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## Divergent androgen regulation of unfolded protein response pathways drives prostate cancer

The unfolded protein response (UPR) is a homeostatic mechanism to maintain endoplasmic reticulum (ER) function. The UPR is activated by various physiological conditions as well as in disease states, such as cancer. As androgens regulate secretion and development of the normal prostate and drive prostate cancer (PCa) growth, they may affect UPR pathways. Here we show that the canonical UPR pathways are directly and divergently regulated by androgens in PCa cells, through the androgen receptor (AR), which is critical for PCa survival. AR bound to gene regulatory sites and activated the IRE1α branch, but simultaneously inhibited PERK signaling. Inhibition of the IRE1α arm profoundly reduced PCa cell growth in vitro as well as tumor formation in preclinical models of PCa *in vivo*. Consistently, AR and UPR gene expression were correlated in human PCa and spliced XBP-1expression was significantly up-regulated in cancer compared with normal prostate. These data establish a genetic switch orchestrated by AR that divergently regulates the UPR pathways and suggest that targeting IRE1α signaling may have therapeutic utility in PCa.

### Biography

Fahri Saatcioglu is professor in molecular and cell biology at the Department of Biosciences at the University of Oslo, Head of the Section for Biochemistry and Molecular Biology, as well as a senior scientist at Oslo University Hospital, Norway. He is also a visiting scientist at Harvard School of Public Health, Boston, USA. His research focuses on basic molecular and cell biology of prostate cancer cells, including translational research. His laboratory has identified a number of highly prostate enriched and androgen regulated genes and has been characterizing the proteins they encode for their function in prostate cancer cells. His work also focuses on signaling pathways in prostate cancer and their crosstalk.

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