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Review

# Novel roles of the unfolded protein response in the control of tumor development and aggressiveness

Nicolas Dejeans[a,b], Kim Barroso[a,b,c,d,e], Martin E. Fernandez-Zapico[c], Afshin Samali[f], Eric Chevet[a,b,d,e,*]

[a] INSERM, UMR-1053, Team "Endoplasmic Reticulum Stress and Cancer", 33000 Bordeaux, France
[b] Université de Bordeaux, 33000 Bordeaux, France
[c] Schulze Center for Novel Therapeutics, Division of Oncology Research, Mayo Clinic, Rochester, MN, USA
[d] ER440 Université Rennes 1, "Oncogenesis, Stress, Signaling", Rennes, France
[e] Centre de Lutte Contre le Cancer Eugène Marquis, Rennes, France
[f] Apoptosis Research Centre, School of Natural Sciences, NUI Galway, Galway, Ireland

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ABSTRACT

The hallmarks of cancer currently define the molecular mechanisms responsible for conferring specific tumor phenotypes. Recently, these characteristics were also connected to the status of the secretory pathway, thereby linking the functionality of this cellular machinery to the acquisition of cancer cell features. The secretory pathway ensures the biogenesis of proteins that are membrane-bound or secreted into the extracellular milieu and can control its own homeostasis through an adaptive signaling pathway named the unfolded protein response (UPR). In the present review, we discuss the specific features of the UPR in various tumor types and the impact of the selective activation of this pathway on cell transformation, tumor development and aggressiveness.



## 1. Introduction

Tumor phenotypes including development and aggressiveness features can dramatically vary depending on the origin of tumor cells and context. The hallmarks of cancer defined by Hanahan and Weinberg [1] have helped to define these characteristics, which were also connected to the status of the secretory pathway (SP) [2,3]. As a consequence this essential cellular component has taken significant importance in the acquisition of cancer cell features. The SP ensures the biogenesis of proteins that are membrane-bound or secreted into the extracellular milieu. It is well accepted that approximately one-third of the polypeptides synthesized by a cell, enter the endoplasmic reticulum (ER), the first compartment of the SP [2,3]. However, the quantity of proteins entering the secretory pathway fluctuates, depending on the cell physiology, function and specific microenvironment. For instance, the synthesis of antibodies, extracellular matrix proteins, membrane receptors or secretory cyto/chemokines is cell-type specific and can impact the workload of the secretory machinery. Moreover, cell migration, differentiation or proliferation features can also create the demand for a higher need for protein secretion. Protein secretion fluctuations affect cell homeostasis, particularly cell amino acid, lipid and sugar metabolism and energy consumption. As such, a strong and reliable adaptive system is central for the cell to cope with the increased demand for protein folding in the ER. This adaptive system is named the unfolded protein response (UPR). In this review, we provide specific examples illustrating how the diversification of UPR signals in many human cell types, particularly in secretory cells, could impact typical cancer initiation, tumor development and cancer cell aggressiveness.

The UPR transmits stress signals from the ER lumen to the rest of the cell by three different proteins called PERK, ATF6 and IRE1. PERK (PKR-like endoplasmic reticulum kinase) is a transmembrane protein with a specific kinase activity in its cytosolic domain. Its main substrate is the translation initiation factor eIF2α. Phosphorylation of eIF2α results in a decrease in translation as well as a preferential translation of key proteins such as CHOP and GADD34, two factors directly involved in the cellular decisions of life or death. The transmembrane protein ATF6 (Activating Transcription Factor 6) is an ER transcription factor. Under stress conditions, ATF6 is exported to the Golgi apparatus, cleaved and released from its membrane attachment by the proteases S1P and S2P, to play its role as nuclear

* Corresponding author at: ER440 Université Rennes 1, "Oncogenesis, Stress, Signaling", Centre de Lutte Contre le Cancer Eugène Marquis, 35000 Rennes, France. Tel.: +33 0223237258.
*E-mail address:* eric.chevet@inserm.fr (E. Chevet).

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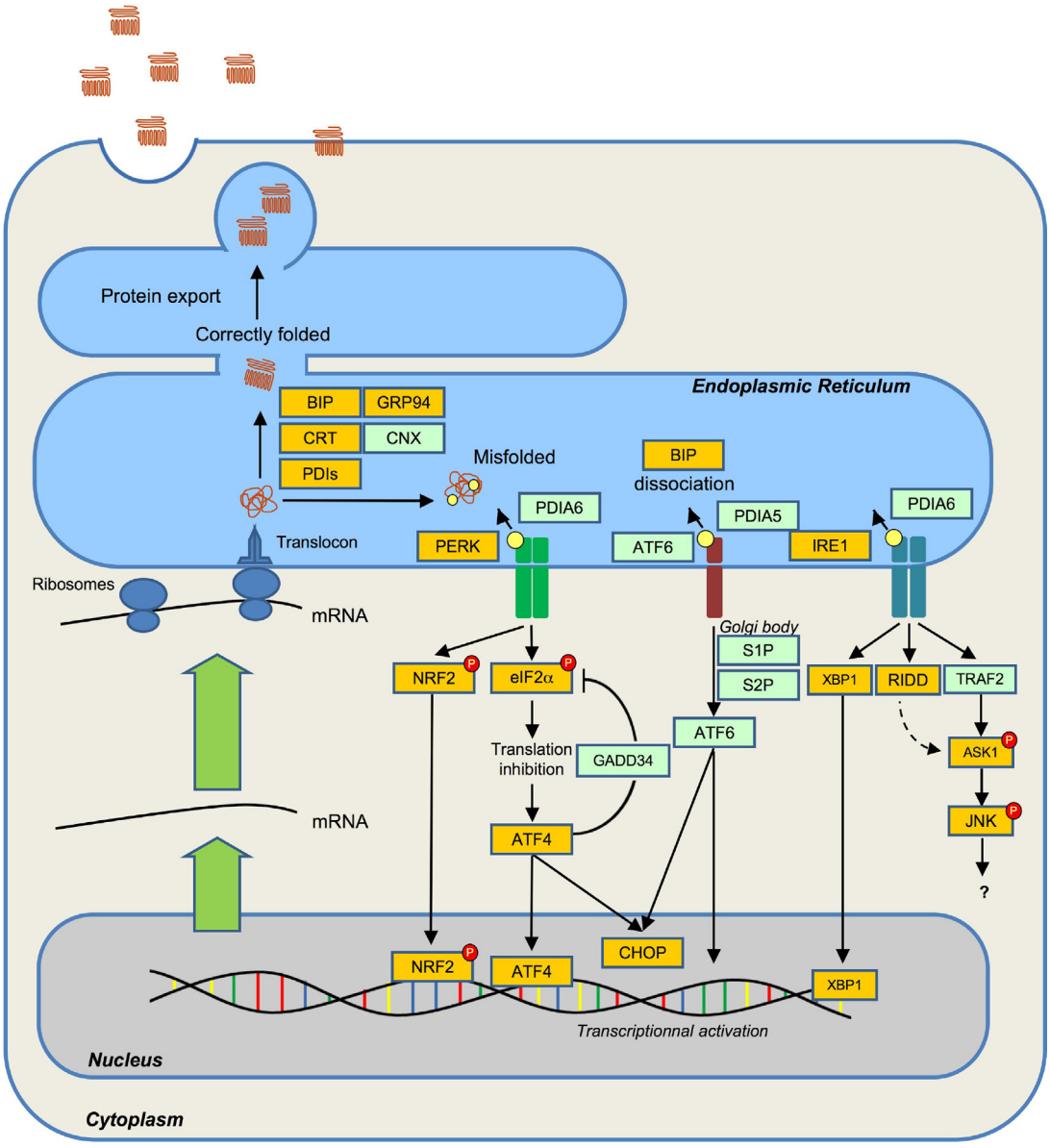


**Fig. 1.** Cancer relevant UPR signaling components. Major UPR signaling modules are drawn. Relevance to cancer is indicated as follows: orange – proteins directly implicated in the modulation of cancer cell features, including initiation, angiogenesis, inflammation, immunogenicity or resistance. Green – proteins whose modulation or activation is observed in cancer tissues or involved with cancer development or aggressiveness, but whose role in the control of cancer features is not clearly defined.

transcriptional activator. Finally, IRE1 (Inositol Requiring Enzyme 1), an ER resident type 1 transmembrane protein, has two enzymatic activities in its cytosolic domain: a serine/threonine kinase and an endoribonuclease activity. The endoribonuclease activity itself has two distinct molecular functions: (i) it participates in the unconventional splicing of the XBP1 transcription factor mRNA [4]; (ii) it degrades the mRNA of several secreted proteins, a process called RIDD (Regulated IRE1-Dependent Decay of RNA) [5]. The integration of signals from these three molecular pathways leads to a general transcription and translation reorientation, in favor of cell survival. Among the cellular processes regulated, the antioxidant capacity is increased, protein synthesis is decreased and the expression of ER chaperones/ER quality control proteins involved in protein folding (BiP, GRP94, CRT, PDIs) and in misfolded protein degradation is enhanced [6–8]. Finally, if ER homeostasis is not restored, ER stress can trigger apoptosis [9,10] (Fig. 1).

It is well established that differentiated cells such as neurons, blood cells, pancreatic β-cells, hepatocytes, all require a dedicated secretory pathway with appropriate specialized regulations [11]. In accordance with this, an increasing number of studies have shown a dependency of specific UPR components for the differentiation of particular cell types. For instance, the IRE1-XBP1 branch is required for the differentiation of pancreatic β cells, plasma cells, or adipocytes [12–16] and disturbance of the PERK-ATF4 pathway triggers defects in oligodendrocytes, pancreatic and skeletal functions [17–21].

## 2. The “secretory switch” in transformed cells

Most cancers have to cope with increasing fluxes of proteins through their secretory pathway. This high secretory protein demand is caused by different hallmarks of cancer [2] and comprises all the processes that increase gene expression, in an unspecific manner, such as aneuploidy or the universal amplifier of transcription, MYC [22,23]. Hence, it is not surprising that