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ER stress and cancer: the FOXO forkhead transcription factor link

Glowi Alasiri[1,3], Lavender Yuen-Nam Fan[1,3], Stefania Zona[1], Isabella Galeno Goldsbrough[1], Hui-Ling Ke[1], Holger Werner Auner[2]*, Eric Wing-Fai Lam[1]*

[1]Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital Campus, London W12 0NN, UK.

[2]Department of Medicine, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK.

[3] Contributed equally and are joint first authors

*Correspondence: Eric W.-F. Lam, Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK Phone: +44-20-7594-2810; Fax: +44-20-8383-5830; E-mail: eric.lam@imperial.ac.uk;

Holger W. Auner, Department of Medicine, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK Phone: +44-20-3313-4017; E-mail: holger.auner04@imperial.ac.uk;

Abstract

The endoplasmic reticulum (ER) is a cellular organelle with central roles in maintaining proteostasis due to its involvement in protein synthesis, folding, quality control, distribution and degradation. The accumulation of misfolded proteins in the ER lumen causes 'ER stress' and threatens overall cellular proteostasis. To restore ER homeostasis, cells evoke an evolutionarily conserved adaptive signalling and gene expression network collectively called the 'unfolded protein response (UPR)', a complex biological process which aims to restore proteostasis. When ER stress is overwhelming and beyond rectification, the normally pro-survival UPR can shift to induce cell termination. Emerging evidence from mammalian, fly and nematode worm systems reveals that the FOXO Forkhead proteins integrate upstream ER stress and UPR signals with the transcriptional machinery to decrease translation, promote cell survival/termination and increase the levels of ER-resident chaperones and of ER-associated degradation (ERAD) components to restore ER homeostasis. The high rates of protein synthesis/translation associated with cancer cell proliferation and metabolism, as well as mutations resulting in aberrant proteins, also induce ER stress and the UPR. While the pro-survival side of the UPR underlies its ability to sustain and promote cancers, its apoptotic functions can be exploited for cancer therapies by offering the chance to 'flick the proteostatic switch'. To this end, further studies are required to fully reevaluate the roles and regulation of these UPR signalling molecules, including FOXO proteins and their targets, in cancer initiation and progression as well as the effects on inhibiting their functions in cancer cells. This information will help to establish these UPR signalling molecules as possible therapeutic targets and putative biomarkers in cancers.