Pharmacological targeting of the unfolded protein response for disease intervention

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© 2019, The Author(s), under exclusive licence to Springer Nature America, Inc.Accumulation of unfolded proteins at the endoplasmic reticulum (ER) is a salient attribute of many human diseases including obesity, liver disorders, cancer, diabetes and neurodegeneration. To restore ER proteostasis, cells activate the unfolded protein response (UPR), a signaling pathway that imposes adaptive programs or triggers apoptosis of damaged cells. The UPR is critical to sustain the normal function of specialized secretory cells (i.e., pancreatic ? cells and B lymphocytes) and to control the production of lipids and cholesterol in the liver. In the context of disease, adaptive UPR responses have been linked to the growth of solid tumors, whereas chronic ER stress contributes to cell dysfunction in brain diseases, metabolic syndromes, among other conditions. Here we discuss recent developments in the design and optimization of novel compounds to manipulate UPR signaling and their efficacy in various