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IN THIS ISSUE

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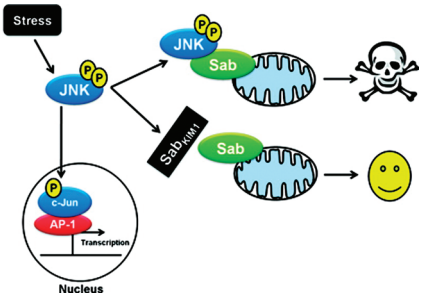
Stopping Stress-Related Cell Death

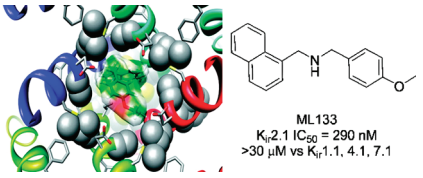
The c-jun N-terminal kinases (JNKs) are serine/threonine protein kinases associated with many important stress-related processes leading to the activation of apoptotic pathways in cells. During stress, mitogen-activated protein kinase kinases, or MAPKKs, phosphorylate JNK, triggering JNK to relocate to the mitochondria and activating subsequent mitochondrial pro-apoptotic transcription factors. Chambers *et al.* (DOI: 10.1021/cb200062a) report an approach to selectively prevent JNK translocation, a result that has enormous implications in the fight against stress-related conditions.



During migration to the mitochondria, activated JNK docks with its scaffold protein and substrate, Sab. Recent reports indicate that JNK phosphorylates and activates Sab *via* the kinase interaction motif 1 (KIM1) present on Sab. The authors thus targeted mitochondrial JNK signaling by siRNA-mediated silencing of Sab or by mimicry with a cell-permeable interfering peptide resembling KIM1. This inhibitory peptide selectively disrupted JNK/Sab binding and prevented downstream mitochondrial stress-related signaling while maintaining important nuclear JNK signaling. This study brings to light an important new drug target in the development of therapeutics against stress-related conditions such as heart attack, stroke, and Parkinson's disease.

Discovery of Specific Inhibitor for Potassium Ion Channel

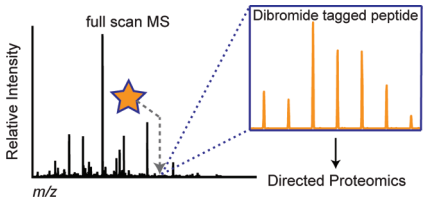
Potassium (K^+) channels are ubiquitous ion channels found in nearly all living organisms. These K^+ channels form K^+-specific permeation pores *via* multimeric membrane-spanning helices and are well-known drug targets for treating cardiovascular, neurological, renal, and metabolic disorders. Several classes of K^+ channels exist. The inward rectifier K^+ channel (K_{ir}) class comprises four membrane-spanning α-helical subunits that preferentially permeate K^+ ions into the cell rather than outward. Recently, K_{ir} channels have been implicated in the treatment of pain and cardiovascular disorders, but no selective small molecule tools are currently available to facilitate K_{ir} channel study. In this issue, Wang *et al.* (DOI: 10.1021/cb200146a) describe the identification and optimization of a specific inhibitor of one K_{ir} channel, $K_{ir}2.1$, in the $K_{ir}2$ family.



The authors performed a high-throughput screen of over 30,000 compounds in search of $K_{ir}2.1$ inhibitors, which led to the discovery of ML133. Interestingly, ML133 works specifically against $K_{ir}2.1$ channels with weak to no observed inhibition of other K_{ir} channels, including other $K_{ir}2$ channels, which display a high degree of structural similarity. Site-directed mutagenesis studies identified amino acid residues critical to $K_{ir}2.1$ specificity to this compound. Thus, the discovery of ML133, and the identification of determinants for its specificity opens the door for developing better therapeutics targeting $K_{ir}2$ channels.

A Proteomic Signature

Proteomics, the study en masse of the proteins produced by an organism, often relies on mass spectrometry for the identification, characterization, and quantification of proteins of interest. While numerous mass spectrometry approaches have been developed for proteomic applications, a common challenge is the detection of proteins of low abundance. Palaniappan *et al.* (DOI: 10.1021/cb100338x) now describe IsoStamp, which stands for isotopic signature transfer and mass pattern prediction, as a method for detecting as low as femtomole quantities of chemically tagged proteins in complex biological mixtures.



The IsoStamp approach is based on the incorporation of a dibrominated chemical tag into a protein. The dibrominated peptides that are generated upon proteomic digestion, which is performed prior to mass spectrometry analysis, exhibit unique isotopic distributions. A pattern-searching algorithm was developed to identify these distributions among the sea of other peptide signals present in the sample. This versatile approach can be applied to any chemical labeling-based proteomics platform, facilitating detection of various protein populations such as those with certain posttranslational modifications or those involved in specific metabolic pathways.

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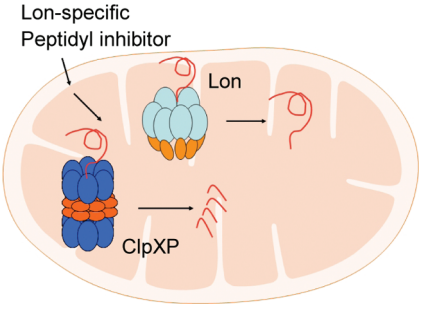
New Probe for Assessing Protein Quality Control

Mitochondrial protein quality is controlled by the activities of two important ATP-dependent proteases, Lon and ClpXP. These proteases selectively degrade misfolded proteins in mammalian cells and are vital to the proper functioning of the mitochondria. Currently, there is no way to accurately assess or differentiate the precise physiological function of these individual enzymes. In this issue, Fishovitz *et al.* (DOI: 10.1021/cb100408w) report the development of chemical probes for studying the role of Lon protease for protein quality control in the mitochondria.



To decipher the individual contributions of Lon and ClpXP proteases in protein degradation, the authors identified a peptide reporter substrate and a peptide inhibitor specific for Lon. Differences in substrate cleavage specificities between the enzymes led to the identification of a Lon specific fluorogenic substrate and peptidyl boronate inhibitor. The inhibitor was shown to potently decrease Lon activity in crude mitochondrial extracts and in cell cultures. These novel chemical tools provide a breakthrough in distinguishing the activities of Lon and ClpXP and, in doing so, offer important insight into the role of these enzymes in diseases linked to misfolding of mitochondrial proteins.

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