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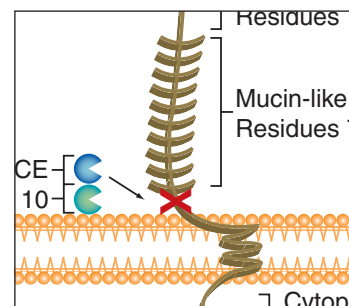
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

263 Fractalkine/CX3CL1: One Target, Many Diseases

A better understanding of the immunological processes governed by cytokines and chemokines has shaped our approach to the design of therapeutics for diseases such as rheumatoid arthritis (RA), atherosclerosis, and other inflammatory disorders. The discovery of chemokines and their receptors as integral components and regulators of inflammation has dramatically contributed to advances in treating these disease states. Among the different classes of chemokines, fractalkine/CX3CL1, with its unique functional and structural characteristics, has been found to participate in inflammation. This viewpoint summarizes the emerging role of fractalkine/CX3CL1 from the historical, functional, and clinical perspective and provides evidence to validate it as a potential therapeutic target in cardiovascular disease, rheumatoid arthritis, as well as other diseases related to vascular inflammation.

Brian Jones, Maria Beamer, and Salahuddin Ahmed



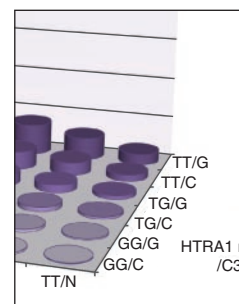
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A "kine" of inflammatory therapy

REVIEWS

271 Age-related Macular Degeneration: Nature, Nurture, and Disease

Age-related macular degeneration (AMD) is the most common cause of visual impairment among the elderly in developed countries, and its prevalence is thus increasing as the population ages. Unfortunately, treatment options remain limited because the etiology and pathogenesis of AMD are incompletely defined. Recently, gene association and mechanistic studies have confirmed that AMD involves the interaction of multiple genetic and environmental factors. The identification of genes that have a substantial impact on the risk for AMD is not only facilitating the diagnosis and screening of populations at risk, but is also elucidating key molecular pathways of pathogenesis. In this way, modern research into AMD exemplifies the power of pharmacogenetic studies, not only with respect to the dawning of personalized medicine, but also in terms of refining our molecular understanding of disease.

Yuhong Chen, Matthew Bedell, and Kang Zhang



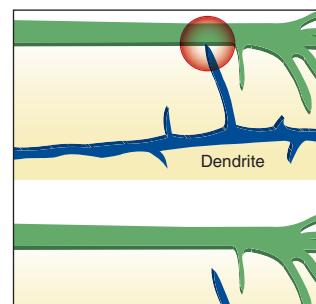
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Eying models

282 In the Beginning: Synaptogenesis

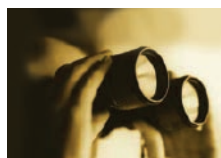
Most of the synapses that appear in the developing central nervous system (CNS) are formed *en passant*, meaning they occur along the length of the extending axon, and not merely at the axon terminus. The construction of CNS synapses thus ensues from the temporal and spatial coordination of contacts between growing neurons, and this coordination is predicated on the formation of subcellular structures in each of the neurons that contribute to synapse formation. This review focuses on the proteins and vesicular processes that corroborate in the formation of presynaptic terminals. Understanding the delivery of vesicular cargo to the developing synapse, along with elucidation of the interplay among protein and

membrane components at the nascent synapse, is relevant for treating brain diseases as diverse as autism, epilepsy, anxiety disorders, brain injury, and Alzheimer's disease.

Luke A. D. Bury and Shasta L. Sabo



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Bridging neurons in the brain

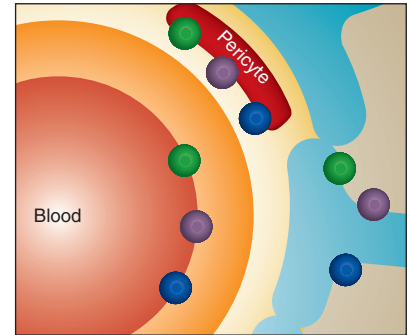


REVIEWS, *continued*

293 **Traversing the Blood–Brain Barrier: Easy as ABC?**

Recognition of the blood–brain barrier (BBB) can be traced back to the late nineteenth century, when Paul Ehrlich observed that intravenously administered water-soluble dyes failed to enter the central nervous system (CNS). Still today, the BBB poses major pharmacological challenges, for example, in the development of effective CNS drugs and the exploitation of certain imaging technologies. It has furthermore become clear that certain pathophysiological processes, such as the inadequate clearance of amyloid species in Alzheimer's disease, may directly reflect BBB functionality. A critical component of the BBB is a group of ATP-binding cassette (ABC) efflux transporters that act to protect the brain from xenobiotics, and a number of therapeutic avenues that would inhibit, activate, or otherwise exploit these ABC proteins have been envisaged. This review highlights a novel strategy—targeting signaling pathways that control ABC transporters at the BBB—for the development of CNS therapies.

Anika M.S. Hartz and Björn Bauer

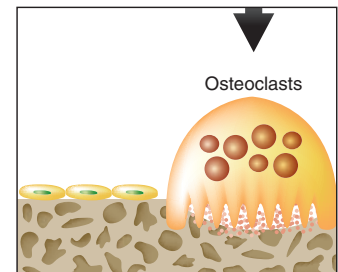


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The ABCs of getting cerebral

305 **Osteoporosis: New Revelations from Strontium Therapy**

Osteoporosis is characterized by reduced bone mass and the deterioration of bone microarchitecture, resulting in bone fragility and increased susceptibility to fractures. Whereas the majority of antiosteoporotic therapies have depended on either antiresorptive drugs or anabolic hormone treatment, a novel mode of action appears to be mediated by strontium ranelate, which has been shown to act both by opposing bone resorption and promoting bone formation *in vitro*. This review article addresses the cellular and molecular mechanisms that have been implicated in the therapeutic strengthening of bone observed upon administration of strontium ranelate to osteoporotic patients. These mechanisms relate to specific pathways of calcium signaling, including complex networks involving nuclear factor of activated T cells (NFAT) and Wnt signaling.

Pierre J. Marie



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Signaling to the bone