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Highlighted Papers

Humanized Glycoprotein VI Mouse to Study Anti-Glycoprotein VI Agents In Vivo

The search for better antiplatelet drugs that efficiently prevent platelet thrombus formation while having a minimal effect on general hemostasis remains a competitive challenge. Glycoprotein VI (GPVI) is considered to be an attractive target for the development of new antithrombotic agents. Mangin et al. developed a genetically modified mouse expressing human GPVI (hGPVI) as a preclinical tool to evaluate the role of human GPVI in various models of thrombosis and to screen anti-GPVI compounds. The mice were viable, fertile, and without hematological defects; platelet aggregation, fibrinogen binding, and P-selectin exposures were normal in response to various agonists. The blocking antibody Fab fragment 9O12.2 (anti-GPVI) inhibited collagen-induced platelet aggregation in vitro and ex vivo. In hGPVI mice, 9O12.2 did not prolong tail bleeding time or increase blood loss. The hGPVI model therefore offers the possibility of establishing the bleeding tendency of anti-GPVI compounds alone or associated in dual or tri-therapy with other antiplatelet agents. This unique animal model may permit evaluation of agents targeting human GPVI in terms of efficacy and safety and enable one to determine more relevant human doses and therapeutic combinations, which may help design future clinical studies.

See article at *J Pharmacol Exp Ther* 2012, **341:**156–163.

Epigenectic Regulation of Angiomyogenesis to Preserve Myocardial Performance

Inhibition of histone deacetylases (HDACs) by trichostatin A (TSA) has previously been shown to induce a pharmacological preconditioning effect against acute myocardial ischemia and reperfusion injury; however, it is not clear whether the mechanism of TSA promotes endogenous angiomyogenesis in infarcted mouse hearts. In the present study, Zhang et al. investigated whether in vivo inhibition of HDAC preserves cardiac performance and prevents cardiac remodeling in mouse myocardial infarction (MI) through stimulation of endogenous regeneration. These studies demonstrate that in vivo inhibition of HDAC improved cardiac functional recovery and antagonized myocardial remodeling in chronic MI. Notably, HDAC inhibition significantly improved animal survival rate after MI, which is associated with the mitigation of both myocardial and serum tumor necrosis factor α levels in MI heart. HDAC inhibition stimulated the self-renewal of cardiac stem cells and resulted in robust increases in proliferation and cytokinesis in the MI hearts, which are associated with the enhancement of the newly formed myocytes and angiogenic responses. HDAC inhibition-induced cardioprotection also involves the activation of Akt-1 and inhibition of apoptosis. This study provides novel evidence that a new therapeutic strategy could be developed based upon HDAC inhibition, eliciting the stimulation of cardiac endogenous regeneration and angiogenesis in the infarcted heart.

See article at *J Pharmacol Exp Ther* 2012, **341:**285–293.

Treating Arthritis through Selective Bruton's Tyrosine Kinase Inhibition

Nonreceptor tyrosine kinases, such as Bruton's tyrosine kinase (Btk), regulate the signal transduction of the B-cell antigen (BCR) and Fc (FcR) receptors that are critical in the development of rheumatoid arthritis (RA); therefore, pharmacological inhibition may affect multiple steps in the pathogenesis of RA and represent a useful therapeutic approach. The study by Xu et al. characterized the role of Btk using the novel, selective Btk inhibitor RN486 [6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2*H*-isoquinolin-1-one] in rodent and in vitro models of immune hypersensitivity and arthritis. The selective Btk inhibitor RN486 blocked BCR- and FcR-mediated biological and immune responses in both human cellular assays (tumor necrosis factor αproduction and CD69 expression) and rodent models (type I and III hypersensitivity), providing evidence for mechanism-based actions relevant to human diseases. RN486 produced robust efficacy in two standard rodent models of RA at concentrations that effectively block immunoreceptor-mediated pharmacodynamic responses, expression of CD69 in mice and PCA in rats. Together, these data show that Btk is a key regulator of immunoreceptor-mediated responses in both rodents and humans. Because these immunoreceptor-mediated responses are conserved between rodents and humans, and are essential for the development of immune arthritis in both species, they suggest clinical relevance and support the development of selective Btk inhibitors as RA therapeutics.

See article at *J Pharmacol Exp Ther* 2012, **341:**90–103.

Cytoprotective Role of the Nuclear Factor (Erythroid-Derived 2)-Like 2 Pathway in the Central Nervous System

Free radicals exert significant oxidative stress on tissues and cells and are implicated in the pathogenesis of neurodegenerative disorders such as multiple sclerosis (MS). The study by Scannevin et al. characterized the potential direct neuroprotective effects of dimethyl fumarate (DMF) and its primary metabolite monomethyl fumarate (MMF) on cellular resistance to oxidative damage in primary cultures of central nervous system (CNS) cells and explored the dependence and function of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in this process. Using multiple assay formats, these studies indicate that both DMF and MMF are able to promote cytoprotective responses in cells by activating the Nrf2 pathway, enabling them to better withstand oxidative stress. The attenuation of H_2O_2-induced calcium accumulation, along with potential mitigation of other cellular events related to toxic oxidative challenge, resulted in MMF or DMF-dependent increase in viability in astrocytes and neurons in an Nrf2-dependent manner. The oxidative injury and challenge paradigms explored are highly relevant to the mechanistic damage that occurs in MS, and these preclinical studies using DMF and MMF collectively provide a compelling rationale for the use of DMF as a therapeutic agent in the treatment of MS.

See article at *J Pharmacol Exp Ther* 2012, **341:**274–284.