Endoplasmic Reticulum Stress Response, the Future of Cancer Research and a New Designated Journal.

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The Endoplasmic Reticulum Stress Response (ERSR), the understanding of its mechanisms, and its contribution to the numerous vital functions of the cell are both the most avant-garde and highest priority in basic and clinical biomedical research fields.

Like many other important fields in biology, ERSR started completely as basic research, with the most important discoveries made in yeast, immunoglobulin assembly and metabolic cellular studies [1,2]. Protein chaperones, such as Grp78 and Grp94, were indeed discovered in glucose starvation experiments between the mid-seventies and eighties by Pastan’s lab [3]. Gething and Sambrook understood the importance of chaperone up-regulation and discovered common elements in their promoters that govern chaperones’ transcriptional control. It was in 1992 when the term “Unfolded Protein Response” (UPR) was first used [4].

The yeast IRE1 trans-membrane kinase and ribonuclease was the first sensor of the accumulation of unfolded proteins in ER cloned in 1998 by two labs, Sambrook and Walter [5,6]. IRE1 is the most evolutionary conserved branch of UPR and the only one present in yeast. The rescue of IRE1 -/- yeast cells by over-expression of Hac1p transcription factor revealed the unique mode of action of IRE1 [ref., thus connecting the sensing of ERS and the massive transcriptional program initiated by UPR signaling.

Beautifully surprising and somehow expected is the story of mammalian UPR sensors’ identification [7-11]. As compared to that of the yeast, the mammalian system shows much more complexity and redundancy due to contributions from at least 3 major pathways of UPR: IRE1α and IRE1β, PERK and ATF6. PERK added extra release to the stressed ER by translational attenuation of new protein synthesis. Before XBP1 was identified and connected to UPR, it was thought that ATF6 fulfilled Hac1 function in higher eukaryotes [12,13].

Slowly, the primary components of UPR have been unveiled; experiments implementing “classical” and artificial UPR inducers, such as Tunicamycin and Thapsigargin, have helped to delineate the core mechanisms of UPR induction as well as the cytoprotective and apoptotic programs initiated by ER stress signaling. Studies in yeast indicate that communication exists between UPR signaling and chromatic remodeling enzymes [14], thus ensuring cellular “memory” and future resistance to similar challenges after initial ERS. Congruently, IRE1 is beginning to emerge as a platform for interactions between different signaling molecules, thus ensuring communication of the ER, nucleus, cytosol and the cell membrane.

Many questions have been pacified with answers, but new knowledge has given rise to more unanswered queries, and as it should be, the field has taken some unexpected turns.

As research in this field progresses, many biologically relevant causes for the deregulation of protein synthesis become more obvious. The scarcity of amino acids, energy limitations, hypoxia, and alterations in Ca²⁺ concentration within ER are only a few examples. UPR has begun to be viewed as a sensor of cell homeostasis and a communications pathway between the ER, nucleus and other cellular compartments, as part of a sophisticated proteostatic cellular network. This system appears to be increasingly complicated, yet maintains uniqueness and elegance in its unusual regulation and broad importance to the cell [15].

Connections to cancer development have also become increasingly evident. It has been well established that cancer cells experience multiple occurrences of ERSR [16]. Cancer cells deficient in UPR genes do not grow well or form metastases and have abnormal vascularization [17]. The dream of each oncologist is to have therapeutics that will render such properties to tumors, and our main challenge is to supply these therapies. Hopefully, it can be done through the cunning design of new therapeutics specific to UPR pathways that will inhibit cytoprotective and dormancy programs configured by ERSR and augment the non -protective apoptotic arm of ERSR [16,18]. This can be accomplished with an in-depth understanding of the contribution of each primary player in cell survival and death in each type of tumor. Examples of such understandings are numerous, but many more are needed. For instance, ER chaperones are important for the...
survival of cancer cells during episodes of hypoxia and nutrient deprivation experienced by every “successful tumor,” and their up-regulation has cytoprotective effects against conventional agents of chemotherapy [19-21]. The expression of ER-resident proteins on the cell surface due to a breach in ER quality control during episodes of UPR has been found to be very “beneficial” for many tumors and directly correlates with a poor prognosis. While BiP has been shown to act as a prosurvival receptor, PDI has proven to contribute to antigen shedding on tumors thus further aiding in their evasion of the immune system [22]. Moreover, tumor dormancy has confirmed its dependence upon UPR signaling through interaction with kinase cascades (p38 and ERK) regulating growth [23,24]. Tumor associated-inflammation and supportive micro-environments are partly a product of UPR associated signaling [25-27]. Induction of UPR through inhibition of proteosomal degradation and UPR-associated apoptotic signaling is thought to be beneficial in treating many tumors when in combination with conventional agents of chemotherapy [28,29]. Numerous clinical trials are currently being performed to validate this approach and to ensure the use of ERS inducers in cancer patients [30,31].

This field is exploding with new knowledge [32]. By 1999, the number of manuscripts published on UPR was in the range of double digits with only a few of them being related to cancer research (Figure 1). Between 2005 and 2010, there was a 306% increase in the number of manuscripts regarding ERSR in general and a 410% increase in manuscripts researching UPR in cancers, indicating tremendous advances in the field. 2081 manuscripts were published in 2011 alone, (Figure 1) with almost a fourth of them being directly related to cancer research. Some years after the initial recognition of UPR, the foundations have been laid for future innovations and advances and we are excited about where the progression of this research will take us. We feel strongly that it is the perfect time to establish a new journal dedicated solely to this topic. The journal is led and supported by the Editorial Board of the internationally recognized scientists with expertise in different areas of research on Endoplasmic Reticulum Stress involvement in cancer development, progression, immune-invasion and sensitivity to chemotherapy (http://versita.com/ersc/editors). The ERSC journal is peer-reviewed and an Open Access, there are also no page charges till 2014. We envision the solidification of work in a dedicated journal that will contribute tremendously to our understanding of the role that ERSR has in cancer pathophysiology, as well as promote communication and the exchange of ideas in the international research community laboring in this endeavor. We hope the journal Endoplasmic Reticulum Stress in Cancers will contribute to the proactive advancement of this field, to its direct effects on cancer treatment and prevention. We look forward to incorporating your work into Endoplasmic Reticulum Stress in Cancers.

![Figure 1](image.png)

Figure 1. Number of manuscripts published between years 1985 and 2011 on ERS (blue) and ERS in Cancers (red). Data was obtained using PubMed

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