INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

GRP78 Inhibitors and Degraders for the Treatment of Cancer, Viral Infection, and Inflammatory Diseases

TECHNOLOGY NUMBER: 2021-276

OVERVIEW

An anti-cancer agent that is non-toxic and overcomes therapeutic drug resistance

- GRP78 inhibition disrupts endoplasmic reticulum homeostasis and induces apoptosis
- A new class of agents that affects ER functioning in immune and cancer cells

BACKGROUND

The endoplasmic reticulum (ER) is a multifunctional cellular organelle responsible for the proper folding of newly synthesized proteins, degradation of misfolded proteins, and maintenance of cellular homeostasis. Cells which are subject to intrinsic stress activate the unfolded protein response (UPR) to mitigate the consequences of ER stress and to maintain cellular homeostasis. UPR can either mitigate the deleterious effects of ER stress or then can activate programmed cell death, or apoptosis. Glucose-regulated protein (GRP78) is a key molecular chaperone in the ER and also serves as a master regulator of ER stress signaling. Cancer cells are highly proliferative and have a greater demand for protein synthesis and folding. Additionally, cancer cells are subject to extrinsic stress in the cancer microenvironment including hypoxia, low pH, and nutrient deprivation. Such conditions contribute to ER stress and impaired ER functions, altering GRP78 functioning. GRP78 regulates UPR by activating ER transmembrane sensors and play important roles in regulating various cellular process required for tumor survival and growth. Thus, redirecting the UPR response to apoptosis in cancer cells is a promising approach for cancer therapy. A need exists to selectively influence the UPR response to promote apoptosis in cancer cells.

INNOVATION

Researchers at the University of Michigan have identified GRP78 inhibitors that¬†function as effective therapeutic agents for treating cancer. The inhibition of GRP78 disrupts ER homeostasis and suppresses its anti-apoptotic properties, providing an avenue to overcome resistance to multiple anti-cancer agents. One GRP78 inhibitor, YUM 70, demonstrates synergy with the FDA approved drugs topotecan and vorinostat in killing pancreatic cancer cells. YUM70 showed significant anticancer activity in an in vivo pancreatic cancer xenograft model with no observed toxicity to normal tissues. The researchers have gone on to synthesize a large number of YUM70 analogues containing novel features including better solubility, physicochemical, and pharmaceutical properties. Beyond production of these inhibitors, this invention therefore dovetails with the creation of a new class of proteolysis targeting chimeric (PROTAC) agents and

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Author(s)
Ding Xue
Joyeeta Roy
Nouri Neamati
Soma Samanta
Suhui Yang

Further information
Stefan Koehler
shkohler@umich.edu

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GRP78 degraders within cells of the immune system and other cancers.