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ER stress and cancer: The FOXO forkhead transcription factor link

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19 Hospital Campus, Du Cane Road, London W12 0NN, UK Phone: +44-20-3313-4017;
20 E-mail: holger.auner04@imperial.ac.uk;**21 Abstract**

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

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