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CFTR in GtoPdb v.2025.3

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Abstract

CFTR is a member of the ABC transporter superfamily, but, uniquely, it is an ion channel, allowing electrodiffusion of Cl^- and $HCO3^-$. It is activated by phosphorylation, mainly by PKA on its regulatory domain (R domain). Conserved nucleotide binding domains (NBD1 and NBD2) couple ATP binding and hydrolysis to gate opening and closing, respectively [8]. CFTR is expressed apically in polarized epithelial cells in various organs where it controls volume and pH of fluid secretions as well as mucin unfolding and release [26]. CFTR transcripts are present in secretory and ionocyte cells in airway epithelia [29, 33], crypt enterocytes, goblet and CFTR-high expressing cells in the intestine [5, 3], pancreatic duct cells [13], intra- and extra-hepatic cholangiocytes 33318612 [48] and others.
Mutations in the CFTR gene cause the genetic disease cystic fibrosis (CF) [38]. The most common mutation, F508del, is present in at least one gene copy in ~80% of patients worldwide, but there are ~1000 different variants known to cause CF. Mutations affect CFTR biogenesis (folding, maturation, trafficking, metabolic stability) and/or ion-channel function. Vertex Pharmaceuticals developed small-molecule CFTR modulator drugs that improve biogenesis ("correctors") or open probability ("potentiators") of defective CFTR variants. Triple combination therapies, including two correctors and one potentiator (*e.g.* Trikafta®: elexacaftor, tezacaftor, ivacaftor), are standard of care for patients carrying at least one copy of the F508del variant. Patients carrying mutations only affecting ion-channel function ("gating mutations" *e.g.* G551D) are treated with ivacaftor (potentiator) alone. Cryo-EM structures of Trikafta-bound F508del-E1371Q-CFTR reveal that all three compounds bind at the protein-membrane interface, in shallow pockets on CFTR's surface [14].
While low/absent CFTR activity causes CF, over-activation of CFTR (due to bacterial toxins such as cholera toxin) results in secretory diarrhoeas, causing large intestinal loss of fluid and alkali [11]. No inhibitors have been approved yet for emergency treatment of secretory diarrhoeas.

Contents

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- Channels and Subunits
  - CFTR
    https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=707

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