molecular interventions
pharmacological perspectives from biology, chemistry and genomics

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DEPARTMENTS

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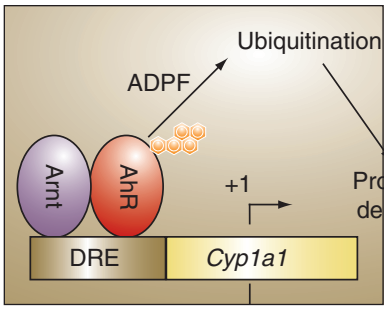
VIEWPOINT

The study of xenobiotic metabolism has long been a core activity in pharmacology. The diverse chemical transformations of xenobiotics in vivo are elegant in themselves, depending as they do on a battery of enzymes that include the cytochomes P450 (CYPs), and their reaction mechanisms have been elucidated by a great many pioneering pharmacologists who helped to launch the discipline. Today, researchers are finding surprising and subtle intricacies in the molecular control that underpins the xenobiotic response. For example, the inducible expression of CYP-encoding genes above normal basal output is controlled by specialized xenobiotic activated receptors (XARs), which include the aryl hydrocarbon receptor (AhR). But because CYP activities can be double-edged, supporting a multiplicity of chemical transformations, their expression levels must be tightly regulated over time and biological space. Indeed, the kinetics of xenobiotic-induced CYP expression suggest multiple checks and balances at both transcriptional and post-translational levels. Recent research points to the regulated degradation of AhR as one aspect of control. A key participant in directing AhR degradation has been identified—the AhR degradation promoting factor (ADPF)—which appears to serve as an E3 ubiquitin ligase. The biological machinery that controls the xenobiotic response thus encompasses an elegance deep beneath the traditional recognition of CYPs as catalysts of xenobiotic degradation.



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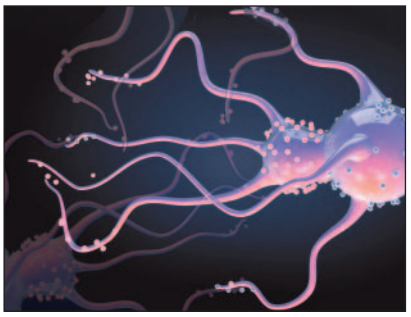
Ubiquitination as a means to control CYP1A1

Qiang Ma

REVIEWS



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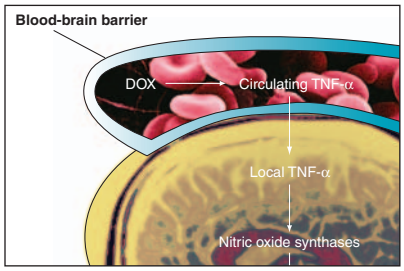
From one, many

Dale postulated that a neuron functions as a metabolic unit, whereby a process occurring in the cell can influence all of the compartments of that given neuron. With the passage of time, this statement has concretized into the more general, if, perhaps, misleading statement that "a single cell releases only one neurotransmitter." In fact, many neurons in the nervous system appear to contain and release more than one chemical acting as a neurotransmitter or neuromodulator. Indeed, cotransmission of a classical neurotransmitter and a peptide is a ubiquitous phenomenon, but several neuron types can also contain more than one classical neurotransmitter. Although the expression of peptide cotransmitters is known to be highly regulated in response to various physiological, chemical, and pathological signals, new data now suggest that a similar situation prevails in neurons that co-release two classical transmitters.

Louis-Eric Trudeau and Rafael Gutiérrez

REVIEWS *continued*

147 Collateral Damage in Cancer Chemotherapy



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Adding oxidative insult to injury?

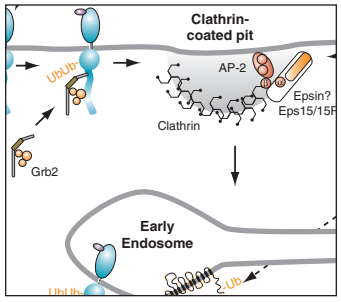
The life-extending effectiveness of anticancer chemotherapy is a major victory of post-World War II medicine. Unfortunately, many of the currently used medicines that combat cancer derive their only source of "specificity" for cancerous tissues from the aberrant rates of cellular growth that typify transformed cells, and damage to nontargeted (i.e., noncancerous) tissues remains the bane of modern chemotherapy. Of the 132 anticancer drugs that have been approved by the US Food and Drug Administration, fifty-six have been reported to cause oxidative damage to cells, often by mechanisms not directly related to their anticancer activities. Cognitive impairment in the "chemobrain" syndrome and heart injury from chemical therapies represent the risks that cancer patients continue to face. But new insights into mechanisms of oxidative stress have begun to point to strategies to protect healthy tissues from the oxidative threats posed by chemotherapeutics. These strategies may include the antioxidant quenching of reactive species generated under oxidative stress, the scavenging of iron ions that are released in response to chemotherapy, and the intervention of signaling molecules (e.g., tissue necrosis factor α) that may promote tissue damage in response to oxidative stress.

Yumin Chen, Paiboon Jungsuwadee, Mary Vore, D. Allan Butterfield, and Daret K. St. Clair

157 Ubiquitination: It's not Just for Protein Degradation Anymore

Many of the original observations of ubiquitination of the endocytic cargo and regulation of endocytosis by ubiquitination were made in yeast *Saccharomyces cerevisiae*. These findings in yeast prompted studies in mammalian cells, which have demonstrated that ubiquitin conjugation occurs on many mammalian growth factor receptors and transporters. Indeed, the function of many receptors and transport proteins at the cell surface is regulated by endocytosis and post-endocytic trafficking. This review describes recent advances in elucidating the mechanisms of ubiquitination of mammalian receptors and transporters using two examples: the receptor for epidermal growth factor and the dopamine transporter. How ubiquitination controls the endocytosis and turnover of these proteins is also discussed.

Manuel Miranda and Alexander Sorkin



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Ubiquitination and the cell surface expression of signaling proteins