Protein synthesis dependent activation of the unfolded protein response enables prostate cancer development and a druggable target for cancer therapy

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Abstract:

Background and objectives: The acquisition of oncogenic lesions stimulates biosynthetically and bioenergetically demanding cellular processes such as protein synthesis to drive cancer cell growth and proliferation. The hijacking of these key processes by oncogenic pathways triggers cellular stress that requires an adaptive or evasive response in order for cancer cells to survive and continue proliferating. We have previously demonstrated that deregulated protein synthesis, which is induced by oncogenic signaling pathways such as Myc and PI3K that are commonly activated in prostate cancer, activates one of the key cytoprotective stress response pathways, known as the unfolded protein response (UPR). The UPR is a cellular homeostatic program engaged when an excess of unfolded/misfolded proteins accumulate within the lumen of the endoplasmic reticulum. It is carried out by three major signaling arms: PERK, IRE1, and ATF6. However, whether and how each of these distinct signaling arms of the UPR is specifically activated by deregulated protein synthesis upon oncogenic insult is poorly understood.

Methods and Results: Here, we show that prostate cancer initiation and maintenance, following combined loss of the PTEN tumor suppressor and overexpression of the Myc oncogene, rely on protein synthesis-dependent activation of the UPR to facilitate tumor cell survival. Specifically, we have employed a novel genetic mouse model coupling PTEN loss with MYC overexpression in the prostate and we observe that overexpression of Myc in the prostate synergizes with PTEN loss to dramatically stimulate the P
ERK and IRE1 signaling arms of the UPR pathway, which correlates with enhanced PIN formation and invasive carcinoma. To dissect the mechanism by which these oncogenic lesions promote UPR signaling, we have developed a cell culture model employing human prostate epithelial cells overexpress MYC, harbor an shRNA targeting PTEN, or the combined overexpression of MYC and shRNA of PTEN. Using this cell culture model, we demonstrate the activation of UPR arms PERK and IRE1 upon oncogenic transformation by Myc overexpression and loss of PTEN. Interestingly, blocking the cytoprotective UPR using PERK or IRE1 inhibitors resulted in a significant increase in cell death and decreased clonogenic potential in cells harboring both oncogenic lesions (MYC/PTEN), but not in normal cells. Furthermore, down-regulation of protein synthesis by the ATP-site mTOR inhibitor MLN0128 further attenuates the UPR response in these cells and synergistically promotes cell death in the presence of a UPR inhibitor.

Conclusion: Experiments are currently underway to test UPR inhibition in a preclinical trial utilizing our *in vivo* PTEN loss model with or without MYC overexpression. Furthermore, we aim to test UPR inhibition in patient derived xenograft (PDX) model of high risk prostate cancer. In addition, we are utilizing gene expression analysis to understand the mechanistic connection between protein synthesis and the specific arms of the UPR. Taken together, our results suggest a critical role of the UPR in ensuring prostate cancer cell progression and serve as a promising opportunity for therapeutically targeting this cancer-specific vulnerability to stress adaptation in order to elicit synthetic lethality.

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