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CFTR: a missing link between exocrine and endocrine pancreas?

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Cystic fibrosis (CF), a life-shortening hereditary disease mainly afflicting people of Caucasian origins, is caused by loss-of-function mutations in the CFTR (Cystic Fibrosis Transmembrane conductance Regulator) gene, which encodes a phosphorylation-activated, but ATP-gated anion channel expressed primarily in epithelial cells. To date, nearly 2000 mutations have been identified as pathogenic, but the deletion of a single amino acid phenylalanine at position 508 (i.e., deltaF508) accounts for ~70% of all disease-associated mutations and thus is present in at least one allele of ~90% of patients with CF. This mutation not only decreases the number of functional CFTR molecules in the plasma membrane due to defective folding of the deltaF508-CFTR protein, but also disrupts ATP-dependent opening and closing (or gating) of the CFTR channel for the minor fraction of deltaF508-CFTR channels that do reach and stay in the cell membrane. While currently there is no cure for this debilitating disease, in the past decades, tremendous efforts have been committed to developing reagents that may help CFTR folding (i.e., correctors) or gating (i.e., potentiators). Recent successes in the discovery of an effective CFTR potentiator VX-770 (or Ivacaftor) and in its subsequent clinical trials not only establish an important precedent for realizing personalized medicine but also may serve as a stepping-stone for attaining the eventual goal of curing CF [1].

The CFTR protein, a member of the ATP Binding Cassette (ABC) Transporter Superfamily, plays a pivotal role in transepithelial anion secretion and absorption in human body. In a host of exocrine tissues, activation of CFTR in the apical membrane of epithelial cells establishes an electric potential that drives the transepithelial movement of a counter ion such as sodium. The osmotic driving force arising from this transepithelial salt movement effects an ultimate isotonic secretion into the lumen of the exocrine gland. Thus, loss of CFTR function by CF-associated mutations results in exocrine malfunction manifested in patients' airways, intestines, reproductive tracts, pancreas, and sweat glands.

As an anion channel, CFTR also serves as a major pathway for the secretion of bicarbonate in the pancreas, and hence dysfunction of the CFTR channel suffices to account for exocrine pancreatic abnormities in patients with CF. However, cystic fibrosis-related diabetes (CFRD), a comorbidity found in ~50% of adult CF patients, is an endocrine disorder that gravely affects the clinical outcomes of CF. Besides this practical consideration of CFRD in CF mortality and morbidity, the pathogenesis of CFRD is of interest in its own right. Although the causes for abnormal glucose metabolism in CFRD may be multifactorial, it is generally held that a diminished insulin secretion due to loss of pancreatic β-cells in patients with CF is secondary to inflammation, fibrosis and destruction of the exocrine pancreas [2]. A recent study by Chan's lab however may shift this paradigm and shed new light in the pathogenesis of CFRD [3].

In this report, the authors presented evidence for the existence of a cAMP-activated chloride conductance in isolated mouse β-cells. This whole-cell anion conductance shows all the hallmarks of CFTR and yet interestingly re-

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sponds to glucose, the physiological stimulus for insulin secretion. The mechanism underpinning glucose-induced insulin secretion has been well established previously: Glucose increases cellular [ATP], which depolarizes the membrane potential by closing ATP-sensitive potassium channels. A depolarized membrane potential subsequently activates voltage-gated calcium channels to increase intracellular [Ca], the final trigger for fusion of insulin-containing vesicles with the plasma membrane. However, in Guo et al. [3], pharmacological inhibition of CFTR not only hyperpolarizes the resting membrane potential, but also dramatically reduces the glucose-induced membrane depolarization, indicating that basal CFTR activities play a critical role in determining the membrane potential in β-cells. Indeed, the observation that CFTR inhibitors effectively abolish glucose-induced membrane electrical activity and considerably reduce insulin secretion implicates an essential physiological function of CFTR in β-cells.

Guo et al. [3] also took advantage of the CF mouse model by extending their studies to include β-cells isolated from mice carrying the deltaF508 mutation. This line of investigation further confirms an indispensible role of CFTR in β-cell function and insulin secretion. More importantly, if these results in mouse cells can be replicated in human β-cells, it means that pharmaceutical correction of CFTR dysfunction will surely lead to symptomatic improvement in patients afflicted by CFRD. Moreover, as the authors implied in the report, the demonstration of a role of CFTR in insulin secretion also opens a new direction of research towards a better understanding of the pathogenesis of diabetes in general, which constitutes a major health issues in the developed world.

This work by Guo et al. [3] also bears significance far beyond its clinical implications in CF and diabetes. From a basic science angle, the study unveils several pertinent issues warranting further investigations. First, abnormal glucose metabolism is not regularly seen in CF mice or pigs, and even in human, CFRD is normally not observed in newborns and the incidence of CFRD increases as patients age. However, a recent study reported abnormal endocrine pancreas function at birth in CF ferrets [4]. It is therefore interesting to find out the mechanism underlying this apparent species difference in the pathogenesis of CFRD. Second, in an intact cell, CFTR's channel activity is usually thought to be mainly controlled by cAMP-dependent protein phosphorylation, while ATP-dependent gating does not play an active regulatory role as cellular [ATP] is nearly always maintained at a maximally effective concentration for CFTR gating. The observation that glucose can drastically modulate CFTR chloride conductance in β-cells suggests that a unique regulatory mechanism for CFTR gating is in place in these cells. Is the CFTR protein undergoing specific post-translational modification in β-cells? Or do they interact with β-cell specific associated proteins? Third, it has been shown that a volume-regulated anion conductance (VRAC) is involved in modulating the membrane excitability of β-cells [5]. Clearly the relative roles of VRAC and CFTR in insulin secretion await further illumination.

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