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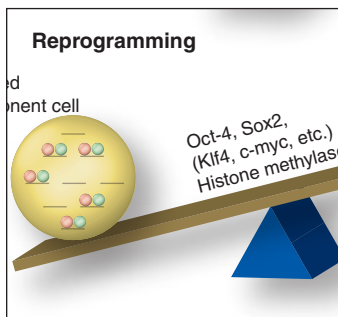
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# molecular interventions

pharmacological perspectives from biology, chemistry and genomics

## VIEWPOINTS

### 15 Histone Methylation: Bivalent Profiles in Pluripotency



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Histone methylation:  
The tipping point of  
pluripotency

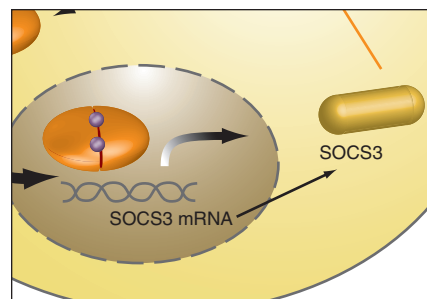
Histone modifications, specifically, methylation of lysine residues in histone 3 (H3), determine chromatin structure and accessibility for transcription. A recent study by Bernstein and Lander identified a unique pattern of H3 methylation at the promoter region of developmental genes in pluripotent stem cells. The pattern consists of the simultaneous presence of a silencing mark [methylation of Lys<sup>27</sup> on H3 (H3K27me)] and an activation mark (H3K4me). This bivalent mark seems associated with a poised state of transcription and resolves upon differentiation largely into either H3K27me or H3K4me. Skin fibroblasts that can be reverted in culture to the pluripotent stage show re-establishment of the bivalent chromatin pattern. This switch in chromatin states may be key to our understanding of developmental and tissue specific regulation of gene expression and may be therapeutically useful in regenerative medicine.

Kathrin Muegge, Sichuan Xi, and Theresa Geiman

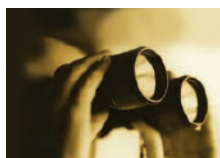
### 19 SOCS3: A Mediator in Hepatocarcinoma and Liver Regeneration

Cytokine responses are stringently controlled by a family of proteins termed the suppressors of cytokine signaling (SOCS), and deregulation of SOCS function is associated with many diseases, including several cancers, disorders in hematopoiesis, and autoimmune diseases. Our current understanding of the divergent roles of SOCS3 has recently improved and indicates that SOCS3 is critical in modulating cytokine-mediated and neoplastic-proliferative responses in the liver. The generation of hepatocyte-specific *Socs3* knockout mice suggests that loss of SOCS3 expression encourages hepatocyte proliferation, survival, and hepatocellular carcinoma formation. By elucidating the regulation of pathways leading to liver regeneration we may gain useful insights to control liver disease and tumor growth.

Joanne Elliott



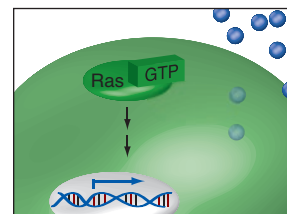
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A "shoe-in" as a molecular target?



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### 22 RAS in Paracrine Signaling: Kill the Messenger

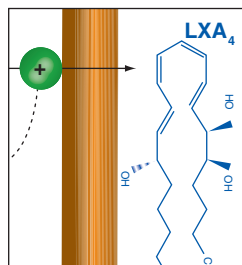
Strategies to combat cancer have expanded beyond therapeutics that attack or exploit the basis of unfettered cell proliferation. In recent years, an increasing emphasis has been placed on understanding the *in vivo* environmental conditions that nourish or otherwise support tumor growth. GTPases of the RAS family are intracellular proteins that normally participate in the relay of signals from the exterior cell surface to the cell nucleus. These proteins are the product of RAS-encoding oncogenes, which become mutated in a significant portion of human cancers and thereby pervert intracellular signals involved in cell division. Intriguingly, RAS also appears to function in cancer by fostering communication among cells from distinct tissues, and this level of RAS-mediated paracrine signaling offers an exciting avenue for the development of anti-cancer drugs. Indeed, modern molecular tools and biologic-based therapeutics show promise in animal models and early translational studies.



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*RAS and cytokines*

Brooke B. Ancrile, Kevin M. O'Hayer, and Christopher M. Counter

### 28 What Makes the Cornea So Privileged? Research into Lipid Autacoids



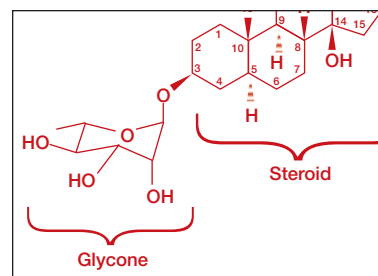
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*Lipid autacoids*

Vertebrate tissues that are exposed to the environment are thereby prone to injury, in which case cell growth and repair must be condoned, but invasion by pathogens must be prevented. Certain aspects of inflammation and wound healing thus rest in a curious balance, which if displaced can result in inflammatory disease or infection. The very tissues that experience this balance most precariously have long been recognized to possess a special resilience to injury and infection, and an understanding of this resilience may well inform ongoing clinical research that addresses many important immune and allergic responses. Lipid autacoids appear to provide a check on processes of inflammation, and investigation into their mechanisms of action reminds us that therapeutic interventions into inflammation must not subvert the programmatic resolution of a highly complex, fundamentally defensive, process.

Karsten Gronert

### 36 New Life for Na<sup>+</sup>,K<sup>+</sup>-ATPase Inhibitors in Cancer Therapy

Digoxin, digitoxin, and ouabain are well-known cardiac glycosides with a reputation as effective agents in the treatment of congestive heart failure and cardiac arrhythmia. Perhaps equally well known is their narrow therapeutic window: plasma concentrations of these drugs in patients must be carefully monitored to safeguard against toxic side effects. Less well known, however, is the emerging role of this category of compounds in the treatment of proliferative diseases such as cancer. Promising findings have shown these compounds to be involved in complex cell signal transduction mechanisms, resulting in the selective control of human tumor but not normal cellular proliferation. As such, they represent a promising form of targeted cancer chemotherapy. New clinical studies of their anticancer potential as single or adjuvant treatments may provide insight into these agents as potent therapeutic options.



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*Through a window narrowly*

Robert A. Newman, Peiyong Yang, Alison D. Pawlus, and Keith I. Block