Cancers thrive under adverse conditions and simultaneously inhibit antitumor immunity. We recently found that endoplasmic reticulum (ER) stress responses driven by the IRE1α-XBP1 pathway not only promote cancer cell survival, but also provoke severe dendritic cell (DC) dysfunction in tumors. Targeting IRE1α-XBP1 represents a two-pronged approach to restrain malignant cells while eliciting concomitant antitumor immunity.

Harnessing the intrinsic ability of our immune system to recognize and eliminate malignant cells is the most promising anticancer strategy since the development of chemotherapy. While this approach was designated the scientific breakthrough of 2013, suppressive microenvironmental conditions within solid tumors inhibit the optimal activity of protective immune cells. Hence, targeting immunosuppression and re-programming immune cell function in the tumor microenvironment are fundamental requirements for developing successful cancer immunotherapies.

The ER is a massive intracellular membrane network that extends throughout the cytoplasm whose vital function is the generation of newly synthesized secretory and transmembrane proteins. Aberrant accumulation of unfolded proteins in this compartment causes a state of “ER stress,” which is a hallmark feature of secretory cells and many diseases, including cancer, neurodegeneration, and diabetes. Adaptation to protein-folding stress is mediated by the activation of an integrated signal transduction pathway known as the ER stress response. This pathway signals through three distinct stress sensors located at the ER membrane: IRE1α, ATF6, and PERK. The most conserved arm of the ER stress response is the dual enzyme IRE1α, which is both a kinase and an endoribonuclease. Activated during periods of protein folding stress, the IRE1α endoribonuclease domain excises a short nucleotide fragment from the Xbp1 mRNA to generate the functional transcription factor, XBP1. This potent, multitasking protein promotes cell survival by inducing the expression of critical genes involved in protein folding and quality control.

Cancer cells are constantly exposed to adverse environmental conditions that induce protein misfolding (e.g. hypoxia, nutrient starvation, oxidative stress, and high metabolic demand). However, they ensure survival by adjusting their protein folding capacity via the ER stress response pathway. In malignant cells, XBP1 overexpression confers drug resistance by preventing drug-induced apoptosis. XBP1 has been demonstrated to drive the pathogenesis of multiple myeloma, and has been implicated in cellular de-differentiation, oncovirus infection and the epithelial-to-mesenchymal transition. Abnormal XBP1 activation has also been shown to promote chronic lymphocytic leukemia, and targeting dysregulated IRE1α function in vivo with selective small molecule inhibitors showed significant anti-leukemic effects. Recently, our group demonstrated that XBP1 drives the pathogenesis of triple negative breast cancer (TNBC) by supporting tumor cell survival and metastatic capacity under hypoxic conditions. Strikingly, therapeutic silencing of XBP1 in TNBC cells leads to suppression of tumor initiation, progression, and recurrence. Increasing evidence therefore supports the concept that dysregulated IRE1α-XBP1 signaling operates in cancer cells to positively influence their growth and survival in vivo. Nevertheless, the role of this conserved cellular pathway in sculpting the cancer immunoenvironment and the antitumor immune response had not been fully appreciated. We hypothesized that aberrant IRE1α-XBP1 activation could also promote malignant progression by blunting antitumor immunity.

Ovarian carcinoma is a highly immunosuppressive malignancy with the remarkable capacity to control DC function in order to inhibit the generation of protective T-cell-based responses. We postulated that adverse conditions in the ovarian cancer microenvironment could trigger ER stress and subsequent activation of the IRE1α-XBP1 pathway in tumor-associated DCs (tDC) to influence their normal function and facilitate immunological tolerance to tumors. We established that DCs residing in human and mouse ovarian cancers exhibited robust IRE1α-XBP1 activation and overexpression of XBP1-dependent genes involved in the ER stress response. In the tumor microenvironment, DCs demonstrated high levels of...
reactive oxygen species that promoted the generation of 4-hydroxynonenal (4-HNE), a lipid peroxidation byproduct that induced ER stress by directly modifying critical ER-resident proteins and chaperones. Notably, 4-HNE has been shown to promote vascular inflammation and atherosclerosis by triggering ER stress in endothelial cells. Using conditional knockout mice, we found that sustained XBP1 activation by tDCs was necessary for the aggressive and accelerated progression of primary and metastatic ovarian cancers in three preclinical models of disease analyzed. Genome-wide transcriptional analyses revealed that constitutively active XBP1 induced a comprehensive triglyceride biosynthetic program in tDCs leading to abnormal lipid accumulation and subsequent inhibition of tDC capacity to support antitumor T cells. Notably, it has been previously demonstrated that a major mechanism mediating DC dysfunction in cancer is in fact aberrant intracellular lipid accumulation, a process that interferes with normal DC antigen cross-presentation pathways. Supporting this crucial concept, we found that DC-specific deletion of XBP1 extended host survival by converting tolerogenic tDCs into potent activators of type 1 immunity in ovarian cancer-infiltrating T cells. Novel and more effective therapeutic strategies are urgently needed in the clinic to improve the dismal prognosis of women with ovarian cancer. We found that therapeutic silencing of XBP1 selectively in tDCs using siRNA-loaded nanocarriers restored their immunostimulatory capacity in situ and significantly prolonged host survival by evoking protective T-cell-mediated antitumor immunity. Thus, controlling the IRE1α-XBP1 pathway in tDCs could represent a new approach to complement standard ovarian cancer treatments based on surgery followed with chemotherapy, which unfortunately have demonstrated sub-optimal efficacy during the last decades. Likewise, it would be valuable to determine whether targeting IRE1α-XBP1 in myeloid immune cells of the tumor microenvironment could augment immunotherapies based on checkpoint blockade or adoptive T cell transfer now in the clinic.

Our study provided the first example of a lethal cancer capable of co-opting IRE1α-XBP1 function in DCs of the tumor microenvironment as a strategy to evade immune control (Fig. 1). It is likely that this process may orchestrate tolerance and immunosuppression in other lethal solid tumors that commonly rely on infiltrating innate immune cells to promote malignant progression. We are currently exploring if other cell types in the cancer immunoenvironment exhibit detrimental ER stress responses, and we are defining the range of cancer types that utilize IRE1α-XBP1 signaling as a novel immunosuppressive strategy.

Since the IRE1α-XBP1 pathway has been demonstrated to promote cancer by operating directly in malignant cells, our new findings raise the possibility of identifying novel small-molecule IRE1α inhibitors with the ability to induce two parallel and mutually reinforcing antitumor mechanisms: direct suppression of cancer cell survival and induction of concomitant antitumor immunity.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Funding**

LHG holds equity in and is on the board of directors of Bristol-Myers-Squibb.

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![Figure 1. ER stress-driven XBP1 overactivation obstructs antitumor immunity by provoking DC dysfunction. Image credit: Sam Spaeth.](Image)
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