IFT in photoreceptor survival suggests that a number of candidate genes for RP would lie in the still poorly characterized group of moieties involved in the process, including both motors as well as cargo. Recent studies show that two proteins implicated in RP, RP1 and RPGR, localize predominantly to the photoreceptor-connecting cilium. RP1, commonly mutated in some forms of RP, shares a region of similarity with the microtubule-binding domain of doublecortin (DCX), a neuronal microtubuleassociated protein involved in neuronal migration. RP1 is a microtubule-binding protein that localizes to the photoreceptor axoneme and helps control its length and stability in vivo. Rp1 mutant mice present with misoriented outer segment discs, suggesting that an axonemal protein is involved in their organization, adding another layer of complexity to the role of cilia-associated proteins in the retina and the pathogenesis of RP. The RP guanosine triphosphatase (GTPase) regulator (RPGR) is essential for photoreceptor maintenance and viability and mutations in the human RPGR gene cause RP3. RPGR is concentrated in the connecting cilia of both cones and rods and its disruption in mice leads to the mislocalization of opsins, suggesting that RPGR may be involved in protein trafficking across the connecting

cilium. Some alleles of RPGR might also be involved in the function of motile cilia given that mutations in RPGR have been found in patients with RP and recurrent respiratory infections, a phenotype characteristic of PCD, with cilia exhibiting ultrastructural problems in the dynein arms and microtubule backbone. This association of defects characteristic of motile and sensory cilia are likely to be more common than expected, given the high overlap in protein content between the two types of cilia.

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