FEATURES

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Axon Guidance and Adhesion Molecules in Olfactory Map Formation

Gerald A. Schwarting and Timothy R. Henion

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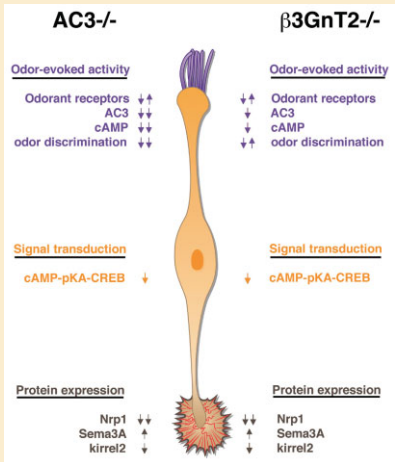
The axons of olfactory neurons expressing the same odorant receptor converge at stereotyped positions in the mouse olfactory bulb, providing a map of odorant activation in the brain. The mechanisms involved in olfactory targeting differ in many respects from other sensory systems. In this issue, Schwarting and Henion review the critical determinants of olfactory axon guidance, including the central role of cAMP in this process. The odorant receptor-dependent stimulation of adenylyl cyclase-3 (AC3) generates localized cAMP signals that regulate both odor-evoked activity in cilia and gene transcription via the pKA/CREB pathway. Consequently, AC3 null mice are anosmic and also exhibit axon guidance defects due to the misregulated expression of guidance information. The glycosyltransferase β3GnT2 modifies olfactory AC3 with poly-N-acetyllactosamine glycans that are essential for enzyme function. Although cAMP production is severely reduced in β3GnT2 null neurons, AC3 traffics normally to cilia, and smell perception is only partially disrupted. However, AC3 and several guidance cues are lost from mistargeted β3GnT2-deficient axons in early development, suggesting a potential role for cAMP in regulating gene expression in growth cones. Thus, the β3GnT2 model provides unique insight into the differential requirements for cAMP in subcellular functions, such as odor-evoked activity and localized gene transcription.



DNA Replication/Recombination and Genomic Stability

Robyn L. Maher, Amy M. Branagan, and Scott W. Morrical

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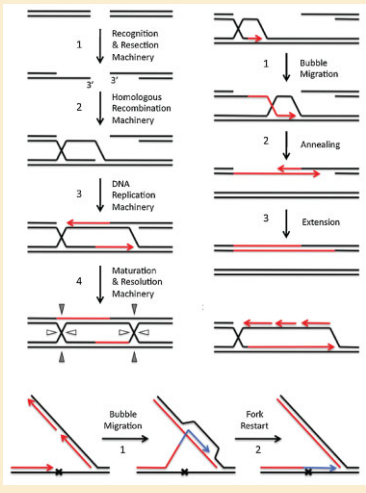
Maintenance of genome integrity is critical to avoidance of death and disease. Homology-directed repair (HDR) provides a mechanism for error-free repair of severe DNA lesions such as double-strand breaks and stalled replication forks. Errors in this pathway are carcinogenic in humans. The mechanism of HDR involves the coordinated activities of the homologous recombination and DNA replication machineries. Both the recombination and replication machineries involve several stages and several proteins that perform the central catalytic roles, as well as accessory proteins that serve to regulate and coordinate these stages. Here we review the function of certain recombination mediator proteins, DNA helicases and DNA translocases. We describe how these proteins function as accessory factors and are essential to coordination of recombination and replication events such that the potentially lethal DNA intermediates are shuttled through the process until the repair is completed. These factors also serve to regulate recombination and replication at various stages, both positively and negatively, to ensure that homology directed repair occurs at the appropriate time and place in the genome.



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Bone Marrow Stromal Cell Therapy

Eva Mezey

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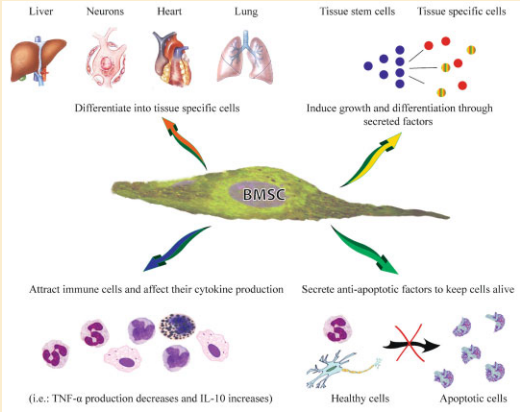

Bone marrow stromal cells (also called mesenchymal stem cells) have received a good deal of attention during the last decade. In addition to replacing bone, cartilage and adipose tissue they have been found to have immune-regulatory functions. They have been used successfully in patients to moderate graft versus host disease following bone marrow transplantation, an effect that resulted from inhibition of T cell proliferation. Subsequently, the stromal cells were studied in additional conditions characterized by immune dysfunction. When they are injected into the blood stream, they appear to be able to sense the environment they find themselves in, and respond by secreting factors that rebalance the immune system when it has gone astray. This is something that chemicals (i.e., drugs) are not "smart" enough to do. Since the stromal cells are readily cultured and stored, and since they are immune privileged and do not have to be matched to their recipients, they are ideal therapeutic agents; and they should play a valuable role in the clinics.

The Regulation of *BRD2*

Enyuan Shang, Qingping Cui, Xiangyuan Wang, Cheryl Beseler, David A. Greenberg, and Debra J. Wolgemuth

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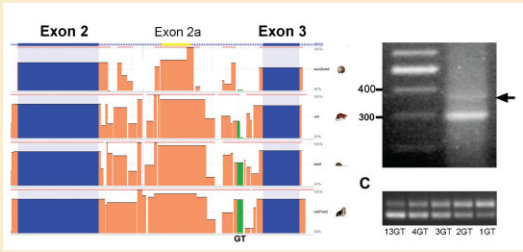

Nature uses various mechanisms to regulate a gene's expression as well as to enhance a gene's diversity of products. In the case of *BRD2's* expression, an evolutionarily ancient and highly conserved bromodomain-containing gene involved in neural development and in epilepsy susceptibility, Shang et al. show that cells utilize almost every step in gene expression – from transcription to splicing to protein translation – to regulate end product levels. They found that *BRD2* expresses mRNAs with different lengths of 5' untranslated regions (5'UTR). These mRNAs originate from multiple promoters. *BRD2* transcripts can also be alternatively spliced. Inclusion of a highly conserved alternative exon results in premature termination of translation. Manipulation of the repeat numbers of a nearby polymorphic microsatellite revealed that the length of the microsatellite affects the ratio of the two alternative splicing products. Further, they found that, among the multiple mRNAs (long and short 5'UTR combined with regular and alternative splicing), only the regularly spliced mRNA with the short 5'UTR yields full-length protein. Consistent with the *in vitro* experiments, they showed in mouse brain that although *Brd2* mRNA is expressed in both the hippocampus and cerebellum, *Brd2* protein can only be detected in the cerebellar Purkinje cells.