Cellular Mechanisms of Endoplasmic Reticulum Stress Signaling in Health and Disease. 3. Orchestrating the unfolded protein response in oncogenesis: an update

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Manié SN, Lebeau J, Chevet E. Cellular Mechanisms of Endoplasmic Reticulum Stress Signaling in Health and Disease. 3. Orchestrating the unfolded protein response in oncogenesis. Am J Physiol Cell Physiol. 307: C901–C907, 2014. First published September 3, 2014; doi:10.1152/ajpcell.00292.2014.—The endoplasmic reticulum (ER)-induced unfolded protein response (UPR) is an adaptive mechanism that is activated upon accumulation of misfolded proteins in the ER and aims at restoring ER homeostasis. In the past 10 years, the UPR has emerged as an important actor in the different phases of tumor growth. The UPR is transduced by three major ER resident stress sensors, which are protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme-1 (IRE1). The signaling pathways elicited by those stress sensors have connections with metabolic pathways and with other plasma membrane receptor signaling networks. As such, the ER has an essential position as a signal integrator in the cell and is instrumental in the different phases of tumor progression. Herein, we describe and discuss the characteristics of an integrated signaling network that might condition the UPR biological outputs in a tissue- or stress-dependent manner. We discuss these issues in the context of the pathophysiological roles of UPR signaling in cancers.

endoplasmic reticulum; metabolism; signaling; stress; cancer
progression. These topics will be described and discussed in the present review.

The UPR: A General Pathway Involved in Cancers

In mammals, there are three classes of ER stress sensors: IRE1α, IRE1β, PERK, and ATF6 (both α and β isoforms) (56) (Figs. 1 and 2).

IRE1α is a kinase that is commonly mutated in human cancers, as revealed in several genomic screens (21, 22, 45). Cells deficient in X-box-binding protein 1 (XBP1) or PERK have a large reduction in their ability to form solid tumors in nude mice (5, 52). The IRE1α arm of the UPR is involved in tumor development in glioblastoma through the regulation of the expression of proinflammatory cytokines and proangio-

Fig. 1. Schematic representation of metabolic pathways activated downstream of the UPR and their involvement in various cancers. Yellow diamonds represent ER stress-induced transcription factors. Pink diamonds represent transcriptional regulators that participate in UPR downstream signaling, and white diamonds represent other targets of XBP1 or RIDD. Gray boxes represent the major metabolic pathways targeted by the UPR. (See text for definition of abbreviations.)

Fig. 2. Schematic representation of the UPR signaling arms and their target genes. Yellow diamonds represent ER stress-induced transcription factors. UPR target genes are indicated in black (nonselective) or red (selective). Circles represent signaling proteins of the PERK or IRE1 cascades. (See text for definition of abbreviations.)
Fig. 3. Schematic representation of the involvement of UPR signaling during cell transformation and tumor growth. The activation status of the three UPR arms is shown at the bottom of the scheme. Green indicates a predominant role of the arm concerned in the tumorigenic process indicated at the top of the scheme (the gradient in green indicates the relative contribution of each arm). (See text for definition of abbreviations.)
microenvironment to which tumor cells are subjected, but also to the nature/stage of the oncogenic process.

ER Stress in Cancer: A Metabolic Perspective

A recognized hallmark of malignant cells is the rewiring of their metabolism to support sustained growth (9). These nutrient requirements eventually exceed the capacity of the cells’ microenvironment due to inadequate vascularization, inevitably leading to hypoxia and nutrient limitation. To survive this metabolic stress, tumors cells induce adaptive responses including activation of the UPR (37). The UPR has critical functions outside of simply facilitating protein homeostasis. For example, the PERK-ATF4 branch upregulates vascular endothelial growth factor (VEGF) to induce angiogenesis (5). Moreover, it is now becoming clear that UPR can directly participate in the reprogramming of tumor metabolism by selectively activating biosynthetic pathways (Figs. 1 and 2).

As it is subjected to anabolic and catabolic regulation, protein metabolism and, more particularly, protein homeostasis (19), also termed proteostasis (4), represents an interesting aspect of the connections that link metabolism and ER stress signaling. Indeed, it is well established that ER stress signaling pathways control protein synthesis, folding, and degradation machineries (56). This is illustrated by the direct regulation of protein synthesis through the PERK-mediated regulation of eIF2α phosphorylation (24), IRE1-mediated RNA degradation (38), or control of the expression of ER proteins involved in folding or degradation (56). Changes in proteostasis have been associated with tumor-associated gain-of-functions that can then be reversed using proteostasis modulators such as proteasome inhibitors (26).

XBP1s has been shown to trigger expression of key hexosamine biosynthetic pathway (HBP) enzymes that convert glucose to UDP-acetylglucosamine (UDP-GlcNac) (13, 58). Generation of UDP-GlcNac provides substrate for N-glycosylation of proteins in the ER and O-glycosylation of cytosolic and nuclear proteins, leading to improved proteostasis and cytoprotection. Hence, activation of the HBP is integral to the UPR. Interestingly, limitation of glucose intermediate into HBP has been reported to trigger proapoptotic UPR signaling (28, 44). In a context of nutrient depletion, XBP1s-induced HBP remodeling can be viewed as an adaptive mechanism that favors the channeling of limited glucose molecules into HBP, to overcome an ER stress barrier to malignancy (25) (Fig. 1). Recent findings have also revealed a state of basal ER stress in triple-negative breast cancer cell lines (7). Within such cells, the constitutive splicing of XBP1 drives tumorigenicity by assembling a transcriptional complex with HIF1α, which regulates the expression of HIF1α targets. HIF1α orchestrates a transcriptional program that upregulates several glycolytic proteins including glucose transporter 1 (GLUT1). These studies indicate that XBP1 actively promotes the stimulation of glucose uptake by cancer cells. Notably, XBP1 appears to have more than one string to its bow to ensure the same biological output. Indeed, elevated O-glycosylation, a consequence of XBP1-upregulated HBP (13, 58), also regulates HIF1α/GLUT1 expression (18).

Recently, links between ER stress signaling and the circadian clock have also been unveiled in cancer models. The circadian clock and the UPR can regulate and be regulated by one another (47). Indeed the existence of these new loops of regulation raises questions regarding the physiological and pathophysiological consequences of this interconnection. The UPR is widely known as a cellular mechanism of adaptation to environmental stresses. However, increasing evidence suggests that the UPR could be central in the control of cellular functions under homeostatic conditions. This role is underlined by the UPR/circadian clock connection, as the rhythmic activation of ATF4 was found necessary for glutathione synthesis (29) and the rhythmic activation of IRE1α to the control of hepatic lipid metabolism (8). In glioblastoma, the inhibition of IRE1α is sufficient to trigger a cellular phenotypic switch (characterized by modulation of the ECM, the cellular ability to proliferate, migrate, and adhere and to produce proinflammatory chemokines) without any apparent stress induction (11, 46). Thus, one can propose that the circadian clock may impact on a number of cellular processes through its connection to the UPR. An element reinforcing this hypothesis is the superposition of physiological processes controlled by both the UPR and the circadian clock. As such, the regulation of PER1 mRNA by IRE1α is a molecular event sufficient on its own to control glioma angiogenesis, invasion, and growth (46).

ER Stress in Cancer: Integration in the Whole Cell-Signaling Map

In addition to the traditional signaling cascades activated downstream of PERK, ATF6, or IRE1 upon accumulation of misfolded proteins in the ER (Fig. 2) that connect the UPR with, for instance, the nuclear factor erythroid 2-related factor 2 (NRF2) or NF-κB pathways, recent observations have also unraveled alternative signaling pathways involving the components of the UPR. The concept that UPR signals could be integrated to other major cellular signaling pathways has been recently illustrated in numerous reports.

First, the cross-talk between cell surface receptors and the UPR has been reported for at least four types of receptors belonging respectively to the death receptor, Toll-like receptor (TLR), TNF receptor, and tyrosine kinase receptor families. Indeed, it was recently reported that TLR signaling can impact on the specificity of ER stress in an inflammatory context (59, 60). In this context, LPS-mediated activation of TLR3/4 signals induces the UPR to ensure essential protein synthesis. Indeed, in such context, increased levels of phosphorylated eIF2α do not lead to CEBP homologous protein (CHOP) induction through a TLR-dependent pathway, thereby reducing apoptosis. This has been shown to occur through protein phosphatase 2A (PP2A)-mediated serine dephosphorylation of eIF2B, thereby leading to its activation and counteracting the effects of phosphorylated eIF2α (59, 60). In a similar manner, signaling of the UPR has been linked to the death receptor pathway through death receptor 5 (DR5) (36). Indeed, ER stress was found to promote apoptosis through cell-autonomous, UPR-controlled activation of DR5, through the combined CHOP-dependent upregulation of DR5 and DR5 RIDD. As such, DR5 integrates opposing UPR signals to couple ER stress and apoptotic cell fate (36). Although the above-mentioned observations were not made in the context of cancer models, another recent study showed that ER stress signaling (mostly through ATF3) sensitized p53-deficient colon cancer cells to TRAIL-induced cell death via DR5 signaling (16). Collectively, these results indicate a strong connection between death receptor signaling and ER stress, which should be investigated more deeply in the future. Similarly, CD40 signaling
upon activation by CD154 was found to increase XBPI mRNA splicing and thus protect the secretory pathway of hepatocytes from ER stress induced by either tunicamycin or oleic acid (55). This observation might also be put in perspective of the discovery of CD40 ligation-mediated XBPI mRNA splicing in plasma cells, thus confirming the link between signaling from CD154/CD40 and IRE1 activation (30). Functional links between receptor tyrosine kinases (RTK) and ER stress signaling have also been established. In cancer cells, fibroblast growth factor-2 (FGF-2) decreases the apoptosis induced by tunicamycin. Indeed, in human hepatoblastoma HepG2 and breast cancer MCF-7 cells, FGF-2 decreases tunicamycin-induced CHOP expression and apoptosis through MAPK activation. Mechanistically, this occurred through an FGF-2-induced proteasome-mediated degradation of NCK1, known to prevent IRE1 signaling towards MAPK (42). These findings show that NCK1 plays a pivotal role in integrating FGF-2 and ER stress signals to counteract the deleterious effect of ER stress on cancer cell survival (35). Recently, it was also shown that NCK1 was important to the modulation of PERK signaling (32, 61), thus representing a connection between RTK and ER stress. Similarly, in endothelial cells, VEGF activates UPR mediators through a PLC-γ-mediated cross talk with the mammalian target of rapamycin complex 1 (mTORC1) (31). ATF6 and PERK signaling contributes to the survival effect of VEGF on endothelial cells, thereby suggesting that ER stress participates in VEGF signaling, thus leading to the regulation of endothelial cell survival and angiogenesis (31). Together, these results also indicate a tight link between RTK and ER stress signaling in the biology of both cancer cells and cells of the tumor microenvironment.

Future Research and Challenging Questions

A better understanding of the molecular functions of UPR in cancer cells represents a unique opportunity to (1) define novel potentially relevant therapeutic targets and (2) design novel therapeutic strategies to target them. However, on the basis of the results presented above it appears that the UPR is tightly interconnected with major metabolic and signaling pathways in cancer cells thus conferring specificity to the signaling outputs produced in those cells. As such, not only the specificities of the tissue of origin, of the cells subjected to the transformation process, might impact on the nature of the UPR signals and their physiological consequences, but also the specificity of the microenvironment and the nature of the stroma are important determinants in defining cell-autonomous and cell nonautonomous activation of the UPR in tumor cells. In recent years, pharmacological compounds targeting PERK (26), IRE1 (20, 26) and ATF6 [although not directly; (27)] have been used in cancer models and are beginning to show promising properties. It is clear that these compounds represent novel and potentially relevant tools for innovative strategies for cancer therapeutics; however, one must keep in mind the secondary impacts of such strategies, especially in view of the central role of ER stress signaling in this pathology.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

S.N.M. and E.C. conception and design of research; S.N.M. and E.C. prepared figures; S.N.M., J.L., and E.C. drafted manuscript; S.N.M. and E.C. edited and revised manuscript; S.N.M. and E.C. approved final version of manuscript.

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