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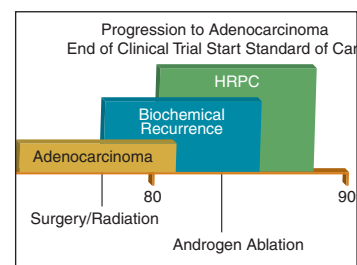
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

197 Cancer Vaccines: Indications for Pre-emptive Use?

Tumor cells frequently express antigens that allow them to be specifically targeted and destroyed by the immune system. Many tumor immunotherapy clinical trials have been conducted, directed at several types of cancer using myriad antigens and multiple immunization strategies. Despite this, only one therapeutic cancer vaccine, sipuleucel-T, has been approved. A groundbreaking study by Jaini et al. recently demonstrated that prophylactic immunization against a breast cancer associated antigen can prevent tumor development, and is far more effective than therapeutic vaccination. This study highlights the urgent need to rethink the clinical testing of tumor immunotherapies; it is time to consider clinical trials of cancer vaccines in the prophylactic setting.

Andrew Gray, Lisa Yan, and W. Martin Kast



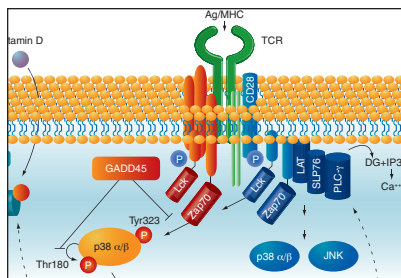
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Prophylaxis rather than disease therapy

204 Tweaking the Function of the Vitamin D Receptor to Effect Changes in T-Cell Responses

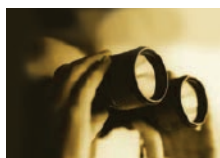
In addition to its well-known regulatory roles in mineral homeostasis, bone formation, and the endocrine system, the active form of vitamin D exerts a wide range of modulatory functions in the immune response. Vitamin D receptor (VDR) agonists are emerging as prominent candidates for immunotherapy, owing to their immunosuppressive effects on different cell-types of the innate and adaptive branches of the immune system, including antigen presenting cells, T cells, and B cells. Recent work by Geisler and colleagues, however, has uncovered an unexpected stimulatory effect of vitamin D3 on human T cells. In this article, we focus on the mechanistic consequences of these new findings, with particular attention to possible novel therapeutic venues that target the role of VDR in the function of T cells in the immunity of inflammation.

Valentino Parravicini and Stefano Caserta



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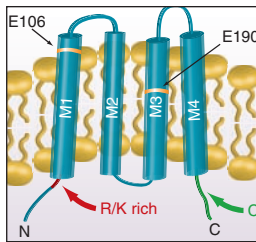
Flipping the switch on effector T cells and inflammation



REVIEWS

209 Store-operated Calcium Entry: ER and Cell Membranes on CRAC

The release of calcium ions from the endoplasmic reticulum (ER) evokes the cell membrane to allow extracellular calcium ions to enter the cell. This influx, also called the calcium release-activated calcium (CRAC) current, has



been recognized as essential to calcium signaling for decades, but the molecular bases of the phenomenon have for almost as long remained elusive. Two distinct protein families—the ORAI and the STIM proteins—have recently been identified in the store-operated calcium entry pathway, and both are intimately involved in pore operation. The STIM component, integral to the ER membrane, responds to depletion of ER-stored calcium by aggregating and migrating to ER–cell membrane junctions. At these junctions, STIM appears to colocalize with the ORAI component, which is strongly implicated as the pore-forming subunit for calcium entry at the cell membrane. The identification of three ORAI subtypes may open up new pharmacological opportunities for the specific targeting of ion signals mediated by alternative forms of the CRAC pore.

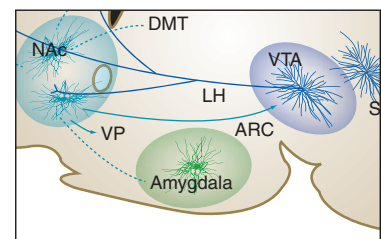
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Pore-forming and
-stimulating proteins

James W. Putney

219 Putting Addiction in Its Place: Δ FosB in Neuronal Transcription and Plasticity

Almost all classes of addictive substances alter the structure and connectivity of diverse neuronal populations throughout the brain. Recent evidence has identified a network of gene expression changes, linked to long-term addictive-like behavior, that alter the structure and function of medium spiny neurons in the nucleus accumbens.

The observed changes in gene expression appear to be coordinated by a complex series of histone modifications that result in either the repression or activation of gene transcription. Intriguingly, the coordination of such epigenetic events occurs, at least in part, through the activity of the transcription factor Δ FosB. In this review, we will discuss recent advances in our understanding of chromatin regulation by cocaine, as well as the consequences of such regulation on structural plasticity and its functional relevance to drug addiction. In addition to helping us better understand the stability of addictive behaviors, new epigenetic insights may lead to novel therapies for counteracting the genetic and physiological adaptations that underlie addiction.

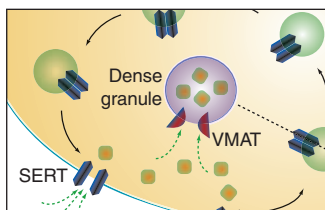


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Addiction and gene regulation

Ian Maze and Scott J. Russo

231 Surface Expression of SERT at the Platelet Plasma Membrane: Regulation by Plasma Serotonin

Long before it received fame as a neurotransmitter, 5-hydroxytryptamine was recognized as a vasoconstrictor in serum and therefore termed “serotonin.” Elevated serotonin levels in the plasma have been linked to hypertension and various cardiovascular diseases. The serotonin transporter (SERT) located in the platelet plasma membrane is the fundamental regulator of plasma serotonin concentration. Intriguingly, the expression of SERT in the platelet membrane is regulated by plasma levels of serotonin, and recent research reveals that the trafficking of SERT between the plasma membrane and platelet cytoplasm occurs in a highly dynamic context that includes phosphate signaling and small G proteins, protein serotonylation, and essential components of platelet activation. The interplay of plasma serotonin and platelet activation may have particular implications for the treatment of cardiovascular disease.



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SERT and platelet function

Charles P. Mercado and Fusun Kilic