

BREAST CANCER

Hypoxia and XBP1S

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XBP1S is involved in maintaining a cancer stem cell-like CD44^{high}, CD24^{low} population
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Tumour cells are subject to various cellular stresses during tumour evolution, including endoplasmic reticulum stress. Laurie Glimcher and colleagues have found that the spliced form of X-box-binding protein 1 (XBP1S), which is activated as part of the unfolded protein response (UPR), regulates a hypoxia-inducible factor 1 α (HIF1 α)-dependent transcriptional network in triple-negative breast cancer (TNBC) cells.

XBP1 is expressed in both basal and luminal breast cancer cell lines, but the expression level of XBP1S

was higher in basal breast cancer cell lines (which mostly consist of TNBC cells) and in biopsy samples from patients with TNBC. Silencing of XBP1 mRNA using short hairpin RNAs (shRNAs) inhibited colony formation of TNBC cells in soft agar and the growth of orthotopic xenografts and metastases to the lung in mice, which the authors showed was owing to a lack of angiogenesis. Additional experiments showed that XBP1S is involved in maintaining a cancer stem cell-like CD44^{high}, CD24^{low} population.

Chromatin immunoprecipitation and DNA sequencing (ChIP-seq) experiments in a basal breast cancer cell line indicated that XBP1 and HIF1 α frequently colocalized to the same regulatory DNA sequences. HIF1 α expression is known to be high in TNBC and is also required for the maintenance of the CD44^{high}, CD24^{low} population. Growth of basal and luminal breast cancer cell lines in low oxygen and glucose levels (conditions that mimic ischaemia) increased the levels of XBP1S and its association with HIF1 α on chromatin in basal but not luminal breast cancer cell lines.

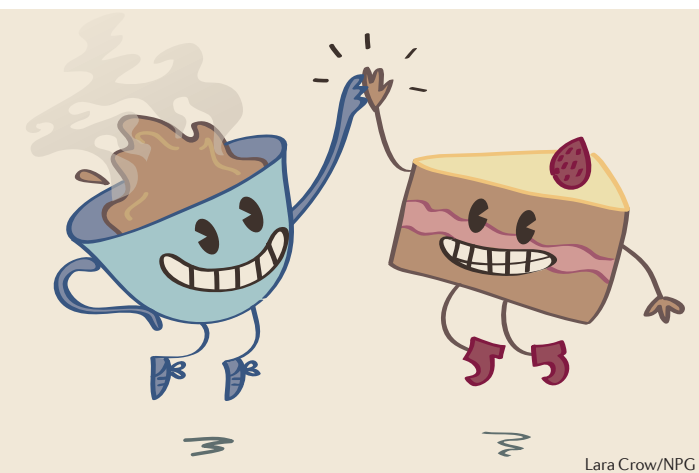
Further immunoprecipitation and cellular subfractionation studies indicated that XBP1S and HIF1 α directly interact in the nucleus under hypoxic conditions and that they colocalize to several well-known HIF1 target genes. *XBP1* or *HIF1A* knockdown using shRNAs indicated that the loss of one factor affects the binding of the other to DNA and prevents the recruitment of RNA polymerase II, thereby preventing gene transcription.

The authors also found that a 96-gene signature of XBP1S activity correlated with a hypoxia-driven gene signature in TNBC cells. This XBP1S gene signature was also associated with a shorter relapse-free survival time, as determined using gene expression data from two independent cohorts of patients with TNBC.

These findings indicate that, as part of the endoplasmic reticulum stress response, XBP1S maintains a HIF1 α -driven hypoxic response in TNBC. These findings also indicate that inhibitors of the UPR, combined with standard chemotherapy, might improve the outcome in patients with TNBC.

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ORIGINAL RESEARCH PAPER Chen, X. et al. XBP1 promotes triple-negative breast cancer by controlling the HIF1 α pathway. *Nature* **508**, 103–107 (2014)



Lara Crow/NPG