Seminars in Cancer Biology 33 (2015) 57–66

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Controlling the unfolded protein response-mediated life and death decisions in cancer

Marion Maurel[a,c], Eoghan P. McGrath[a], Katarzyna Mnich[a], Sandra Healy[a], Eric Chevet[b,c], Afshin Samali[a,*]

[a] Apoptosis Research Centre, National University of Ireland, Galway, Ireland
[b] Inserm U1052, F-33000, University of Bordeaux, Bordeaux, France
[c] Centre de Lutte Contre le Cancer Eugène Marquis, 35000 Rennes, France

ARTICLE INFO

Keywords:
Apoptosis
Cancer
Cell death
ER stress
UPR

ABSTRACT

Cancer cells are exposed to intrinsic (oncogene) or extrinsic (microenvironmental) challenges, leading to activation of stress response pathways. The unfolded protein response (UPR) is the cellular response to endoplasmic reticulum (ER) stress and plays a pivotal role in tumor development. Depending on ER stress intensity and duration, the UPR is either pro-survival to preserve ER homeostasis or pro-death if the stress cannot be resolved. On one hand, the adaptive arm of the UPR is essential for cancer cells to survive the harsh conditions they are facing, and on the other hand, cancer cells have evolved mechanisms to bypass ER stress-induced cell death, thereby conferring them with a selective advantage for malignant transformation. Therefore, the mechanisms involved in the balance between survival and death outcomes of the UPR may be exploited as therapeutic tools to treat cancer.

1. Introduction

The main functions of the endoplasmic reticulum (ER) include protein folding and maturation, and the maintenance of lipid and cellular Ca^{2+} homeostasis [1,2]. If ER protein homeostasis is disturbed, improperly folded proteins accumulate in the ER, a condition termed ER stress. This results in the activation of the unfolded protein response (UPR), an adaptive pathway that aims to restore ER homeostasis [3]. The UPR is mediated by inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6f), and protein kinase RNA-like ER kinase (PERK), three ER membrane localized stress sensing proteins [4]. Upon accumulation of misfolded proteins, glucose regulated protein 78(GRP78) is displaced from the sensors, thereby prompting their activation [5]. Initially the UPR acts to restore ER homeostasis by halting protein synthesis, enhancing protein degradation (ER-associated protein degradation (ERAD)), upregulating the expression of chaperones and foldases and expanding the ER membrane [4]. However, if these measures are ineffective, the UPR becomes pro-apoptotic, although the precise mechanisms underlying this switch remain unclear [6].

Upon ER stress, IRE1 monomers juxtapose and trans-autophosphorylate, producing multimers with functional cytoplasmic endoribonuclease (RNase) domains [7]. The IRE1 RNase domain unconventionally excises a 26-nucleotide intron from X-box binding protein 1 (XBP1) mRNA [8] which is then ligated by RNA 2′,3′-cyclic phosphate and 5′OH ligase (RTCB) [9]. Spliced XBP1 (XBP1s) is a pro-survival transcription factor that drives the homeostatic phase of the UPR [3]. IRE1 also cleaves a variety of mRNA, miRNA and rRNA transcripts through a process termed regulated IRE1-dependant decay of mRNA (RIDD) [10]. Intriguingly, RIDD and XBP1 splicing are differently regulated and can lead to opposite effects on cell fate decisions [11]. IRE1 can also signal through a protein scaffold named the UPRosome [12]. Under stress conditions the dissociation of GRP78 causes ATF6 to be exported to the golgi complex [13] where it is cleaved into its active form, ATF6f, by site 1 and 2 proteases [14]. ATF6f then translocates to the nucleus where it selectively activates UPR gene transcription [15]. Following GRP78 dissociation, PERK oligomerizes and trans-autophosphorylates leading to the phosphorylation the eukaryotic initiation factor 2α (eIF2α) at Ser51, thereby attenuating general translation [16]. This also allows the selective translation of a particular subset of transcripts [17], including activating transcription factor 4 (ATF4), causing subsequent upregulation of adaptive genes [18]. However, ATF4 also upregulates C/EBP homology protein (CHOP), a pro-death transcription factor [19] (Figs. 1 and 2).

* Corresponding author at: Apoptosis Research Centre, Biosciences Research Building, Corrib Village, NUI Galway, Dangan, Galway, Ireland. Tel.: +353 91492440; fax: +353 91494596.
E-mail address: afshin.samali@nuigalway.ie (A. Samali).

http://dx.doi.org/10.1016/j.semcancer.2015.03.003
1044-579X/

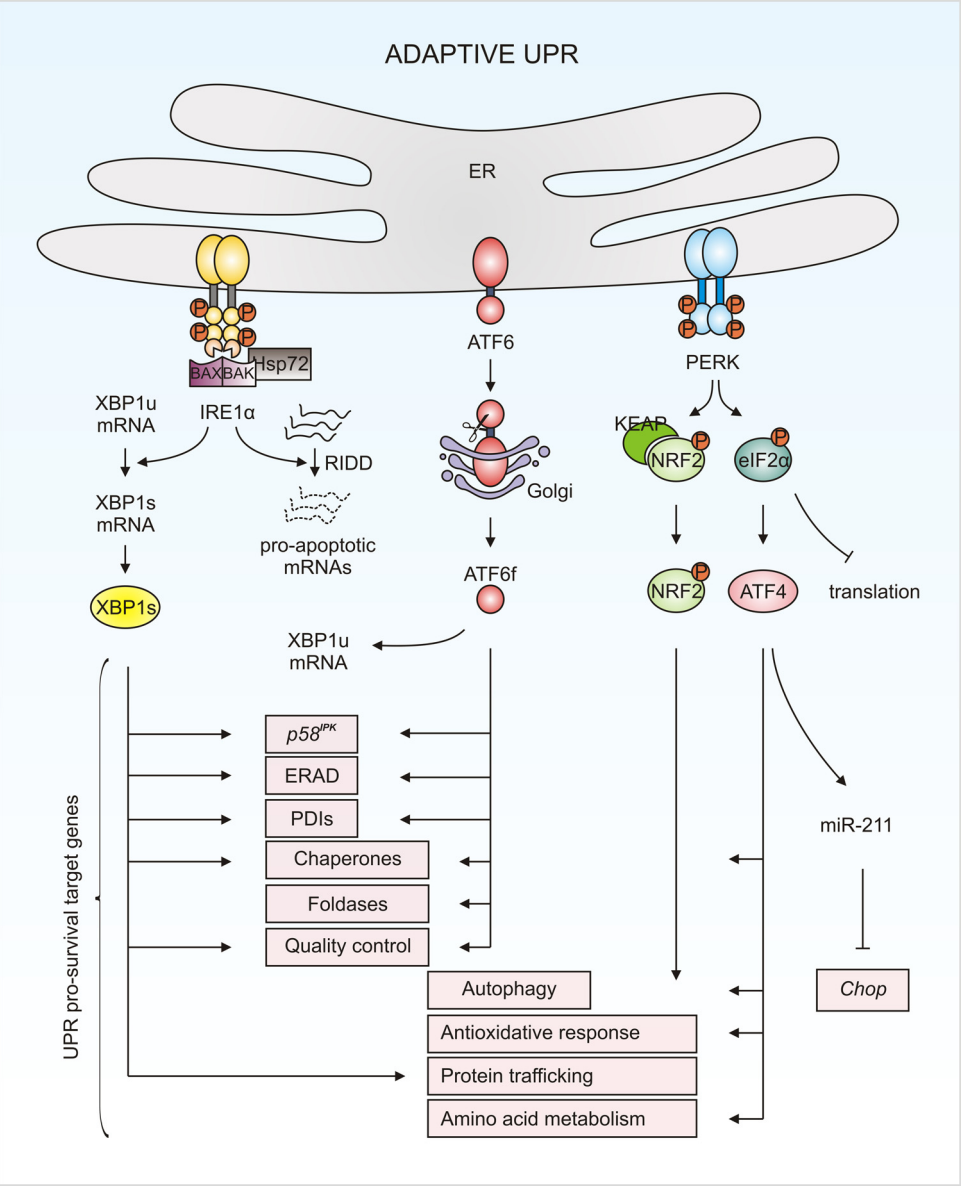

Fig. 1. UPR regulatory mechanisms of adaptive responses to ER stress. Active IRE1 RNase regulates pro-survival response through RIDD and unconventional splicing of XBP1. The latter induces expression of pro-survival UPR genes including $p58^{IPK}$, a negative feedback regulator of PERK. IRE1 interaction with HSP72, BAX and BAK enhances XBP1s signaling. PERK phosphorylates NRF2 to induce expression of antioxidant and detoxifying enzymes, and eIF2α to turn off global protein synthesis. ATF4 is selectively expressed and regulates transcription of pro-survival genes. In addition ATF4 increases miR-211 levels to inhibit CHOP expression. Golgi-translocated and cleaved ATF6 (ATF6f) upregulates XBP1u and targets genes to reduce ER stress independently or in cooperation with XBP1s.

Subversion of the cell fate machinery underlies many of the hallmarks of cancer [20], so it comes as little surprise that the UPR plays a pivotal role in malignant transformation, from oncogenesis to tumor progression and metastasis. Indeed, the oncogene-induced rapid proliferation of cancer cells requires enhanced production of membrane and secretory proteins which increases the demand on the cellular protein folding machinery. Moreover, the tumor microenvironment is characterized by physiological stresses such as hypoglycemia, oxidative stress, and hypoxia that lead to unremitting ER stress and a constantly activated UPR. In normal cells this stress level would tip the balance in favor of a pro-apoptotic UPR response with cell death as the outcome. However, cancer cells have an enhanced capacity to resist cell death thus allowing them to selectively benefit from the pro-survival effects of the UPR [2]. Approaches to therapeutically target the UPR by inhibiting UPR regulated survival pathways and/or increasing pro-death signaling in order to tip the balance toward cell death have attracted a lot of attention in the past few years. However, the paradox that UPR signaling can lead to both cell survival and cell death is a distinct challenge for targeting the UPR as an anti-cancer strategy. To add further complexity, each arm of the UPR has both pro-death and pro-survival potential. For example, UPR mediated phosphorylation of eIf2α inhibits its translational activity thereby reducing the protein load in the ER and is therefore considered cytoprotective; however prolonged phosphorylation of eIf2α induces cell death. To circumvent this paradox a comprehensive knowledge of UPR signaling, and how it pertains to a particular disease state is essential. Here we review our current understanding of pro-survival and pro-death UPR signaling in the context of their involvement in cancer development and progression and evaluate how this integrated signaling pathway could be used as a therapeutic target to reduce or prevent tumor growth.