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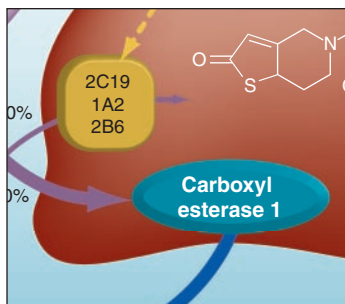
molecular interventions

pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

12 Individuality Is Nontransferable: Clopidogrel and Personalized Medicine

In 1997, clopidogrel was approved in the US for the prevention of cardiovascular diseases and received EU approval one year later. The large heterogeneity of the individual pharmacodynamic response of patients to this drug at the recommended doses was evident quite soon after marketing. Nevertheless, the mechanism(s)



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Clopidogrel metabolism

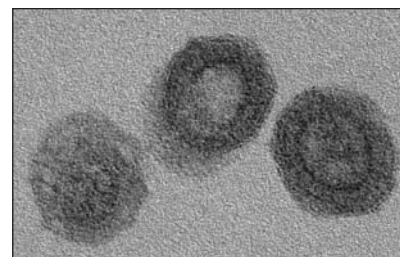
underlying this variability have been more clearly characterized in the past five years. The in vivo generation of the active metabolite from the pro-drug clopidogrel is the final result of a complex balance between bio-activating and bio-inactivating enzymatic reactions. The complex pharmacokinetics—not pharmacodynamics—of clopidogrel has been recognized as a major source of individual variability in drug response, as assessed by diverse assays of platelet inhibition. Pharmacogenetics and drug interactions modulate the enzymatic efficiency of the two-step bioactivating processes, which are mediated by different subfamilies of the cytochromes P (CYP) 450. Genetic variants of some CYP450s affect the generation of active metabolite, platelet (pharmacodynamic) response, and clinical outcomes of clopidogrel-treated patients. These findings have rapidly brought clopidogrel into the “personalized medicine” realm.

Bianca Rocca and Giovanna Petrucci

20 The XMRV Files: The Truth Is Out There

The xenotropic murine leukemia virus-related virus (XMRV) was first detected several years ago in prostate cancer tissue. A recent report links this virus to a different type of human disease, chronic fatigue syndrome (CFS), and demonstrates that infectious virus can be isolated from the blood of infected individuals. CFS has previously been linked to the presence of other viruses, including human herpes virus-6 and Epstein-Barr virus, but a causal relationship was never proven; thus, the new finding of an association to XMRV has stirred some controversy. Although XMRV, like HIV, is a retrovirus, XMRV is most closely related to viruses found in the genomes of certain mice. The large body of knowledge generated during decades of studying both human and non-human retroviruses provides important clues about the biology of XMRV and approaches for the development of therapeutic regimens. If there is something that both believers and skeptics can agree on, it is that an ongoing investigation is needed to clarify some of the current mysteries involving the biology of XMRV replication and its threat to human health.

KyeongEun Lee and Kathryn S. Jones



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Hazardous xenotropism:
Of mice and men

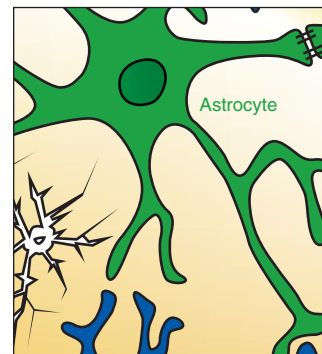


REVIEWS

25 Astrocytes: New Star Players in the Nociceptive Milieu?

During the early days of neuroscience, all the non-neuronal stuff that exists in nerve tissues was referred to as “glia,” which is Greek for “glue.” Such simplification was necessary as scientists began to investigate the complex connections and chemical signals that transpire at the synapse. More recently, the three major cell types that occur in the glia (i.e., microglia, astrocytes, and oligodendrocytes) have begun to receive attention for their functional roles within the multiple contexts. The revelation that glial cells may participate in synaptic function per se is particularly intriguing. For example, astrocytes appear to modulate neurotransmission in nociception, and dysfunction of this role may be an important factor in the development of pain states. Drugs that specifically affect non-neuronal cells and thereby alter synaptic transmission have been identified, and these “glia blockers” are helping neuroscientists to understand the role of astrocytes in the manifestation of pain. Glia blockers not only reflect the essential participation of non-neuronal cells to synaptic function, but may also suggest new therapeutic opportunities for controlling neuron–neuron communication in a number of pathological conditions.

Camilla I. Svensson and Ernst Brodin

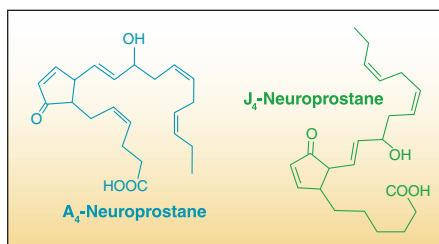


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Starring roles

39 Reversible Modifiers: Electrophiles as Lipid-Based Signaling Mediators

Over the past several years, research on biologically relevant electrophiles has been replete with new insights, expanding our understanding of the roles electrophiles play in vivo. Importantly, many electrophiles can form reversible covalent adducts with both proteins and small-molecule thiols in cells. This post-translational protein modification has important ramifications, including changes in protein enzymatic activity, the transduction of signals within and between cells, and alterations in gene expression. Electrophiles modulate a variety of cellular signaling processes that are involved in several major diseases with inflammatory components. The electrophilic fatty-acid derivatives discussed in this work are naturally occurring products of redox reactions and enzymatic activity. Furthermore, several of these electrophilic species and their derivatives represent potential therapeutic candidates.

Alison L. Groeger and Bruce A. Freeman



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Neuroprostanes produced by
non-enzymatic lipid peroxidation