Selective Small Molecule Activators of the Apoptotic Arm of the Unfolded Protein Response

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Technology description

The invention involves the successful development of a first-in-class, potent, not generally cytotoxic, chemical probe, that selectively activates the apoptotic but not the adaptive arm of the Unfolded Protein Response.

Overview

Tremendous advances in our understanding of pathologic mechanisms have recently revealed that defective protein processing within the secretory pathway is an integral component of many genetic and environmental diseases. Diverse disease states ranging from diabetes, Alzheimer’ s disease, and Parkinson’ s disease, to hemophilia and lysosomal storage diseases have all been characterized by folding defects or impaired transport from the endoplasmic reticulum (ER). Very recently it has come to light that deregulation of protein synthesis may be a key component in the pathogenesis of cancer and metastasis. When misfolded protein accumulates in the ER lumen, the cell activates the Unfolded Protein Response (UPR) to clear the malfolded proteins and restore homeostatic protein processing. When a stress is prolonged or robust the UPR employs a genetic pathway that results in cell death. Current research into the UPR is focused on identification and characterization of drug-like small molecule regulators of two distinct arms of the UPR. This aim is predicated on the hypothesis that the adaptive arm of the UPR can be pharmacologically overwhelmed and lead to a productive CHOP-mediated apoptotic response in human cancer cells.

How it works

The probe and associated analogs demonstrate efficacy in inducing cell death through activation of the apoptotic arm in relevant cells. Additionally, these molecules activate genes associated with the apoptotic arm of the UPR. These molecules may serve as tool compound for activation of the apoptotic arm of UPR as a therapeutic modality in certain diseases.

Application area

Pharmaceutical companies interested in selective cancer cell death

Researchers interested in selectively activating the apoptotic arm of the UPR
Companies interested in research and development of drugs used to treat diabetes, Alzheimer’s, Parkinson’s, hemophilia, and lysosomal storage diseases

Advantages

Demonstrated efficacy in inducing cell death in targeted cells
Compounds are first-in-class, potent, and selectively targeted towards pathogenic cells

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