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Mitochondrial HSP90s and tumor cell metabolism

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The control of protein homeostasis, or proteostasis, has been traditionally viewed through the lenses of a general housekeeping function that all cells need, regardless of pathway specification or link to defined cellular responses. A more updated perspective considers proteostasis as an essential adaptive mechanism, taking place in specialized subcellular organelles, and maintaining the functionality of defined cellular networks. Fresh experimental evidence now identifies heat shock protein 90 (HSP90) chaperones as pivotal regulators of proteostasis in mitochondria, selectively in tumor cells. This function connects to a global network of cellular compensation, linking autophagy, endoplasmic reticulum (ER) stress and metabolic reprogramming in a single adaptive continuum, and offers prime opportunities for novel cancer therapeutics.

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Despite great progress in mapping cancer genes and their pathways, the efficacy of conventional or targeted anticancer agents is invariably hampered by resistance mechanisms. These are spurred by the enormous selective pressure introduced by drug treatment, which ultimately endows a successful malignant clone(s) with a better chance of surviving environmental challenges. Both autophagy and metabolic reprogramming, the so-called Warburg effect, have been thought of as adaptive mechanisms that help tumor cells cope with almost any kind of unfavorable environment, whether it be nutrient or oxygen deprivation, exposure to cytotoxic stress, or attack by the immune system. Although these processes come at a cost for tumor cells in terms of organelle catabolism and inefficient energy production, they play a key role in tumor maintenance, especially in advanced disease stages. There is also evidence that autophagy and tumor metabolism may be closely interconnected, so that identifying upstream regulators of both processes may help in developing "pathway" inhibitors, agents that target compensatory mechanisms irrespective of tumor heterogeneity.

Work recently contributed by our group now suggests that HSP90 chaperones may function as an upstream connector between the control of protein folding and adaptive mechanisms of autophagy and cancer metabolism. Intriguingly, this did not involve the abundant HSP90 pool in the cytosol, but a discrete subset of the chaperone and its ATPase-directed homolog, TNF receptor-associated protein-1 (TRAP1), compartmentalized in mitochondria, selectively of tumor cells. Using a straightforward protein folding assay, it was shown that inhibition of mitochondrial HSP90s caused misfolding of peptidylprolyl isomerase D/cyclophilin D (PPID/CYPD), a matrix prolyl isomerase best known for its role in organelle permeability transition and apoptosis. In turn, PPID misfolding induces the release of the first enzyme of the glycolytic cascade, HK2 (hexokinase 2), from the mitochondrial outer membrane, obliterating its enzymatic activity. Because of the over-reliance of tumor cells on aerobic glycolysis, this results in a sudden decrease in ATP production, a drop in glucose consumption and reduced lactate generation.

Tumor cells sense these changes as acute energetic stress, and mount an immediate, compensatory response. Within minutes of mitochondrial proteotoxic stress, tumor, but not normal cells, phosphorylate

the energy rheostat AMP-activated kinase (AMPK), shut off the mechanistic target of rapamycin (MTOR) pathway, and activate autophagy. These all improve cell survival, as blockade of AMPK, inhibition of autophagy and further ablation of glycolysis potently enhance tumor cell killing. In addition, energy starvation imposed by mitochondrial proteotoxic stress reduces the amount of ATP available for protein post-translational modifications in the ER. This triggers a canonical unfolded protein response (UPR), leading to extensive transcriptional changes in nuclear gene expression. One of the molecules upregulated in this mitochondria→ER UPR signaling is HSPA5/GRP78, a pleiotropic chaperone that further improves tumor cell survival and proliferation.

All of these adaptive changes were reproduced in a genetic model of prostate cancer in mice, and when their implications were explored in primary patient samples, increased HSPA5 expression emerged as a strong predictor of unfavorable disease and abbreviated survival in patients with non-small cell lung cancer.

What can be learned from these data? First, the results seem to uncover a broad signaling network that connects mitochondria, the ER, and nuclear gene expression in a single continuum. The main node in this network is an adaptive control of mitochondrial proteostasis, maintained by the organelle pool of HSP90s, and regulating PPID folding in both permeability transition and aerobic glycolysis. A second point is the dynamic functionality of this network that exploits multiple, nonoverlapping mechanisms of autophagy, ER UPR and bioenergetics to compensate for mitochondrial imbalance, and maintain cell proliferation and cell survival in the face of organelle stress. Based on the correlative data in mouse models and patient samples, we are to conclude that these mechanisms do occur in tumors, in vivo, and may have important consequences for disease outcome. Why this pathway is selectively exploited in tumors, compared with normal cells, remains to be fully determined. One plausible explanation is that tumor cells have higher biosynthetic needs than normal tissues, and must more tightly control their protein folding environment especially in mitochondria; hence the recruitment of HSP90s to tumor mitochondria as buffers of metabolic reprogramming and cell fate decisions.

And, last, can we turn this adaptive tumor network into something useful for our patients? Intriguingly, none of the diverse HSP90 antagonists currently in the clinic has the ability to accumulate in mitochondria; so these studies used a novel design of an HSP90 ATPase inhibitor engineered to selectively accumulate in mitochondria (*Gamitrinib,* GA mitochondrial matrix inhibitor). By inducing PIID misfolding, Gamitrinib acts as a unique dual inhibitor of metabolism and cell survival selectively in tumors, features that bode well for its future development as an anticancer agent. Plus, even concentrations of Gamitrinib that are by themselves harmless quickly shut down aerobic glycolysis, making tumor cells sharply dependent, perhaps even "addicted" to autophagy for their survival. With the growing interest in autophagy inhibitors as potential cancer therapeutics, one can envision the simultaneous blockade of autophagy and mitochondrial HSP90s to rationally disable a panoply of metabolic and survival adaptive mechanisms in a broad spectrum of genetically heterogeneous tumors.