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Prokaryote remedy to genetic misfolding diseases: Inactivated bacterial subunit toxoids block ER associated degradation of misfolded proteins to rescue the phenotype

Statement of the Problem: Many (>30) genetic diseases result from a single amino acid or small mutation which leaves considerable residual activity but induces a degree of misfolding of the mutant protein which targets it for endoplasmic reticulum associated degradation (ERAD), resulting in the complete loss of mutant protein activity. ERAD, rather than the mutation per se, precipitates disease symptoms.

Methodology & Theoretical Orientation: Several pathogenic bacterial protein subunit toxins have evolved to hijack ERAD as a means for A subunit access to the cytosol where the pathological effect becomes manifested. These toxins e.g. cholera toxin, shiga toxin, use the same ER translocon as is used in ERAD. Indeed the A subunit contains a C terminal sequence which mimics an unfolded protein. Such toxins provide a basis for the direct control of the ERAD translocon and hence temporarily block ERAD to rescue the mutant protein and ameliorate disease symptoms. We have inactivated the catalytic A subunit activity and added a hydrophobic C terminal addition to generate toxoids which reverse disease symptoms in cell and animal models

Findings: Cholera toxin and shiga toxin with a 0, 9 or 18 polyleucine tail, were able to partially block ERAD of F508del CFTR cystic fibrosis cells and G370S GCC Gaucher disease cells and increase CFTR mediated chloride transport and GCC glucocerobrosidase activity in these cells and their mouse models without significant induction of ER stress.

Conclusion & Significance: These benign prokaryotic toxoids represent a new means to treat a large number of inherited diseases

Speaker Biography

Clifford Lingwood completed his PhD at the University of London in 1974, and Post-doctoral studies at the Universities of Washington and Toronto. He has been a Full Professor at the University of Toronto since 1997 and is a Senior Scientist within the Molecular Medicine Program of the Research Institute at the Hospital for Sick Children, Toronto. His research program is concerned with the biochemistry, chemistry, metabolism and function of glycosphingolipids with a view to the therapy of diseases in which they are involved. He has published more than 200 papers in reputed journals.

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