What is CF?

Cystic fibrosis (CF) is a lung-affecting autosomal recessive genetic disorder. It is characterised by breathing difficulties due to production of viscous thick secretion which, in turn, is a result of abnormalities in the transport of chloride ions across epithelial membranes. Although other organs such as intestine, pancreas and liver can be affected as well, the effect of CF on the lungs is the most severe and leads to multiple lung infections (Ratjen and Döring, 2003).

The underlying course of the CF is the mutations in the gene encoding for cystic fibrosis trans-membrane conductance regulator (CFTR) protein. This protein is an ion channel that transports chloride ions across the cell membrane in epithelial cells. Mutations affect the ability of protein to perform this function thus leading to reduced flow of chloride ions from the cells. This results in the build-up of thick mucus within the lungs.

The CFTR gene is complex. It contains 27 exons and codes for 1480 residues long polypeptide (Sheppard and Welsh, 1999). Alternative splicing mechanisms take place in different tissues resulting in formation of different isoforms of protein. The structure of protein is equally complex. CFTR protein has 5 domains: two trans-membrane domains each containing 6 alpha helices, nucleotide binding domain (NBD), regulatory domain (R-domain) and C-terminal PDZ-interacting domain. The latter domain connects the protein to cytoskeleton (Short et al., 1998).

Like other ion channels, CFTR does not actively transport ions but opens and close the gate allowing ions to flow in the direction of electrochemical gradient. The gate opens due to conformational changes that occur in response to the binding of ATP to the NBD domain.

How mutations in CFTR cause CF?

Mutations in CFTR lead to CF as a result of conformational changes in the protein leading to its inability to regulate the ions flow in response to various signals.

Cystic Fibrosis is one of the most common genetic disorders in humans. One in 24 people is a carrier of mutation in the CFTR gene. Frequency and nature of mutations varies significantly between different ethnic groups (Bobadilla et al., 2002). CF-causing mutations are more frequent among Caucasians.

Almost 2000 mutations in CFTR gene are connected with cystic fibrosis (Sosnay et al., 2013). The most frequent mutation affecting 66% of CF patients is ΔF508. This is a deletion of three nucleotides that form a codon for phenylalanine at position 508 of CFTR protein. The lack of this single amino acid causes defects of processing of CFTR protein. Around one third of all CF patients have this mutation but its frequency varies from 50 to 70% in different populations. Other mutations are much less common. None of them accounts for more than 5% of carriers.

Around 3% of patients with clinical manifestations of CF do not have identified mutations. This may indicate that genetic alteration in CFTR is not the only possible

mechanism for development of this disease, and other mechanisms can be at work to cause the same symptoms. Involvement of various gene expression regulators in such cases is hypothesized (Castellani et al., 2008).

Importance of the C-termini of the CFTR for stability of the protein

Relatively small 100 amino acids long C-terminal PDZ-interacting domain of CFTR protein plays key role in anchoring CFTR to the actin cytoskeleton and thus immobilizing protein at the certain position on the cell membrane (Haggie et al., 2006). The C-terminal domain also plays important role in maturation and stability of the protein towards degradation (Gentzsch and Riordan, 2001). The stability of protein is influenced by interactions of C-terminal domain with protein NHERF1. Mutations in C-terminal domain may affect its conformation and thus result in the lack of proper interaction with NHERF1 (Guerra et al., 2005).

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