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ANTIVIRAL DRUGS

Salubrious inhibition

A common cellular stress response can be therapeutically modulated with a small molecule through the selective inhibition of dephosphorylation by phosphatases, report Michael Boyce and colleagues in *Science*. Until now, inhibition of phosphatases, and the modulation of the activity of the proteins they regulate through dephosphorylation, was seen as problematic because of their relative lack of substrate specificity — inhibiting phosphatases could prevent the dephosphorylation of many different proteins and therefore have wide-ranging and unwanted side effects.

Boyce and colleagues studied a protein called eukaryotic initiation factor 2 α (eIF2 α) that functions in the unfolded protein response (UPR), which is activated by endoplasmic reticulum (ER) stress — a result of strains placed on the cell, such as heavy protein synthesis. A dysregulated UPR is seen in a range of pathological conditions, including Alzheimer's disease and viral infection, and ER stress can induce apoptosis in stressed cells.

In the study, ~19,000 chemicals were screened for those that protected against ER-stress-induced apoptosis in mammalian cells. A chemical dubbed salubrinal dose-dependently inhibited apoptosis in this model, and suppressed apoptotic proteins such as caspases; however, it is not a general apoptosis inhibitor as it was ineffective in non-ER-stress-induced apoptosis.



Salubrinal lives up to its name by inducing eIF2 α phosphorylation and its downstream effects. Phosphorylation of eIF2 α is cytoprotective by virtue of its capacity to widely downregulate the production of proteins and ensure the correct expression of UPR genes — which in the case of a viral infection reduces the manufacture of new viral particles.

Using infection of cells with herpes simplex virus (HSV), Boyce and colleagues probed whether salubrinal is a selective inhibitor of eIF2 α dephosphorylation. HSV infection leads to eIF2 α phosphorylation, which quiets translation of host and viral proteins. In response, HSV expresses ICP34.5, which, in conjunction with host proteins, dephosphorylates eIF2 α , thereby taking the block off the synthesis of viral proteins. Salubrinal inhibits ICP34.5-mediated eIF2 α dephosphorylation, and so translation is shut down and viral protein synthesis muted.

The significance of this work lies in the fact that salubrinal inhibits a known dephosphorylation event that can be modulated for a therapeutic

effect. Crucially, salubrinal does not affect many other dephosphorylations in the cell. The problem that was thought to beset phosphatases — their lack of specificity, and the consequent wide-ranging and unpredictable side effects resulting from their inhibition — is overcome by targeting a protein complex required for the specific dephosphorylation of eIF2 α . This work therefore establishes the viability of targeting specific phosphatases in disease with small molecules without causing indiscriminate deregulation of phosphorylation.

A greater understanding of the mechanism of action of salubrinal could aid in the discovery of other selective inhibitors of dephosphorylation, which might be able to restore a variety of dysregulated pathways in pathological states. Such inhibitors, if successfully developed as drugs, could find uses in fields as diverse as neurodegeneration, cancer and infection.

Daniel Jones

References and links

ORIGINAL RESEARCH PAPER Boyce, M. *et al.* A selective inhibitor of dephosphorylation protects cells from ER stress. *Science* **307**, 935–939 (2005)