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molecular interventions

pharmacological perspectives from biology, chemistry and genomics

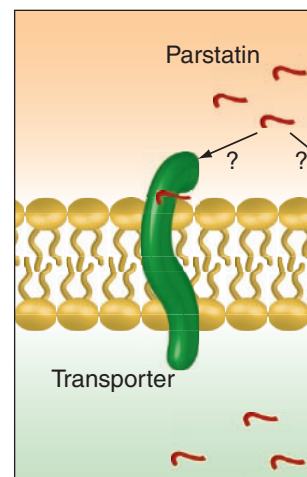
VIEWPOINTS

168 Anti-angiogenic role for a forgotten protein fragment, parstatin

Angiogenesis, the process of forming new blood vessels, is a well established and clinically relevant feature of a variety of disease states. Whether blood vessels sprout in a given tissue environment depends on the balance between factors that stimulate angiogenesis and those that impede it. Potent pro-angiogenic factors such as vascular endothelial growth factor (VEGF) have been identified, validated, and successfully used in the clinic. Likewise, anti-angiogenic factors are also emerging as biologically relevant and therapeutically useful entities. PAR1 is a G protein-coupled receptor (GPCR) that participates in hemostasis and vascular development and that mediates the angiogenic activity of thrombin. PAR1 is activated through proteolytic cleavage of its first forty-one extracellular residues by a variety of proteases, most notably thrombin. However, little effort has focused on the forty-one-residue peptide fragment liberated during PAR1 activation.

Tsopanoglou and colleagues have now demonstrated that this peptide, parstatin, has intriguing anti-angiogenic activity, and, in a follow-up study, they demonstrate its potential pharmacological utility using a rat model of ischemic heart disease.

Michael B. Duncan and Raghu Kalluri

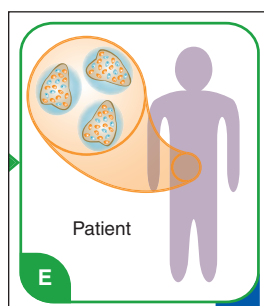


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Regulating the regulator:
Keeping PAR1's pro-angiogenic activity in check?

171 Making β cells: Small molecules for the treatment of Diabetes

Regenerative medicine utilizes cutting-edge technologies to repair and replace damaged cells, tissues, and organs for functional restoration. This broadly interdisciplinary field draws from cell and molecular biology, genetics, immunology, surgical sciences, physiology, biomedical and tissue engineering, chemical and material sciences, and nanotechnology. Certainly, pharmacology serves as an integral component of regenerative medicine, a concept first elucidated in depth in this journal. We operationally define regenerative pharmacology as the application of pharmacological sciences to accelerate, optimize, or characterize the development, maturation, and function of bioengineered and regenerating tissues, either in vitro or in vivo. Diabetes mellitus, a condition defined by elevated levels of glucose in the blood, represents a compelling target for regenerative medicine, through a variety of complementary strategies. A recent report from the laboratory of Peter Schultz of small molecules capable of stimulating the proliferation of insulin-producing pancreatic β cells highlights the potential of regenerative pharmacology to develop novel treatments for this important disease.

Mark E. Furth and George J. Christ



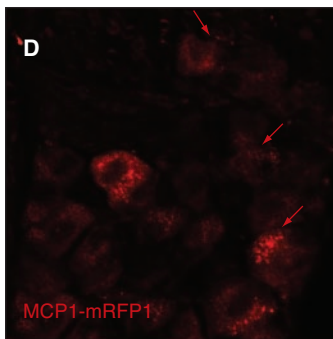
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Proliferating β cells:
Big things from
small molecules



REVIEWS

175 Where does it hurt? Chemokine signaling in neuropathic pain

Chemokines are chemoattractant proteins, secreted by a great many cell types, that function particularly to direct the migration of cells of the immune system. Chemokine receptors are G protein-coupled and have been implicated in a number of important disease states, including cancer, inflammatory disorders, and AIDS/HIV. Neuroinflammatory aspects of chronic pain are also



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G protein-coupled pain

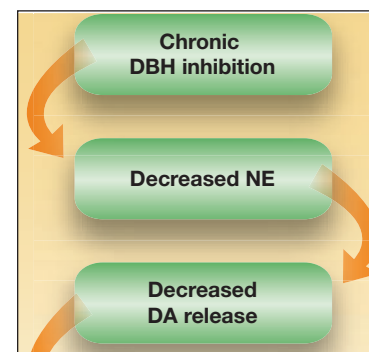
chemokine-dependent, and given the many clinical difficulties that often arise in the treatment of chronic pain, novel therapeutics are urgently needed. Chemokine receptors would thus appear to be in ideal target for drug development, and indeed, animal models of neuropathic pain have allowed pharmacologists to identify a number of cell types and signaling pathways that are essential to the initiation and maintenance of chronic pain. In this regard, the chemokine receptor CCR2, activated by a chemokine known as monocyte chemoattractant protein 1, has been attributed to a number of specific regulatory and neural activation processes that contribute to chronic pain. But in order to target chemokine receptors such as CCR2 and thereby develop effective treatment, investigators must identify, from among many cell types and peripheral and central neural pathways, the relevant sites of CCR2 function.

Fletcher A. White, Polina Feldman, and Richard J. Miller

188 Beyond alcohol and adversity: Antabuse kicks cocaine

In the 1930s, presumably after the repeal of prohibition, laborers who came to work at a certain rubber factory found that a drink at the end of the working day did little to relax them. Flushing and nausea, vertigo, headache, and hypotension were the more obvious effects of the workers' intake of alcohol. It turned out that exposure to disulfiram, a chemical used at the rubber factory, made the imbibing of alcohol aversive. By 1951, disulfiram was dispensed as a drug, named Antabuse, for the treatment of alcoholism. Disulfiram functions as an inhibitor of aldehyde dehydrogenase, and the accumulation of acetaldehyde in patients who receive disulfiram and then drink alcohol is the basis of the disulfiram-ethanol reaction. So why should disulfiram, clearly implicated in inhibiting ethanol metabolism, be effective in treating cocaine addiction? At first consideration, a number of psychological and social explanations come to mind: cocaine use is comorbid with alcohol abuse; the psychological deterrent created in treated alcoholics is transferred to the effects of cocaine intake. A series of clinical trials has established that disulfiram is specific for cocaine use per se; indeed, disulfiram inhibits dopamine β -hydrolase and thereby plays directly to the mechanisms of cocaine reward. But disulfiram is no cure for addiction; enzyme inhibition by disulfiram as it is understood cannot address the psychosocial and biological underpinnings of addictive behaviors. Nevertheless, clinical trial data and neuropharmacological insights from disulfiram research enable investigators to make specific hypotheses for best treating the complexity of addiction.

Meriem Gaval-Cruz and David Weinshenker



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Inhibiting addiction