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molecular interventions

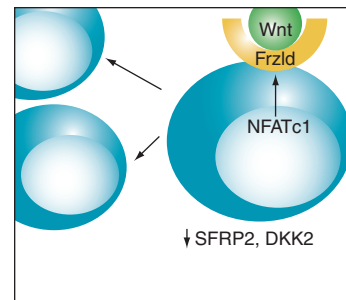
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

193 Controlling Bone Formation: NFAT Is a Positive Mediator

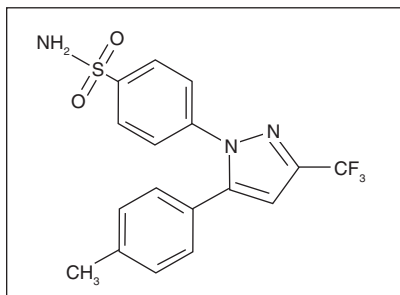
New findings reveal that the calcineurin-NFAT signaling pathway helps to promote osteoblast differentiation. Three recent papers reveal somewhat different mechanisms by which this could occur. In one study, transduction of calcineurin $A\alpha$ increased expression of osteoblast differentiation markers, including Runx-2. In another study, NFATc1 cooperatively enhanced Osterix activation of the collagen 1a1 promoter, but did not enhance Runx-2 activity; evidence was provided for the formation of a novel NFATc1-Osterix complex. In a third study, expression of nuclear NFATc1 enhanced Wnt signaling. The observation that the Wnt pathway promotes bone formation is intriguing, because NFATc1 also is critical for osteoclastogenesis. The current findings could be relevant for the osteoporosis seen in patients given the calcineurin inhibitor cyclosporine to prevent transplant rejection, although the results need to be reconciled with aspects of the clinical picture.

Paula H. Stern



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NFAT: Good to the bone

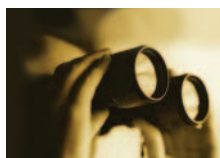
196 How Do You Define “Specific”?



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“Specificity”: A qualitative or quantitative term?

With the push to develop the next blockbuster drugs, continued surveillance of current bestsellers may not be given the full attention due. Upon wide-spread use, unexpected adverse effects begin to emerge. Although touted as highly specific, many of the newly developed drugs are likely to have secondary molecular targets—a potential cause of adverse effects. A molecular pharmacology approach that screens for multiple drug targets may shed light on the mechanisms that underlie both desired and adverse side-effects.

Wolfgang Sadée and Laura M. Bohn

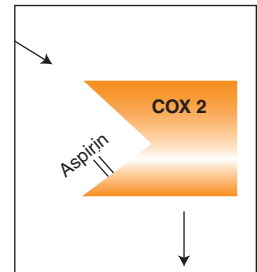


REVIEWS

199 COX-2: A Double Agent in Inflammation

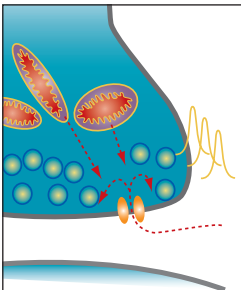
In view of the widespread and effective use of the nonsteroidal anti-inflammatory drugs (NSAIDs), the importance of limiting the side effects of these agents is self-evident. A major goal for both clinicians and drug developers has thus been to improve the specificity with which novel NSAIDs would inhibit their canonical targets, the cyclooxygenase (COX) enzymes. A number of lessons, in a variety of arenas, have been learned in the pursuit of this goal. Some of these lessons have unearthed new challenges in understanding the biology and pharmacology of the COX enzymes. Particularly important is the growing recognition that the inhibition of the COX enzymes, even with the attainment of absolute specificity for one or both of the major COX isoforms, may itself undermine anti-inflammatory therapy or even exacerbate inflammatory disease.

Ravindra Rajakariar, Muhammad M. Yaqoob, and Derek W. Gilroy



page 199
Friend and Foe?

208 Mitochondria Modulate Plasticity and Neurotransmitter Release



Mitochondria produce energy in the form of ATP for highly energy-dependent processes of synaptic vesicle recycling and the operation of ion pumps. Mitochondrial localization to presynaptic sites alters the kinetics of transmitter release by the localized production of ATP and by calcium buffering. BCL-xL changes the conductance of mitochondrial membranes and alters mitochondrial bioenergetics to enhance the life of the synapse. Therapeutic attempts to modulate neuroplasticity and other synaptic activities may thus rest on a more thorough understanding of the organellar trafficking and constitution of neurons.

Elizabeth A. Jonas

page 208
Mitochondria directing transmitter release

223 Warfarin Dosing: Pharmacogenomics 101

As with most drugs, the prescription of warfarin is a balancing act. In this case, the patient who receives too much is at risk for hemorrhagic complications, whereas the patient who receives too little may not be adequately protected against thromboembolism. Dose-response curves for warfarin are especially complex, and the basis of this complexity lies in part in the interindividual variability among patient genomes. Research into the pharmacogenomics of warfarin responsiveness, based on an appreciation of the multiple gene products that metabolize or mediate the efficacy of the drug, has arisen as a model for the considerations that must be addressed in bringing personalized medicine into practice.

Allan E. Rettie and Guoying Tai

Amino acid change	Daily Dose	Res Phe
Val ²⁹ → Leu	14 mg	Mod
Ala ⁴¹ → Ser	16 mg	
Arg ⁵⁸ → Gly	32-36 mg	Maj
Val ⁶⁶ → Met	27-35 mg	
Leu ¹²⁸ → Arg	> 45 mg	Seve
Val ¹⁴⁵ → Ala	Target INR	

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Taking it personally