Computer simulations point to key molecular basis of cystic fibrosis

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Researchers from the University of North Carolina at Chapel Hill have identified a key molecular mechanism that may account for the development of cystic fibrosis, which about 1 in 3000 children are born with in the US every year. The findings, published February 29 in the open-access journal *PLoS Computational Biology*, add new knowledge to understanding the development of this disease and may also point the way to new corrective treatments.

Cystic fibrosis (CF) is a fatal disease caused by a defective gene that produces a misshapen form of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. People with cystic fibrosis do not have enough CFTR for their cells to work normally because their bodies quickly destroy the mutant protein. The deletion of this protein specifically occurs in a major domain of CFTR called NBD1. Earlier experimental studies have shown that the mutant NBD1 has an increased tendency to misfold, resulting in the premature degradation of CFTR.

In CF, the molecular basis of this increased misfolding tendency has remained elusive, said team leader Nikolay Dokholyan.

“Understanding molecular etiology of the disease is a key step to developing pharmaceutical strategies to fight this disease,” Dokholyan said.

Using molecular dynamics simulations, the researchers performed extensive simulations of how normal and mutant NBD1 folded.

Molecular dynamics simulation is akin to a “virtual experiment” wherein atoms and molecules are allowed to evolve according to known physical laws. Using computers, this virtual experiment allows researchers to view how atoms actually move. These simulations, when applied to the NBD1 protein, showed that the disease-causing mutant exhibits a higher misfolding tendency.

More importantly, by comparing the structures of the normal and the mutant NBD1 domains as they fold, the authors were able to determine critical pairs of amino acid residues that must come together for NBD1 to fold correctly. These interactions are modulators of CFTR folding, and hence, they are potential modulators of CF.

“Computer simulations approximate our understanding of natural phenomena. That our simulations correlated with known experimental studies is remarkable,” Dokholyan said. “More importantly, the molecular details of aberrant NBD1 folding provides guidance for the design of small molecule drugs to correct the most prevalent and pathogenic mutation in CFTR.”

Citation: Serohijos AWR, Hegedu½ s T, Riordan JR, Dokholyan NV (2008) Diminished Self-Chaperoning Activity of the DF508 Mutant of CFTR Results in Protein Misfolding. PLoS Comput Biol 4(2): e1000008. doi:10.1371/journal.pcbi.1000008 (www.ploscompbiol.org/doi/pcbi.1000008)

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