What is the potential of Lumacaftor as a chemical chaperone in promoting hERG trafficking?

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Abstract

Lumacaftor (LUM), approved by the FDA for the treatment of cystic fibrosis(CF), has shown great therapeutic potential in protein conformational diseases. As a chemical chaperone, LUM corrects the F508del CFTR mutation and increases the expression of chloride channels on the alveolar cell membrane. After Mehta et al's research, the selectivity of LUM has been challenged. In human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), LUM has been also confirmed to be effective against heterozygous mutants (type II mutations) that cause cardiac hERG protein trafficking defects, which can clinically lead to long QT syndrome type 2 (LQT2). The effect of LUM in hERG protein reverses the clinical phenotype of LQT2. Recent studies have shown that LUM has an effect on more similar mutants in the hiPSC-CMs cells rather than heterologous TSA201 cells, among which may lead to more severe clinical phenotypes. Besides, comparing the negative effects of LUM in other hERG mutants and the different effects on mutations at the same site, what is the therapeutic potential and stereoselectivity of LUM for protein conformational diseases? And what this therapeutic effect should be attributed to requires further understanding.

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