IRE1 Signalling Pathway:
A Target Approach for Cancer Therapy

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Abstract

The abnormal accumulation of misfolded proteins in the endoplasmic reticulum (ER) can lead to the condition termed ER stress, resulting in the activation of unfolded protein response (UPR). Inositol-requiring enzyme type 1 (IRE1) signalling pathway is one of the three main branches of UPR and is involved in many types of cancer. This review focuses on the downstream events of IRE1 and its potential as a novel cancer drug target.

Introduction

- The presence of misfolded proteins causes the activation of UPR.
- Three proteins of UPR – **IRE1, protein kinase R-like endoplasmic reticulum kinase (PERK) and activation transcription factor 6 (ATF6).**
- Persistent ER stress leads the response to change from a **pro-survival response** to a **pro-apoptotic response** and is **highly prevalent in cancer progression.**
- Among the three, IRE1 is the most conserved and has the potential to be used as a drug target.

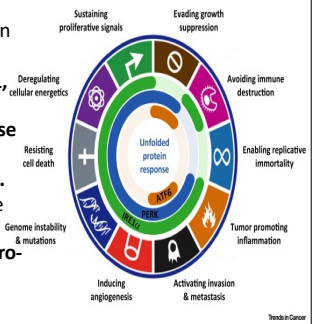

Figure 1: Comparison of the three UPR proteins (IRE1, ATF 6 and PERK) effects on cancer outcomes. IRE1 is found to be involved in most cancer hallmarks (Urra et al., 2016).

Interactions with other branches

ATF 6

- ATF6 is involved in the **splicing of X-box binding protein 1(XBP1) mRNA** and facilitates ER-associated degradation (ERAD) and protein folding together with XBP1.
- However, it was also found that **ATF6 inhibition can cause the overproduction of IRE1.**

PERK/ATF4

- Increase the expression of IRE1
- Blocking IRE1/XBP1 pathway can enhance the ATF4 production
- **PERK pathway remains activated** in prolonged intense stress conditions, while IRE1 halts the functions.

Downstream Pathways

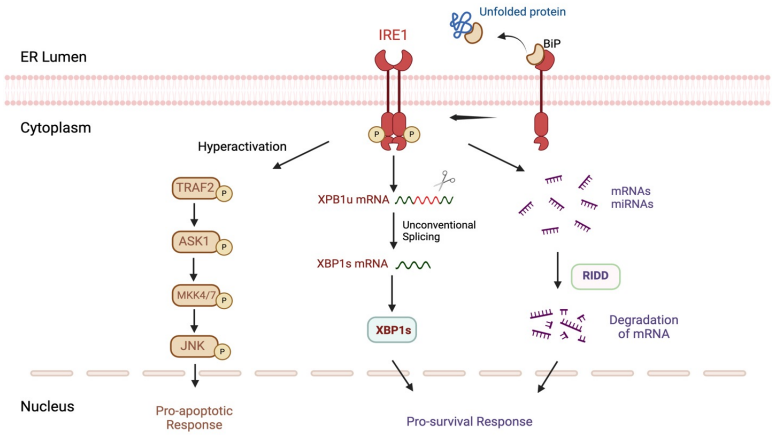

Figure 2: Diagram illustrating the downstream pathways of IRE1 signalling leading to two main responses: Pro-apoptotic and pro-survival (Created with Biorender.com)

XBP1 and RIDD in Cancer

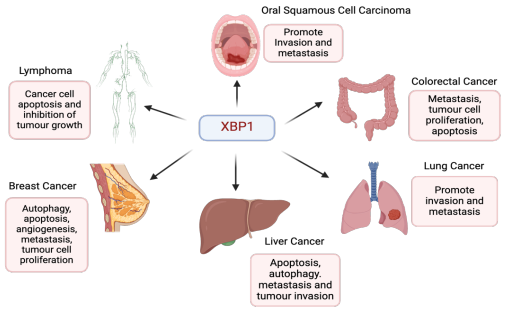

Figure 3: The involvement of XBP1 in various types of cancer development and outcome. It can cause both inhibition and activation of tumours depending on the cancer type and stages (created with Biorender.com).

Regulated IRE1-dependent degradation (RIDD)

- The first mechanism to be activated upon ER stress
- When the XBP1 pathway is unable to control ER stress, **RIDD is stimulated to produce pro-apoptotic responses.**
- Due to its involvement in **supporting ER homeostasis**, it is challenging to use the RIDD axis as a cancer drug target.

IRE1 Targeted Cancer Therapies

Two mechanisms of using the IRE1 pathway for cancer

- Inhibition of the IRE1/XBP1 axis to stop excessive tumour cell proliferation via **RNase domain** or **Kinase domain**
- Overactivation of IRE1 activities to stimulate **RIDD-related pro-apoptotic responses**

Table 1: Different types of IRE1 inhibitor drugs and their binding sites

Binding domain	Drug name	
RNase Domain	Salicylaldehydes	
	Toyocamycin	
Kinase Domain	Type 1	Sunitinib
		IPA
		APY29
	Type 2	KIRA analogs
		C27H23F3N6O

Conclusion and Future Aspects

- **Although IRE1 is the most studied among the three branches, its exact involvement in tumour proliferation and metastasis remains unclear.**
- **It is still challenging to use IRE1 as a cancer drug target due to its dual role in cancer development and RIDD functions in maintaining ER homeostasis.**
- **However, with selective inhibitors, off-target effects are found to be reduced and give better control of the interrelations with other branches.**

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Key References

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