The cystic fibrosis transmembrane conductance regulator (CFTR) is an anion channel regulated by cAMP-dependent phosphorylation, which is expressed in epithelial cells of a wide variety of tissues including the reproductive tracts. Mutations in the gene encoding CFTR cause cystic fibrosis, a common genetic disease in Caucasian populations with a multitude of clinical manifestations including infertility/subfertility in both sexes. However, the physiological role of CFTR in reproduction and its involvement in the pathogenesis of reproductive diseases remain largely unknown. This review discusses the role of CFTR in regulating fluid volume and bicarbonate secretion in the reproductive tracts and their importance in various reproductive events. We also discuss the contribution of CFTR dysfunction to a number of pathological conditions. The evidence presented is consistent with an important role of CFTR in reproductive health and disease, suggesting that CFTR might be a potential target for the diagnosis and treatment of reproductive diseases including infertility.
absence of obvious anatomical abnormalities in the female reproductive tract, except thick and tenacious cervical mucus with altered water and electrolyte content (Kopito et al. 1973; Oppenheimer et al. 1970), has led to the general belief that abnormal mucus contributes to the reduced fertility of CF women by acting as a barrier to sperm passage. However, the exact role of CFTR in reproductive physiology and the contribution of CFTR dysfunction to infertility in both sexes are far from understood. This is surprising because CFTR expression along the entire length of both reproductive tracts has been known for a long time (Trezise & Buchwald, 1991; Tizzano et al. 1994). Here, we review the function of CFTR in reproductive physiology and discuss the molecular mechanisms underlying various reproductive events and disorders causing reproductive disease or infertility.

Role of CFTR in reproductive physiology

Regulation of fluid volume – implications for sperm transport and blastocyst implantation. While the fluids in both male and female reproductive tracts are important for a series of reproductive events, their basic function is to carry or transport sperm produced by the testis to their final destination in the oviducts or the fallopian tubes where they meet the egg for fertilization. During their transit through both male and female reproductive tracts, sperm are surrounded by a luminal fluid varied in volume and composition, which is created by the epithelia lining different regions of both reproductive tracts. As an apical Cl\(^{-}\) channel expressed along both reproductive tracts, CFTR plays a key role in regulating Cl\(^{-}\) secretion, and thus fluid volume. In the male system, extensive studies have been carried out on primary cultures of rat epididymal epithelial cells, demonstrating functional expression of CFTR and its involvement in the regulation of Cl\(^{-}\) secretion and fluid formation in the epididymis (for review, see Wong, 1998). Under basal conditions, the epididymis generally reabsorbs fluid to concentrate sperm. However, the observation that neurohormonal factors stimulate CFTR-mediated Cl\(^{-}\) secretion by epididymal epithelia (Wong, 1998) suggests that epididymal fluid secretion may be stimulated to create the optimal fluid environment for sperm maturation, storage, and even transport during ejaculation. CFTR expression and its involvement in mediating neurotransmitter-stimulated anion secretion have also been demonstrated in a porcine vas deferens epithelial cell line, consistent with a role of CFTR in promoting fluid secretion for sperm transport (Carlin et al. 2006). CFTR is expressed in the Sertoli cells of the testis, but the biophysical properties of CFTR in mature rat Sertoli cells show some differences from the human CFTR Cl\(^{-}\) channel (Boockfor et al. 1998). Interestingly, short-circuit current measurements on primary cultures of Sertoli cell epithelia from immature rats demonstrate large increases in Cl\(^{-}\) secretion in response to extracellular ATP, but only small increases in response to cAMP agonists (Ko et al. 1998), excluding a primary role of CFTR in regulating Cl\(^{-}\) and fluid secretion in the seminiferous epithelium, at least at early developmental stages. It is possible that CFTR is not fully expressed at this early stage. Alternatively, fluid formation in the testis may be regulated by a CFTR-independent mechanism. In fact, non-CFTR Cl\(^{-}\) channels have recently been identified in Sertoli cells from immature rats (Auzanneau et al. 2006). Further studies are required to clarify the role of CFTR in the testis, particularly in Sertoli cells.

More than 80 years ago, large fluctuations in uterine fluid volume were first observed during the oestrous cycle of the rat, with a maximal fluid volume observed during prooestrus and oestrous and a minimum at dioestrus (Evans & Long, 1922). Similar cyclic changes in fluid volume were also observed in the cervical mucus of humans, with the absence of the mid-cycle surge in water and electrolytes reported in CF patients (Kopito et al. 1973). This observation, made long before the cloning of CFTR, might now be interpreted to suggest that CFTR regulates fluid volume in the female reproductive tract. While CFTR is expressed in almost all parts of the female reproductive tract, including the vagina, cervix, uterus and fallopian tubes, in rodents and humans (Chan et al. 2002; Tizzano et al. 1994), most evidence supporting its functional role has been obtained from primary cultures of mouse endometrial epithelial cells (for review, see Chan et al. 2006, 2007). Functional data acquired using the patch-clamp and short-circuit current techniques in conjunction with pharmacological agents indicate a key role of CFTR in regulating uterine fluid volume (for details, see Chan et al. 2006, 2007).

The observed oestrous cycle-dependent expression of CFTR, i.e. at prooestrus in the vagina and cervix, and at oestrus in the uterus, is consistent with the cyclic profile of ovarian hormones. Stimulation of CFTR expression by oestrogen both in vivo and in vitro (Rochwerger & Buchwald, 1993; Rochwerger et al. 1994) has also been demonstrated and down-regulation of CFTR by progesterone reported (Mularoni et al. 1995). The ovarian hormone-dependent regulation of CFTR expression provides a physiological basis for the cyclic change in fluid volume. Interestingly, CFTR is found to be coexpressed with the epithelial sodium channel, ENaC, in an out-of-phase fashion in the uterus, i.e. high expression of CFTR, but low ENaC expression at oestrus and low CFTR expression, but high ENaC expression at dioestrus (Chan et al. 2002). This may explain maximal fluid secretion during the early phase of the oestrous cycle when the level of oestrogen is at its highest. Similarly, down-regulation of CFTR to attenuate fluid production and up-regulation of ENaC...
to increase the rate of reabsorption may account for the disappearance of uterine fluid observed at dioestrus. The negligible expression of CFTR at dioestrus may further augment ENaC function to facilitate fluid reabsorption, because CFTR has also been shown to act as a negative regulator of ENaC (Stutts et al. 1995; Chan et al. 2001). The out-of-phase coexpression of CFTR and ENaC in the uterus may be of physiological significance. While maximal CFTR expression at oestrus may enable a higher rate of uterine fluid production to facilitate sperm transport, as well as sperm capacitation via HCO$_3^-$ (see below), down-regulation of CFTR and up-regulation of ENaC at metoestrus and dioestrus may reduce the fluid

Figure 1. Role of CFTR in regulating fluid volume and HCO$_3^-$ secretion in mouse uterus/oviduct with functional implications in various reproductive events (e.g. sperm transport, capacitation, embryo development and blastocyst implantation)

Cl$^-$ and HCO$_3^-$ are accumulated in the cell by basolaterally located Na$^+$–K$^+$–2Cl$^-$ (NKCC) and Na$^+$–HCO$_3^-$ contransporter (NBC), respectively, with Na$^+$–K$^+$–ATP as the battery. HCO$_3^-$ can also be produced by CO$_2$ hydration catalysed by carbonic anhydrase (CA) with basolateral H$^+$ extrusion by a Na$^+$/H$^+$ exchanger (NHE). Cl$^-$ is secreted into the lumen through CFTR while HCO$_3^-$ can be secreted by CFTR and/or anion exchanger (SLC26A6). Water flow following the electrolyte gradient into the lumen facilitates sperm transport while secreted HCO$_3^-$ can promote capacitation of sperm in the lumen. Fluid reabsorption may take place when epithelial sodium channel (ENaC) is up-regulated (e.g. during implantation). Increasing HCO$_3^-$ concentrations from the uterus to oviduct, as indicated by the changing colour of the lumen, provides an optimal microenvironment for sperm capacitation, fertilization and embryo development to take place in the oviduct.
Regulation of bicarbonate secretion – implications for sperm capacitation. Mammalian sperm are unable to fertilize eggs until they undergo an activation process, known as capacitation, in the female reproductive tract (Chang, 1951). The luminal fluid environment of the female reproductive tract is considered critical for sperm to acquire their final fertilizing capacity. Although several factors, including Ca^{2+} and high density lipoprotein, have been considered likely to mediate capacitation (Evans & Florman, 2002), recent studies have suggested that HCO_{3}^{-} plays a central role in sperm capacitation by directly activating a bicarbonate-sensitive soluble form of adenylyl cyclase (sAC) (Chen et al. 2000; Cann, 2004) that may control a number of phosphorylation events leading to sperm capacitation (Visconti et al. 1999). In fact, HCO_{3}^{-} is present at much higher concentrations, ranging between 35 and 90 mM, in the female reproductive tract than in many other tissues (Vishwakarma, 1962), suggesting that it plays an important role in modulating sperm function in the female reproductive tract. Our recent studies demonstrate that CFTR, as well as an apically located anion exchanger, are responsible for HCO_{3}^{-} secretion into the lumen of the mouse uterus (Wang et al. 2003), while a basolaterally located Na^{+}–HCO_{3}^{-} cotransporter and Na^{+}/H^{+} exchanger are responsible for HCO_{3}^{-} uptake and H^{+} extrusion (Fig. 1). The details of this model have been reviewed elsewhere (Chan et al. 2006, 2007). The importance of the CFTR-mediated HCO_{3}^{-} secretion in sperm capacitation is further demonstrated by an epithelium–sperm coculture system, the details of which are described below (see Infertility in cystic fibrosis).

As for the oviduct, where high HCO_{3}^{-} content is also found and in vivo sperm capacitation and fertilization most likely to occur, no detailed studies of its HCO_{3}^{-} transport mechanisms have been reported. However, since CFTR is functionally expressed in the oviduct (Chan et al. 2002), it may also contribute to the high HCO_{3}^{-} content of the oviduct. Results from our recent studies strongly suggest an oviductal HCO_{3}^{-} secretory mechanism similar to that observed for the endometrial epithelium, involving both CFTR and a Cl^{-}/HCO_{3}^{-} exchanger (Chen et al. unpublished data). Therefore, CFTR-mediated HCO_{3}^{-} secretion, either in the uterus or oviduct, may be required to support sperm capacitation. The concurrent secretion of Cl^{-} and HCO_{3}^{-} by CFTR (Chan et al. 1997) and maximal expression of CFTR, together with other HCO_{3}^{-} transporters, at oestrus (He et al. unpublished data) suggest that CFTR promotes not only Cl^{-} and fluid secretion to facilitate sperm transport, but also HCO_{3}^{-} secretion to enable sperm capacitation at a time immediately before ovulation. The coordinated sequence of events prior to the final meeting of the gametes, which largely depends on CFTR, appears to hold the key to the success of fertilization (Fig. 1).

Regulation of bicarbonate entry into sperm – implications for sperm function. It is now clear that the regulatory effect of HCO_{3}^{-} on capacitation is mediated by sAC (Chen et al. 2000), which is distinct from the G protein–regulated, transmembrane adenylyl cyclases (tmACs). sAC is located inside the membrane and possesses no transmembrane domains, and thus it cannot be activated by extracellular HCO_{3}^{-} (Chen et al. 2000). Therefore, it is of interest to know how HCO_{3}^{-} gains access to the interior of the sperm, since membrane permeability to HCO_{3}^{-} is generally thought to be low in many cell types (the exception being erythrocytes). The transport mechanism underlying the entry of HCO_{3}^{-} into the sperm membrane remains controversial. Several mechanisms have been proposed, including a Cl^{-}/HCO_{3}^{-} exchanger (Spira & Breitbart, 1992) and a Na^{+}–HCO_{3}^{-} cotransporter (Demarco et al. 2003).

The demonstrated dependence of sperm capacitation on the HCO_{3}^{-} content of the uterine tract and the ability of CFTR to conduct HCO_{3}^{-} prompted us to hypothesize that CFTR may also be expressed in sperm, where it plays a role in mediating HCO_{3}^{-} entry important for the fertilizing capacity of sperm. In a recent study (Xu et al. 2007), we examined the possible involvement of CFTR in HCO_{3}^{-} transport into sperm. We detected CFTR expression in both human and mouse sperm by immunostaining and Western blotting. Moreover, either CFTR_{inh}-172 or a monoclonal CFTR antibody against the C-terminus significantly reduced sperm capacitation, and the associated HCO_{3}^{-}-dependent events including increases in intracellular pH (pH_{i}), cAMP production and membrane hyperpolarization. The fertilizing capacity of the sperm obtained from heterozygous CFTR mutant mice was also significantly lower as compared to that of the wild-type mice. These results suggest that in sperm CFTR may be involved in the transport of HCO_{3}^{-} important for sperm capacitation. However, it remains unknown whether CFTR is directly or indirectly involved in HCO_{3}^{-} entry. Given that Na^{+}–2HCO_{3}^{-} cotransport by pNBC1 or Na^{+}–3HCO_{3}^{-} transport by kNBC1 cannot cause HCO_{3}^{-} influx at a membrane potential more negative than −80 mV (Gross et al. 2001; Kurtz et al. 2004) and that CFTR is unlikely to mediate a higher inward than outward pH gradient at hyperpolarized membrane potentials, none of these transporters seem capable of directly mediating HCO_{3}^{-} entry into sperm during capacitation. Alternatively, SLC26A3, which mediates 2Cl^{-}/HCO_{3}^{-} in an appropriate Cl^{-} gradient (Shcheynikov et al. 2006), appears to be the most likely transporter to load HCO_{3}^{-} into sperm during capacitation. Indeed, we have recently discovered that capacitation in guinea pig sperm requires Cl^{-} as well as HCO_{3}^{-} (Chen et al. 2008), suggesting the involvement of a Cl^{-}/HCO_{3}^{-} exchanger for HCO_{3}^{-} entry into sperm. We have further demonstrated the expression of SLC26A3 in guinea pig sperm and the inhibition of
sperm capacitation by an SLC26A3 antibody (Chen et al. 2008). Thus, CFTR appears to play an important role in mediating HCO$_3^-$ entry into sperm by working in parallel with SLC26A3 and providing a recycling pathway for Cl$^-$ (Fig. 2). Considering the fact that a number of sperm functions, including motility, hyperactivation, capacitation and acrosome reaction, depend on HCO$_3^-$ (Neill & Olds-Clarke, 1987; Sabeur & Meizel, 1995; Esposito et al. 2004), CFTR appears to have a profound role in regulating sperm function.

**Involvement of CFTR in pathological conditions of the reproductive tracts**

The involvement of CFTR in defining the fluid micro-environment crucial for a series of reproductive events suggests its paramount importance. This can also be highlighted by disorders or diseases with disturbed reproductive events or infertility resulting from CFTR dysfunction or unphysiological activity of CFTR.

**Infertility in cystic fibrosis.** Women with CF are known to have reduced fertility, but the cause remains obscure. As discussed above, thick cervical mucus was thought to be the cause of reduced fertility in CF women. However, the role of CFTR in mediating uterine HCO$_3^-$ secretion and the critical role of HCO$_3^-$ in spermatozoa function, especially sperm capacitation, led us to propose an alternative hypothesis: defective CFTR-mediated HCO$_3^-$ secretion might lead to impaired sperm fertilizing capacity and thus reduced fertility in CF women. To test this hypothesis, Wang et al. (2003) used a mouse sperm-endometrial epithelial cell coculture system. The percentage of capacitated sperm was significantly attenuated when CFTR expression in the cocultured endometrial epithelial cells was suppressed with antisense against CFTR, or when sperm were cocultured with CFTR defective epithelia. In vitro fertilization assays on zona-intact mouse eggs further demonstrated that the number of two-cell embryos obtained with sperm capacitated in conditioned medium from CFTR antisense-treated endometrial cells was significantly reduced as compared to that obtained from sense-treated controls. Taken together, these results suggest that CFTR-mediated uterine HCO$_3^-$ secretion is important for sperm capacitation and that impaired HCO$_3^-$ secretion caused by defective CFTR results in reduced sperm fertilizing capacity. These results provide an alternative explanation for the reduced fertility of

![Figure 2. Involvement of CFTR in the HCO$_3^-$ entry is necessary for sperm capacitation](image-url)

HCO$_3^-$ entry is mediated by SLC26A3 with an exchange of 2Cl$^-$/HCO$_3^-$. CFTR, apart from its reported role in conducting HCO$_3^-$ directly, may act as a Cl$^-$ channel to provide a recycling pathway for Cl$^-$, which is required for the operation of SLC26A3. The HCO$_3^-$-dependent events, including activation of soluble adenylate cyclase (sAC), leading to sperm capacitation are also shown. CNG: cyclic nucleotide-gated channels.
CF women. In fact, clinical studies on CF women undergoing assisted reproduction showed that in some cases pregnancy could only be achieved with in vitro fertilization but not with sperm insemination (Epelboin et al. 2001). These clinical cases suggest defects beyond the cervix in CF women leading to infertility, which is consistent with our findings. It appears that impaired HCO$_3^-$ secretion along the female tract due to defects in CFTR or its regulation (neural or hormonal) might also be the cause of some unexplained cases of female infertility because other reproductive events, such as embryo development, are also known to be dependent on HCO$_3^-$ (Zhao et al. 1995). It should be noted that recent evidence from CF mouse models suggests that infertility in CF females is multifactorial, including aberrant oestrous cycles and decreased oocyte ovulation rates, raising the possibility that CFTR is involved in these processes (Hodges et al. 2008).

While CF males are infertile mostly due to CBAVD and obstructive azoospermia, studies have reported a higher prevalence of CFTR gene mutations in otherwise healthy men presenting with reduced sperm quality as compared with controls with normal sperm parameters (van der Ven et al. 1996). Cuppens & Cassiman (2004) report that mutations are identified in about 80% of the CFTR genes isolated from CBAVD patients. Moreover, a recent study demonstrated that the frequency of CFTR heterozygosity in infertile males is twofold higher than in the general population (Schulz et al. 2006). These results suggest that CFTR mutations may result in other forms of male infertility than CBAVD. This notion is supported by the demonstrated functional expression of CFTR in spermatids, suggesting its role in spermiogenesis (Gong et al. 2001). Together with the recently demonstrated involvement of CFTR in mediating HCO$_3^-$ entry into sperm (see above), these data provide a biological rationale for poor sperm quality in men with CFTR mutations. This may unravel the mysteries surrounding many unexplained cases of male infertility, considering the fact that more than 1500 mutations have been identified in the CFTR gene (The Cystic Fibrosis Mutation Database, http://www.genet.sickkids.on.ca/cftr/). It is therefore reasonable to propose that CFTR may be considered as a potential target for diagnosis of male and female infertility of unknown aetiology.

**Ovarian hyperstimulation syndrome.** Increasing numbers of women with fertility problems seek solutions through assisted reproduction. Ovarian hyperstimulation syndrome (OHSS) is one of the most life-threatening complications of assisted reproduction treatments, arising from excessive stimulation of the ovaries by exogenous gonadotropins administered during in vitro fertilization procedures. OHSS is characterized by massive fluid shift and accumulation in the peritoneal cavity and other organs, including the lungs and the reproductive tract. The pathogenesis of OHSS remains obscure, and no definitive treatments are currently available. We suspected that rapid passage of fluid into luminal spaces, as seen in OHSS, may be a consequence of abnormal ion transport across epithelia. Because excessively high levels of oestrogen are well documented in OHSS (Manau et al. 1998) and known to up-regulate CFTR (Rochwerger & Buchwald 1993; Rochwerger et al. 1994), we therefore hypothesized that abnormally up-regulated CFTR expression and function may be the cause of OHSS. In an OHSS rat model, OHSS symptoms as well as up-regulated CFTR expression and enhanced CFTR channel activity were observed, which could be mimicked by administration of oestrogen alone, but not progesterone, in ovariectomized rats. Administration of progesterone that suppresses CFTR expression or antisera against CFTR to OHSS animals resulted in alleviation of the symptoms. Furthermore, ovarian hyperstimulation did not induce detectable OHSS symptoms in CFTR mutant mice, confirming the involvement of CFTR in the pathogenesis of OHSS (Ajonuma et al. 2005b). Thus, we have demonstrated a pathological condition caused by abnormally up-regulated CFTR with increased channel activity leading to excessive fluid accumulation in different organs. This suggests that OHSS resembles secretory diarrhoea, a condition caused by hyperactivation of CFTR (Kunzelmann & Mall, 2002), but it contrasts markedly with CF, a disease caused by CFTR dysfunction (Quinton, 1999).

**Hydrosalpinges and bacterial infection.** Hydrosalpinx (HSP) is characterized by abnormal fluid accumulation in the Fallopian tubes, with unknown aetiology, but is generally caused by bacterial infections. Although HSP accounts for about 30% of tubal factor infertility, it has received little attention. The apparent fluid disturbance in HSP led us again to hypothesize that CFTR might be involved in its pathogenesis since CFTR is expressed in the cervix in CF women leading to infertility, which is consistent with our findings. It appears that impaired HCO$_3^-$ secretion along the female tract due to defects in CFTR or its regulation (neural or hormonal) might also be the cause of some unexplained cases of female infertility because other reproductive events, such as embryo development, are also known to be dependent on HCO$_3^-$ (Zhao et al. 1995). Together with the recently demonstrated involvement of CFTR in mediating HCO$_3^-$ entry into sperm (see above), these data provide a biological rationale for poor sperm quality in men with CFTR mutations. This may unravel the mysteries surrounding many unexplained cases of male infertility, considering the fact that more than 1500 mutations have been identified in the CFTR gene (The Cystic Fibrosis Mutation Database, http://www.genet.sickkids.on.ca/cftr/). It is therefore reasonable to propose that CFTR may be considered as a potential target for diagnosis of male and female infertility of unknown aetiology.
CFTR expression observed in HSP patients. In fact, recent studies show that C. trachomatis inoculated into healthy Sprague–Dawley rat uteri induced uterine infection, massive uterine fluid accumulation (as seen in HSP) and increased CFTR mRNA expression (Ajonuma et al. 2008). These data support the notion that infection may lead to up-regulation of CFTR with concomitant changes in ion flux across the fallopian tubal epithelium accompanied by increased fluid accumulation resulting in HSP. We further speculated that cytokines released during infection may be responsible for up-regulation of CFTR since some of them, such as interleukin (IL)-1β, are known to be potent modulators of CFTR expression (Cafferata et al. 2000). Indeed, administration of IL-1β to the peritoneal cavity up-regulated uterine CFTR expression with increased uterine wet-weight, mimicking HSP (Ajonuma et al. 2008). These results suggest that abnormally up-regulated CFTR is responsible for the formation of HSP fluid.

It should be noted that pelvic inflammatory disease, which is caused by bacterial infection, is the most common cause of infertility worldwide. However, the exact cause of infertility, as in the case of C. trachomatis infection, remains largely unknown. As discussed earlier in this review, the dynamic changes in the fluid microenvironment, particularly the fluid volume, in the female reproductive tract are dictated by CFTR expression, which is normally regulated by ovarian hormones throughout the cycle accommodating various reproductive events. Abnormal up-regulation of CFTR with fluid accumulation upon bacterial infection, especially at the time of implantation when CFTR expression level and luminal fluid volume are normally at their lowest, may prevent ‘closure’ of the luminal surface and hence, blastocyst implantation failure. We have tested this hypothesis by administrating a large dose of oestrogen to mice 24 h before implantation, which induced 100% implantation failure with obvious fluid accumulation in the uterus (He et al. unpublished data). Therefore, accumulation of HSP fluid in the fallopian tubes and its regurgitation into the uterine cavity may be a contributing factor to the observed infertility of HSP patients, with impaired implantation or endometrial receptivity of transferred embryos during IVF (Mansour et al. 1991).

Bacterial infection also contributes to male infertility with the majority of cases unexplained, apart from obvious bacterial toxicity. It seems possible that abnormal up-regulation of CFTR by bacterial infection may also play a role in infection-induced male infertility. For example, if CFTR is abnormally up-regulated in the epididymis where fluid should normally be reabsorbed to concentrate sperm, diluted semen with insufficient sperm count may result in infertility, as seen in the oestrogen receptor knockout mice with swollen epididymis due to a failure to reabsorb fluid in an oestrogen receptor-dependent manner (Hess et al. 2000). However, this notion will require confirmation from further studies.

**Future directions**

Recent investigations into the role of CFTR in reproductive health and disease have made it clear that CFTR plays a key role in regulating fluid volume and composition and that defects in CFTR expression and function may lead to disturbance of the fluid environment resulting in various pathological conditions and infertility. However, our understanding of the function of CFTR in reproductive physiology and pathophysiology is far from complete and there are still many interesting avenues of research into its role in various reproductive processes, such as spermatogenesis, oogenesis, embryo development, as well as reproductive tract host defence since HCO₃⁻ has also been implicated in bacterial killing. Another interesting line of research is the significance of the interaction between CFTR and ENaC in various reproductive events such as during blastocyst implantation. Some of these questions are actively being pursued in the authors’ laboratory. We expect our results to enhance the understanding of the far-reaching effects of CFTR on human reproduction and provide new methods for diagnosis and treatment of reproductive diseases and infertility as well as possible strategies for contraception.

**References**


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