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Letter from the editor

CFTR and male fertility—Impact beyond cystic fibrosis

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The gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) was cloned in 1989[1,2] and its major mutation ΔF508 was identified in over 70% of patients with CF,[3] an autosomal recessive disease commonly found in Caucacian and Western populations. CF is characterized by a hallmark defect in electrolyte and fluid transport in almost all tissues with exocrine function, with a wide spectrum of clinical manifestations, including chronic lung disease, pancreas insufficiency, and infertility.[4] Although CFTR has been shown to be a cAMP-activated anion channels conducting both Cl^- and HCO_3^-,[5,6] our knowledge, 24 years after its discovery, is still limited on how mutations in the gene encoding this channel protein result in a multitude of disorders, including male infertility.

According to Taussing et al.,[7] over 97% of male CF patients are infertile. Early studies on CF adults with azoospermia revealed bilateral absence of the vas deferens and incomplete development of the epididymis in all patients examined.[8] Reporting similar findings, Holscalaw et al.[9] speculated a common genetic basis of CF and congenital bilateral absence of the vas deferens (CBAVD). Indeed, Dumer et al.[10] reported an increased frequency of the major *CFTR* mutation ΔF508 in azoospermia men with CBAVD, which was confirmed by several following studies, showing other *CFTR* mutations, in addition to ΔF508, associated with CBAVD.[11] It is generally accepted that CF male infertility is due to obstructive azoospermia with CBAVD as the major cause. It has been speculated that the structural changes in CF male reproductive tract are related to early obstruction by dehydrated secretion in the genial tract due to defective CFTR ion channel function. Thus, much of the early studies were focused on the role of CFTR in regulating epithelial ion and fluid secretion in the male genital tract, the epididymis in particular,[12] while the possible role of CFTR in other processes of male reproduction was not explored till recently.[13]

The first hint for broader impact of CFTR on human reproduction other than CBVAD in CF came from the screening study on 13 *CFTR* mutations showing increased mutation frequencies in a general population of men with reduced sperm quality.[14] A possible role of CFTR in sperm function was further suggested by the demonstrated involvement of CFTR in mediating uterine HCO_3^- secretion and its effect on the fertilizing capacity of sperm.[15] It was speculated that CFTR might also be present in sperm and mediate the HCO_3^- entry required for sperm motility and capacitation. Indeed, CFTR protein was found in mouse and human sperm and demonstrated to be important for the activation of the HCO_3^--dependent soluble adenylyl cyclase (sAC) and downstream cAMP/PKA signaling known to be involved in both sperm motility and capacitation.[16] Sperm from CF mice were shown to have reduced sperm motility and capacitation with reduced fertility rate in vitro and in vivo,[16] clearly indicating a role of CFTR in sperm functions. Interestingly, a recent study on aging Chinese males has also demonstrated that reduced sperm qualities, such as motility and fertilizing capacity, in aging sperm are associated with age-dependent downregulation of CFTR and impairment of CFTR/ HCO_3^--dependent cAMP signaling.[17] This finding further supports an important role of CFTR in normal sperm function that is beyond CBAVD and CF.

Conflicting results have been reported on testes of CF patients, with either normal spermatogenesis[18] or reduced sperm number,[8] casting doubts on whether CFTR may affect spermatogenesis. A recent study reported reduced testicular size in CF mice, suggesting defective spermatagenesis.[19] The study also showed that inhibition of CFTR in Sertoli cells or depletion of extracellular HCO_3^- could reduce FSH-stimulated, sAC-dependent cAMP production, and phosphorylation of CREB, the key transcription factor in spermatogenesis. This has demonstrated for the first time the involvement of CFTR in a signaling pathway important for regulating spermatogenesis. More importantly, downregulation of CFTR with abnormal CREB phosphorylation was observed in testicular samples from Chinese men with azoospermia,[19] again indicating a broader impact of CFTR on human reproduction beyond CBAVD and CF. More recently, CFTR has been demonstrated to be involved in regulating testicular tight junctions (TJs) through NFκB/COX-2/PGE2 pathway.[20] In that study, downregulation of CFTR accompanied by activation of NFκB, upregulation of COX-2 and downregulation of TJ proteins was observed in a cryptorchidism mouse model. Given the importance of TJs in spermatogenesis,[21] this finding provides a possible molecular mechanism underlying defective spermatogenesis observed in cryptorchidism. Interestingly, CFTR has recently been demonstrated to play a role in cancer development and metastasis.[22,23] This suggests possible additional roles of CFTR in the process of spermatogenesis, considering the similarities between cancer and male germ cell migration and survival.[24]

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What we have learnt about CFTR functions so far indicates that CFTR has far- reaching effect on many aspects of male reproduction, with impacts well beyond CBAVD and CF. Ironically, although CBAVD was the first abnormality in the male genital tract reported to be associated with *CFTR* mutations, we still know very little how *CFTR* mutations lead to CBAVD or abnormal development of the male genital tract. While CFTR was found to be expressed throughout the entire genital tract,[25] we are yet to know its exact role in most of the male accessory glands other than the epididymis. Although the role of CFTR as a Cl^- channel in the male reproductive system is best studied in the epididymis, how the CFTR-mediated Cl^- secretion is related to sperm maturation in the epididymis remains elusive. Similarly, although *CFTR* mRNA in spermatids was first detected 20 years ago, its role in male germ cells remains unclear. What we know for certain is that CFTR does not merely act as a simple ion channel, but also a versatile signaling molecule and an important regulator, as suggested by its name and its predicted interactions with more than 180 other proteins. Future investigation into the molecular actions of CFTR will not only advance our understanding of how *CFTR* mutations lead to male infertility in CF, but also the role and impact of CFTR on a wide range of physiological functions, including spermatogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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