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Vicki Mercado
Pepperdine University

Jay L. Brewster
Pepperdine University

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The Survivin and cIAP1 anti-apoptotic proteins are differentially downregulated in response to endoplasmic reticulum stress

Vicki Mercado, Dr. Jay Brewster
Summer Undergraduate Research in Biology
Pepperdine University Malibu, California 90263

Abstract

The endoplasmic reticulum (ER) is an organelle tasked with synthesis and transport of 90% of new cellular proteins. Dysfunction within this organelle creates signals for repair, adaptation, and, in severe cases, cellular apoptosis. Multiple human diseases have been associated with ER dysfunction, and the activation of apoptosis in important populations of cells. Inhibitor of Apoptosis (IAP) proteins are cytosolic proteins that play an anti-apoptotic role in the cytosol. The relationship between endoplasmic reticulum (ER) stress and the expression/ stability of IAPs is not well characterized. The objective of this study was to characterize the affect of ER stress on the expression/stability of IAP family members in BHK21, A549, A549 cells.

We also assessed inhibition of the PI3K/Akt pathway affects expression of these proteins. In model cell lines (BHK21, A549), Survivin and cIAP1 expression was detected via immunoblot. ER stress was shown to induce a reduction of both Survivin and cIAP1 in a time and dose dependent manner, with Survivin displaying a more dynamic response. The phosphatidylinositol-3-kinase (PI3K) pathway has been associated with regulating expression of some IAP proteins. Inhibition of the PI3K decreased Survivin expression in both cell lines. Further research is required to confirm the effects of ER stress upon regulation of IAP expression (PI3K) and upon stability.

Results

Three transmembrane proteins, PERK, ATF6, and IRE1α, serve as ER stress sensors involved in the activation of the UPR. Binding of immunoglobulin protein (IgB) unbinds from the transmembrane proteins to refold misfolded proteins. This activates several pathways leading to transient arrest of protein translation, degradation of proteins through the proteasome, and the upregulation of chaperones in an effort to repair the cell by preventing programmed cell death, known as apoptosis [2].

In addition to the UPR, a parallel cell survival mechanism involving Akt kinase, the Extracellular regulated Kinase (ERK) pathway, and cytosolic inhibitor of apoptosis proteins (IAPs) has also been identified. A baculovirus IAP domain that promotes binding with, and regulation of, pro-apoptotic caspases is conserved in IAPs [4,6]. By inactivating and ubiquitinating caspases, IAPs work alongside the UPR to regulate the apoptotic response in mammalian cells [2,8]. Prolonged ER stress exhausts the protective measures of the cell. If the UPR cannot regulate the amount of unfolded proteins to restore homeostasis, a caspase cascade is activated resulting in apoptosis [2].

Previous studies have shown increased cell susceptibility to apoptosis, and inhibition of proliferation in cancer cells as a result of IAP downregulation [2,8]. While it is known that altering IAP expression affects the cells susceptibility to apoptosis, the impact of ER stress on IAP expression in relation to apoptosis is not fully understood. As abnormal expression of IAPs has been linked to numerous malignancies such as cancer and neurodegenerative disorders, therapeutic options may benefit from elucidation of the relationship between ER stress and IAP expression.

The objective of this study was to characterize the affect of ER stress on the expression/stability of five members of the IAP family: XIAP, cIAP1, cIAP2, Survivin, and Livin. Data from our lab shows distinct responses of the cell with varying degrees of ER stress. A protective response is observed in cell’s facing low ER stress; cells can be rescued and have a reduced apoptotic response compared to cell’s managing high ER stress. Ultimately we want to assess how intensity of ER stress affects the expression of these proteins, how these proteins are involved in the protective response against low ER stress, and if IAP expression is regulated through the Akt pathway in the ER stress response.

Works Cited


Conclusion

• In BHK21 and A549 cells Livin, XIAP and cIAP2 expression is not detected.
• ER stress induced by TUNI causes downregulation of Survivin and cIAP1 expression/stability in a time and dose dependent manner in BHK21 cells.
• In BHK21 cells, Survivin has a more dynamic response to ER stress.
• A549 a downward trend of survivin is observed in response to greater ER stress, while cIAP1 expression remains relatively stable.
• The P13 kinase pathway is involved in regulating IAP expression/stability in the ER stress response in BHK21 and A549 cells.

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