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VEGF SIGNALS THROUGH ATF6 AND PERK TO PROMOTE ENDOTHELIAL CELL SURVIVAL AND ANGIOGENESIS IN THE ABSENCE OF ER STRESS.

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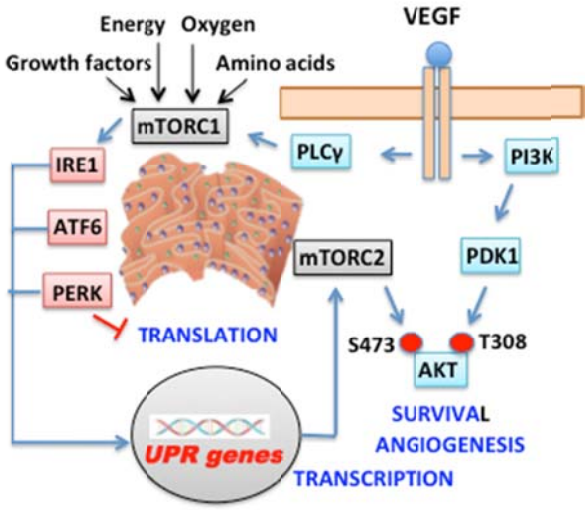
The ER is the major intracellular reservoir of calcium and is important in the biogenesis of peroxisomes and autophagosomes. Moreover, it plays a key role in metabolic processes, such as gluconeogenesis, lipid synthesis and protein folding of the secretory pathway. The latter being regulated via integration of environmental and cellular signals may in certain cases of cell stress lead to the generation of unfolded proteins in the ER (ER stress) that initiate the IRE1α, ATF6 and PERK cascades triggering a transcriptional/translational response known as Unfolded Protein Response (UPR). The transcriptional regulation targets genes that increase the protein folding capacity of the ER, whereas the translational control contributes by decreasing the load of proteins entering the ER. All these responses attempt to restore the ER homeostasis; however, prolonged UPR in which homeostasis cannot be re-established is associated with apoptotic cell death.



Karali et al show that the ER plays an important role in the signal transduction system of VEGF. Two multi-protein complexes, mTORC1 and mTORC2, and three unfolded protein sensors IRE1α, ATF6 and PERK reside on the membranes of the ER being integrated in the signaling machinery of VEGF. VEGF activates UPR mediators through a PLCγ-mediated cross-talk with the mTORC1 complex without accumulation of unfolded proteins in the ER. Activation of ATF6 and PERK contributes to the survival effect of VEGF on endothelial cells (ECs) by inducing mTORC2-mediated phosphorylation of AKT on Ser473, which is required for full activity of AKT. Concomitant instability of the mRNA and CHOP protein allows ECs to evade the pro-apoptotic effect of this UPR product. Depletion of PLCγ, ATF6 or eIF2α dramatically inhibited VEGF-induced vascularization in mouse Matrigel plugs suggesting that the ER and the UPR machinery constitute components of the VEGF signaling circuit that regulates endothelial cell survival and angiogenesis extending their role beyond adaptation to ER stress.

These findings demonstrate that the UPR machinery is not an exclusive tool for the cell to cope with ER stress and accumulation of unfolded proteins, but participates in physiological adaptations such as the VEGF signaling. This is a novel and fundamental pathway that had not been reported before for any growth factor integrating growth factor signaling events with the UPR machinery and metabolic/biosynthetic processes of the cell. The involvement of mTORC1 and mTORC2 further supports this notion. It appears that endothelial cell response to extracellular signals, such as the presence of VEGF, is integrated with the energy and nutrient status of the cells via metabolic

sensors, such as mTORC1, to carry out tailored translational and transcriptional regulatory adaptations through selected components of the UPR machinery.

Further understanding of the mechanisms by which VEGF utilizes the UPR machinery to achieve cell survival by integrating also context-dependent mTORC1 checkpoints sensing the metabolic state of the cell might help elucidate the underlying mechanisms of the different cell fates supported by the UPR machinery (apoptosis, survival, differentiation). Such information might provide critical information about developing future therapeutic interventions for many important human diseases. Indeed, the pathogenesis of cancer, diabetes, autoimmune diseases and neurodegenerative diseases, which are characterized by protein misfolding and aggregation (Parkinson's, Alzheimer's, ALS), involves a certain degree of ER stress that is currently the focus of therapeutic intervention towards these diseases.

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