313 Cystic Fibrosis

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CLINICAL FEATURES

Cystic fibrosis (CF) is an autosomal recessive exocrinopathy affecting multiple epithelial tissues. The gene product responsible for CF (the cystic fibrosis transmembrane conductance regulator [CFTR]) serves as an anion channel in the apical (luminal) plasma membranes of epithelial cells and regulates volume and composition of exocrine secretion. An increasingly sophisticated understanding of CFTR molecular genetics and membrane protein biochemistry has facilitated CF drug discovery, with a number of new agents advancing through the clinical testing phase.

Respiratory Manifestations The major morbidity and mortality associated with CF is attributable to respiratory compromise, characterized by copious hyperviscous and adherent pulmonary secretions that obstruct small and medium-sized airways. CF airway secretions are exceedingly difficult to clear, and a complex bacterial flora that includes *Staphylococcus aureus, Haemophilus influenzae*, and *Pseudomonas aeruginosa* (among other pathogens) is routinely cultured from CF sputum. Robust pulmonary inflammation in the setting of inspissated mucus and chronic bacterial infection leads to collateral tissue injury and further aggravates respiratory decline. Organisms such as *P. aeruginosa* exhibit a stereotypic mode of pathogenesis; a sentinel and early colonization event often engenders lifelong pulmonary infection by the same genetic strain. Over the course of many years, *P. aeruginosa* evolves in CF lungs to adopt a mucoid phenotype (attributable to release of alginate exoproduct) that confers selective advantage for the pathogen and poor prognosis for the host. Infection with other bacterial organisms such as *Burkholderia cepacia* also indicates a less favorable pulmonary outlook. Strategies to eradicate organisms such as *P. aeruginosa* early in the pathogenesis cascade have been successful and are thought to improve prognosis significantly if sustained.

Pancreatic Findings The complete name of the disease, *cystic fibrosis of the pancreas*, refers to profound tissue destruction of the exocrine pancreas, with fibrotic scarring and/or fatty replacement, cyst proliferation, loss of acinar tissue, and ablation of normal pancreatic architecture. As in the lung, tenacious exocrine secretions (sometimes termed *concretions*) obstruct pancreatic ducts and impair production and flow of digestive enzymes to the duodenum. The sequelae of exocrine pancreatic insufficiency include chronic malabsorption, poor growth, fat-soluble vitamin insufficiency, high levels of serum immunoreactive trypsinogen (a diagnostic test used in newborn screening), and loss of pancreatic islet cell mass. CF-related diabetes mellitus is a manifestation in over 30% of adults with the disease and is likely multifactorial in nature (attributable to progressive destruction of the endocrine pancreas, insulin resistance due to stress hormones, and other factors).

Other Organ System Damage As in CF lung and pancreas, thick and tenacious secretions compromise numerous other exocrine tissues. Obstruction of intrahepatic bile ducts and parenchymal fibrosis are commonly observed in pathologic specimens, with multilobular cirrhosis in 4–15% of patients with CF and significant hepatic insufficiency as a resulting manifestation among adults. Contents of the intestinal lumen are often difficult to excrete, leading to meconium ileus (a presentation in approximately 10–20% of newborns with CF) or distal intestinal obstructive syndrome in older individuals. Men typically exhibit complete involution of the vas deferens and infertility (despite functioning spermatogenesis), and approximately 99% of males with CF are infertile. The etiology of this dramatic anatomic defect in the male genitourinary system is not understood but may represent a developmental abnormality secondary to secretory obstruction of the vas. Abnormalities of female reproductive tract secretions are likely contributors to an increased incidence of infertility among women with CF. Radiographic evidence of sinusitis occurs in most CF patients and is associated with pathogens similar to those recovered from lower airways, suggesting that the sinus may serve as a reservoir for bacterial seeding.

PATHOGENESIS

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) CFTR is an integral membrane protein that functions as an epithelial anion channel. The ~1480-amino-acid molecule encodes a passive conduit for chloride and bicarbonate transport across plasma membranes of epithelial tissues, with direction of ion flow dependent on the electrochemical driving force. Gating of CFTR involves conformational cycling between an open and closed configuration and is augmented by hydrolysis of adenosine triphosphate (ATP). Anion flux mediated by CFTR does not involve active transport against a concentration gradient but utilizes the energy provided from ATP hydrolysis as a central feature of ion channel mechanochemistry and gating.

CFTR is situated in the apical plasma membranes of acinar and other epithelial cells where it regulates the amount and composition of secretion by exocrine glands. In numerous epithelia, chloride and bicarbonate release is followed passively by the flow of water, allowing for mobilization and clearance of exocrine products. Along respiratory mucosa, CFTR is necessary to provide sufficient depth of the periciliary fluid layer (PCL), allowing normal ciliary extension and mucociliary transport. CFTR-deficient airway cells exhibit depleted PCL, causing ciliary collapse and failure to clear overlying mucus **(Video 313-1)**. In airway submucosal glands, CFTR is highly expressed in acini and may participate both in the formation of mucus and extrusion of glandular secretion onto the airway surface **(Fig. 313-1)**. In other exocrine glands characterized by abrogated mucus transport (e.g., pancreatic acini and ducts, bile canaliculi, intestinal lumen), similar pathogenic mechanisms have been implicated. In these tissues, a driving force for apical chloride and/or bicarbonate secretion is believed to promote CFTR-mediated fluid and electrolyte release into the lumen, which confers proper rheology of mucins and other exocrine products. Failure of this mechanism disrupts normal hydration and transport of glandular secretion and is widely viewed as a proximate cause of ductular obstruction, with concomitant tissue injury.

Pulmonary Inflammation and Remodeling The CF airway is characterized by an aggressive, unrelenting, neutrophilic inflammatory response with release of proteases and oxidants leading to airway remodeling and bronchiectasis. Intense pulmonary inflammation is largely driven by chronic respiratory infection. Macrophages resident in CF lungs augment elaboration of proinflammatory cytokines, which contribute to innate and adaptive immune reactivity. CFTR-dependent abnormalities of airway surface fluid composition (e.g., pH) have been reported as contributors to impaired bacterial killing in CF lungs. The role of CFTR as a direct mediator of inflammatory responsiveness and/or pulmonary remodeling represents an important and topical area of investigation.

MOLECULAR GENETICS

DNA sequencing of *CFTR* from patients (and others) worldwide has revealed almost 2000 allelic variants; however, only about 10% of these have been well-characterized as disease-causing mutations. Distinguishing the single nucleotide transversions or other polymorphisms with causal relevance often presents a significant challenge. The CFTR2 resource (*www.cftr2.org/*) delineates gene variants with a clear etiologic role.

CFTR defects known to elicit disease are often categorized based on molecular mechanism. For example, the common F508del mutation (nomenclature denotes omission of a single phenylalanine residue [F] at CFTR position 508) leads to a folding abnormality recognized by cellular quality control pathways. CFTR encoding F508del retains partial ion channel function, but protein maturation is arrested in the endoplasmic reticulum, and CFTR fails to arrive at the plasma membrane. Instead, F508del CFTR is misrouted and undergoes endoplasmic reticulum–associated degradation via the proteasome. CFTR mutations that disrupt protein maturation are termed class II defects and are by far the most common genetic abnormalities. F508del alone accounts for ~70% of defective *CFTR* alleles in the United States, where