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Paper Title : **Cell Biology**

Unit 3 : **Cell Signaling**

Module Name :- **Cystic fibrosis transmembrane conductance regulator (CFTR)**

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NOTES

CFTR stands for Cystic fibrosis transmembrane conductance regulator. It is a membrane protein that serves as a chloride channel in vertebrates. It is involved in the conduct of chloride ions across epithelial cell membranes. It is encoded by the CFTR gene. It belongs to family of ABC transporter-class ion channel proteins. Mutations of the CFTR gene affecting chloride ion channel function lead to dysregulation of epithelial fluid transport in the lung, pancreas and other organs, resulting in cystic fibrosis. Complications include thickened mucus in the lungs with frequent respiratory infections, and pancreatic insufficiency giving rise to malnutrition and diabetes. The CFTR is found in the epithelial cells of many organs including the lung, liver, pancreas, digestive tract, and the female and male reproductive tracts. In the airways of the lung, CFTR is most highly expressed by rare specialized cells called pulmonary ionocytes. In the skin CFTR is strongly expressed in the sebaceous and eccrine sweat glands.

The CFTR gene is located on the long arm of chromosome 7, at position q31.2, and ultimately codes for a sequence of 1,480 amino acids. The CFTR gene is approximately 189 kb in length, with 27 exons and 26 introns. CFTR is a glycoprotein with 1480 amino acids. The protein consists of five domains. There are two transmembrane domains, each with six spans of alpha helices. These are each connected to a nucleotide binding domain (NBD) in the cytoplasm. The first NBD is connected to the second transmembrane domain by a regulatory "R" domain that is a unique feature of CFTR, not present in other ABC transporters. The ion channel only opens when its R-domain has been phosphorylated by PKA and ATP is bound at the NBDs.

CFTR functions as a phosphorylation and ATP-gated anion channel Channel opening is activated by phosphorylation of the R domain by a protein kinase, which in turn is activated by an increase in cyclic AMP (cAMP), a small intracellular signaling molecule. Opening of the channel also requires sequential binding of two ATP molecules to the two NBD domains. ATP-drives conformational changes in CFTR which allow opening and closing of ion channel ATP binds to both NBD, causes NBD dimerization, rearrangement of helices, exposes cargo binding site to outward facing position, outward chloride movement.

Cystic Fibrosis is caused due to defective CFTR gene Autosomal recessive disease Mutation: ΔF5O8 – deletion of Phenyl alanine at 508 position Characterized by thickening of mucous layer, clogging of airways in lungs and recurrent bacterial infection.