

Curcumin and Cystic Fibrosis Defects: A Spicy Treatment

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Cystic fibrosis (CF) is an inherited disorder that causes severe damage mostly to the lungs but also the digestive system including pancreas, liver, kidneys and intestine. In this disease the secretory fluids mucus, sweat and digestive juices become thick and sticky. Instead of acting as a lubricant, the secretions plug up tubes, ducts and passageways, especially in the lungs and pancreas. CF is most common in white people of Northern European ancestry, but also occurs in Hispanics, African-Americans and some Native Americans and rare in Asian. The disease occurs in 1 in 2,500 to 3,500 white newborns and affecting 70,000 people worldwide [1]. Genetically, it is caused by the presence of mutations in both copies of cystic fibrosis transmembrane conductance regulator (CFTR) gene, which involved in production of fluids and electrolytes [2]. The most common mutation is DeltaF508 (deletion of a phenylalanine in position 508) that results in the production of a misfolded CFTR protein. This mutant protein retained in the endoplasmic reticulum and further targeted for degradation by proteasome instead of making its way to the plasma membrane and forming a chloride channel.

Therapeutic strategies have been developed to enhance processing of the defective deltaF508 CFTR molecule so that a functional ion channels translocate to the target cell membrane [3]. Therefore, compounds that enhance either the function or biosynthetic processing of the CFTR chloride ion channel may be of value in developing new treatments for CF. Curcumin, derived from the spice turmeric, has antioxidant, anti-inflammatory, anticancer, antimicrobial and other activities [4]. However it has also shown to correct defects associated with the homozygous expression of DeltaF508 CFTR through modulating multiple molecules, which include chaperones, ATPases, ions, channels, and others.

There are several attempts have been made to provide molecular "chaperones" to transport the abnormal CFTR to cell membrane through the endoplasmic reticulum (ER). Because some chaperone proteins are dependent on high calcium levels, thus reducing the calcium levels in the endoplasmic reticulum might liberate the mutant CFTR, and increasing the chances to reach cell surface. Sarco/endoplasmic reticulum calcium ATPases (SERCAs) are known to require for the active transport of calcium into the ER. Therefore, it hypothesized that the suppression of SERCA could reduce the level of calcium and further transportation of abnormal CFTR to the plasma membrane. Curcumin was reported a weak but safe SERCA inhibitor in a CF mouse model. It was found to correct electrolyte abnormalities and prevent intestinal obstruction [5]. As an inhibitor of the SERCA, curcumin was shown to correct CF defects in some model systems, whereas others have reported no or little effects on CF after curcumin treatment, suggesting that curcumin effect is not due to simple inhibition of the Ca(2+)-ATPase. Therefore, other members of the P(2)-type ATPase superfamily have been studied and found involvement of Na,K-ATPase activity, which is inhibited by curcumin treatment. Curcumin decreased the apparent affinity of Na,K-ATPase for K(+) and increased it for Na(+) and ATP [6]. However, studies also failed to reproduce that curcumin corrects CF through inhibition of SERCA [7]. It was shown that curcumin could not induce maturation of deltaF508 CFTR, or induce Cl⁻ secretion, as observed in a variety of model systems ranging from cultured cells to in vivo studies [3].

The deltaF508 mutation also shown to disrupt the opening of

CFTR channels, even they reach the cell surface. Thus, CF therapies may also require the use of channel openers to activate mutant CFTR channels at the cell surface [8]. In a study, curcumin has shown to influence channel function. Curcumin increased CFTR channel activity by reducing channel-closed time and prolonging the channels opened time through the increased phosphorylation of channels in presence of ATP. Curcumin also increased the activity of wild-type as well as DeltaF508 channels [9]. Moreover, curcumin opened CFTR channels without the requirement of either ATP or the second nucleotide-binding domain (NBD2), indicating this compound is potent also on those that are defective for the normal ATP-dependent mode of gating and channels that lack NBD2. This is possibly mediates through the R domain that can modulate channel opening without affecting ATP binding to the NBDs or their heterodimerization [10]. Besides these, recent studies have revealed that many channels and transporters are modulated by curcumin, such as voltage-gated potassium (Kv) channels, high-voltage-gated Ca(2+) channels (HVGCC), volume-regulated anion channel (VRAC), Ca(2+) release-activated Ca(2+) channel (CRAC), aquaporin-4 (AQP-4), glucose transporters, etc. [11]. Curcumin reversibly inhibited the Kv1.4K+ [12]. Curcumin increased G551D-CFTR whole-cell and single-channel currents [13]. These studies indicate that curcumin regulates CFTR channels, which is critical for the treatment of CF.

Retention of mutant CFTR in the ER is dependent on chaperone proteins. Most of the chaperones like calnexin require calcium for optimal activity. Thus limiting the ER calcium level could inhibit the F508del-CFTR/calnexin interaction and to restore the cAMP-dependent CFTR chloride transport to correct abnormal trafficking. Curcumin maintains a threshold level of calcium that facilitates F508del-CFTR transport activity [14]. Other ER chaperone calreticulin has also shown to negatively regulate the CFTR cell surface expression and activity. Curcumin suppressed calreticulin expression and increased wild-type CFTR but did not affect DeltaF508 CFTR expression ([15]). These suggest curcumin's efficacy against CF through modulation of chaperones proteins.

The keratin 18 (K18) network is also implicated in DeltaF508-CFTR trafficking. Curcumin restores a functional DeltaF508-CFTR to the plasma membrane acting via the K18 network. This curcumin-mediated phenomenon occurs by a remodeling of the K18 network and a significant increase in K18 Ser52 phosphorylation [16]. Curcumin has also shown effect on cross-linking CFTR polypeptides into SDS-resistant oligomers. Both mature CFTR polypeptides at the cell surface and immature CFTR protein in the endoplasmic reticulum were cross-

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linked by curcumin, although the latter pool was more susceptible to this modification. Curcumin cross-linked two CF mutant channels (Delta F508 and G551D) as well as a variety of deletion constructs that lack the major cytoplasmic domains [17]. These crosslinking could be helpful in correcting CF.

Besides curcumin, poly lactic-co-glycolic acid (PLGA) nanoparticles encapsulated with has also synthesized and used to correct the defects associated with CF by improving bioavailability of the compound. It has been found that oral administration of curcumin PLGA nanoparticles enhances the effects of curcumin therapy in CF mice, as compared to delivery of nonencapsulated curcumin [18].

Curcumin also potentiates CFTR activation in normal cells. It enhances CFTR activation in an ATP-independent but phosphorylation-dependent manner [19]. Curcumin potentiates the phosphorylation-dependent activity of human CFTR in a Fe^{3+} -dependent as well as Fe^{3+} -independent manners. The Fe^{3+} -dependent curcumin potentiation results from removal of endogenous inhibitory Fe^{3+} at the interface of the regulatory (R) domain and intracellular loop (ICL) 3. It has also shown a spontaneous disulfide crosslinking between curcumin-sensitive ICL1 and S795 that promote channel opening by curcumin. Thus, curcumin potentiates CFTR activity not only by removing inhibitory Fe^{3+} to release the R domain from ICL3 but also by inducing or stabilizing the stimulatory R-ICL1/ICL4 interactions [20].

From these reports it is clear that curcumin has efficacy to correct the F508del-CFTR processing defect, suggesting a novel potential therapeutic agent against CF. Curcumin modulates various molecules associated with translocation, opening of CFTR channel and function of mutated CFTR as well as it increases CFTR activation in non-mutated cells. Although attempt has made to improve the efficacy of curcumin by synthesizing nanoparticles, more effective and bioavailable analogues and derivatives of curcumin are needed to fully realize its potential. Since curcumin is safe, effective and affordable, designing a drug based on curcumin is also very much desired. However, more in vitro, animal and clinical trials are warranted.

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