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Signal transduction pathways that protect cells from stress, and the effects of their activation in tumor cells

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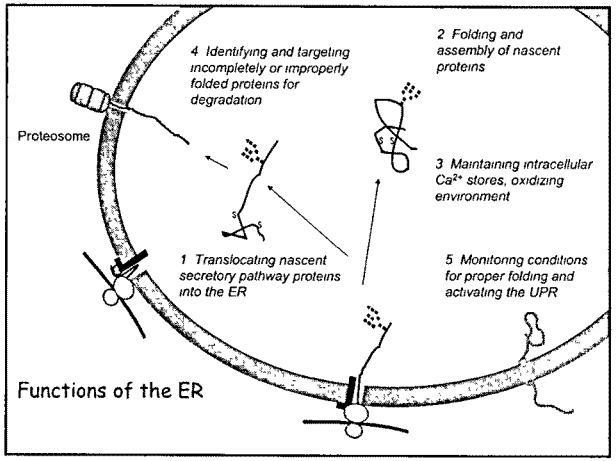
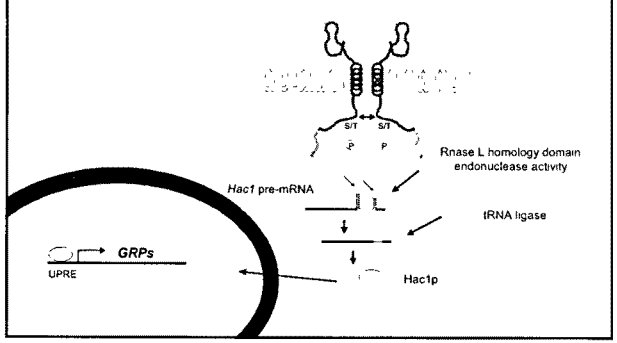
During normal growth and differentiation, cells encounter variations in their environment that can adversely affect their physiological functions. These conditions can cause both genotoxic and cytotoxic stresses.Signal transduction pathways exist to detect and respond to these insults.In the case of genotypic stresses, DNA damage is monitored at various cellular check-points, and if unresolved, apoptotic pathways are initiated to protect the organism.Conversely, cytotoxic stresses, which can occur frequently and are readily reversible, initiate responses that are more geared toward cytoprotective measures.It has been well-documented that genotoxic stresses occur in many cancer cells and that the cellular responses to control this damage are often disabled. Thus after accumulating mutations that alter cell cycle and apoptotic checkpoints, the major obstacle the cancer cell faces is the restricted supply of nutrients and oxygen.These conditions impinge on protein folding in the endoplasmic reticulum and activate the cytoprotective unfolded protein response (UPR), which may contribute to the establishment and growth of tumors as well as alter their response to chemotherapy. There has been much progress in identifying conditions that activate the UPR, in delineating the signaling components, and in determining the consequences of UPR activation.Data will be presented to describe what is known about the UPR and its role in cancer biology.

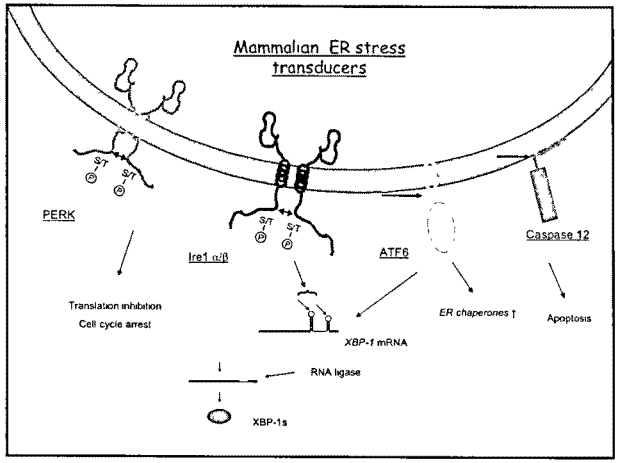


Major aspects of the UPR

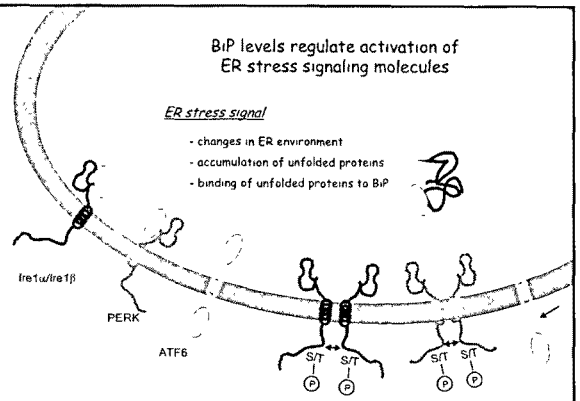
- Up-regulation of ER chaperones (BiP, GRP94, GRP170)
  - prevents protein aggregation and promotes refolding
- Inhibition of protein translation
  - limits the accumulation of unfolded proteins
  - not restricted to secretory pathway proteins
- Increased degradative capacity of the cell.
  - reduces load of unfolded proteins
- Arrest of cells in the G1 phase of cell cycle
- Activation of apoptotic pathways if stress persists

Components of yeast unfolded protein response (UPR)

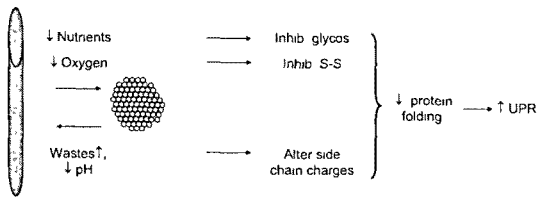




BiP levels regulate activation of ER stress signaling molecules



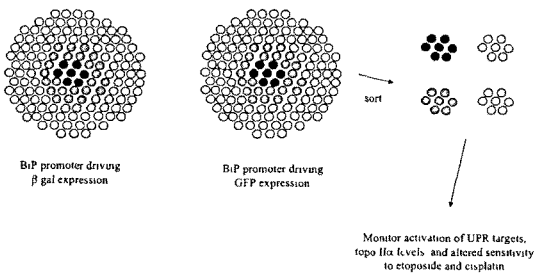
Alterations in the Environment of Solid Tumors Induce Cellular Stress Pathways



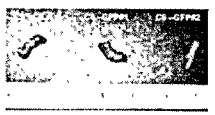
Major questions and approaches

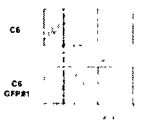
1. Is the UPR actually activated in solid tumor cells, and if so:
   - at what stages?
   - in what percent of the cells?
   - how does this affect topoisomerase IIα levels and drug sensitivity to topo II-targeted drugs and cisplatin?
2. Is the altered sensitivity to chemotherapeutic agents and/or loss of topoisomerase IIα a direct consequence of UPR activation or a secondary effect of the pharmacological agents used?
3. Which components of the UPR are responsible for loss of topoisomerase IIα altered drug sensitivity?

Is the UPR activated in solid tumors, and which cells show evidence of activation?

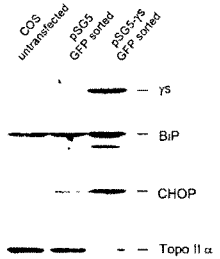


Tumors formed from rat C6 glioma cells activate the UPR

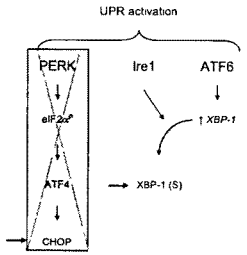


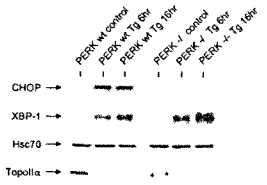


Over-expression of incompletely folded Ig heavy chain is sufficient to activate the UPR and leads to topo II α loss



UPR activation in PERK$^{-/-}$ cells





Topo II loss is not dependent on PERK activation!

Conclusions

- Mammalian cells have evolved complex methods to protect themselves from adverse physiological or chemical conditions
- If the stress conditions are not alleviated, cell death pathways are initiated to kill the cell in order to protect the organism
- Adverse physiological conditions are encountered by tumor cells during their growth that would be expected to activate the UPR and protect cells from chemotherapeutic agents
- Now that many of the components of the UPR signaling cascade are known, it should be possible to identify the molecule(s) that is responsible
- *This could allow design of a small molecular inhibitor that could improve the efficacy of some chemotherapeutic treatments*