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PK-01
SMALL COMPOUNDS MODULATING BI-DIRECTIONAL ALLOSTERY IN PROTEIN KINASES: A NEW GRIP ON AN OLD TRICK?

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Over the last 20 years we investigated the molecular mechanisms of regulation of a large group of kinases, termed AGC kinases (PDK1, PRKs, aPKCs, S6K, SGK, Akt/PKB, RSK, etc.). We identified a regulatory site in the small lobe of PDK1, termed "PIF-binding pocket" that participates in the docking interaction of PDK1 with a subset of substrates, i.e. S6K, SGK, but not PKB/Akt. In addition, the PIF-pocket of PDK1 -and the equivalent PIF-pocket site in other AGC kinases- participates in the mechanism of activation and inhibition of these kinases, by phosphorylation or interaction with other domains. The binding of synthetic small compounds to the PIF-pocket can "close" the kinase domain and allosterically "activate" PDK1 in vitro, or allosterically affect the ATP-binding site and be allosteric inhibitors of other AGC kinases. I will describe the allosteric process, induced by compounds binding to the regulatory site and affecting the ATP-binding site and how this modulation can be "reversed" by small compounds binding to the ATP-binding site. Thus, different compounds binding with high affinity to the ATP-binding site can produce different "reverse" allosteric effects on the PIF-pocket of PDK1, i.e. displace or enhancing docking interactions, and ultimately can produce different effects in cell signaling. I will further present studies on the allosterc processes induced by small compounds in protein kinases outside of the AGC group of protein kinases, i.e. Aurora kinase, Polo-like Kinase 1 (PLK1) and others. The studies unviel the bi-directional use of the allosteric process for innovative drug discovery in protein kinases

PK-02
ROLE OF PKA IN PROTEIN TRANSLATION REGULATION DURING ADVERSE ENVIRONMENTAL GROWTH CONDITIONS

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In response to environmental stress conditions, the cellular protein content is readjusted through signalling pathways, such as cAMP-PKA, that alter different processes connected to transcriptional, translational and post-translational programs. In *S. cerevisiae,* PKA is a hetero-tetramer composed of two regulatory subunits encoded by the *BCY1* gene, and two catalytic subunits encoded by three genes, *TPK1*, *TPK2* and *TPK3*. We have reported that Tpk2 and Tpk3 differentially localize to mRNA processing bodies (PBs) and stress granules (SGs) in response to glucose starvation, strong osmotic stress, severe heat stress and stationary phase. Deletion of *TPK3* or *TPK2* genes differentially impacts on the capacity of cells to form PBs or SGs as wll as on the global translation and translational fitness of specific mRNAs. We also found that Tpk2 and Tpk3 showed different dynamics and mechanisms of interaction with SGs and PBs. Moreover, Tpk2 and Tpk3 kinase activity and the Tpk2 Q-rich domain are involved in the mechanism of assembly of PBs and SGs in a stress type-dependent manner. A global characterization of granular enriched fraction from mild and severe heat stress showed different protein composition under both conditions. The results suggest that Tpk2 and Tpk3 localized in PBs/SGs could interact with a complex network of distinct protein and potential substrates. Our findings contribute to the concept that different stress conditions induce specific cellular responses, and highlight a different potential role for each isoform of PKA on fundamental processes such as protein synthesis.

PK-03
STUDY OF PI3K/AKT/mTOR PATHWAY IN BREAST CANCER PROGRESSION.

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Deregulation in the PI3K/AKT/mTOR pathway is associated with breast cancer development. Using experimental models of breast carcinogenesis induced in mice, xenografts of tumor cell lines, and tumors from patients we found a differential role of AKT1 and AKT2 isoforms in breast cancer progression. That is, AKT1 regulates nuclear proteins related to cell proliferation, such as cyclin D1 and pS6, whereas AKT2 regulates proteins related to cell migration and invasion such as vimentin, integrin b1, F-actin and FAK. Furthermore, activation of AKT1 promoted the hormone-independent and endocrine resistant phenotype, whereas activation of AKT2 lead to a more aggressive phenotype and lung metastasis. We analyzed 98 luminal breast carcinomas and found that nuclear AKT1 associates with low grade tumors, while cytosolic AKT2 associates with high grade tumors. Furthermore, presence of cytosolic AKT2 was positively correlated with a shorter time to progression of the disease (earlier relapse). In addition, based on our results and data analysis from public databases of The Cancer Genome Atlas, we postulate that throughout the progression of the disease there would be a switch between AKT1 and AKT2 isoforms, which maintains AKT2 inhibited while AKT1 prevails in the early stages. In the more advanced stages, this inhibition is lost and AKT2 prevails. Specific miRNAs are good candidates involved in this regulation and are now been tested in our lab in different experimental and clinical conditions. We propose the use of AKT1 and AKT2 isoforms determined by immunohistochemistry as prognostic markers that could help to better stratify breast tumors and direct more specific therapies