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Cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels are essential mediators of salt transport across epithelia. Channel opening normally requires ATP binding to both nucleotide-binding domains (NBDs), probable dimerization of the two NBDs, and phosphorylation of the R domain. How phosphorylation controls channel gating is unknown. Loss-of-function mutations in the CFTR gene cause cystic fibrosis; thus, there is considerable interest in compounds that improve mutant CFTR function.

Here we investigated the mechanism by which CFTR is activated by curcumin, a natural compound found in turmeric. Curcumin opened CFTR channels by a novel mechanism that required neither ATP nor the second nucleotide-binding domain (NBD2). Consequently, this compound potently activated CF mutant channels that are defective for the normal ATP-dependent mode of gating (e.g. G551D and W1282X), including channels that lack NBD2. The stimulation of NBD2 deletion mutants by curcumin was strongly inhibited by ATP binding to NBD1, which implicates NBD1 as a plausible activation site.

Curcumin activation became irreversible during prolonged exposure to this compound following which persistently activated channels gated dynamically in the absence of any agonist. Although CFTR activation by curcumin required neither ATP binding nor heterodimerization of the two NBDs, it was strongly dependent on prior channel phosphorylation by protein kinase A.

Curcumin is a useful functional probe of CFTR gating that opens mutant channels by circumventing the normal requirements for ATP binding and NBD heterodimerization. The phosphorylation dependence of curcumin activation indicates that the R domain can modulate channel opening without affecting ATP binding to the NBDs or their heterodimerization.

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