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In This Issue

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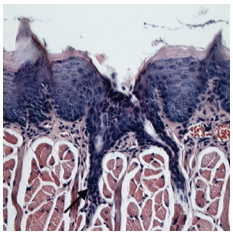
Mouse model of oral-esophageal cancer. Oral and esophageal cancers are common and associated with high mortality. Until now, the few animal models of these diseases all used chemical carcinogens. The two most frequently documented genetic alterations associated with progression to oral and esophageal cancers are the overexpression of cyclin D1 and mutations in p53. Seeking to generate a genetic model of oral and esophageal squamous cell cancers, Anil Rustgi and colleagues have generated transgenic mice that overexpress cyclin D1 in oral-esophageal epithelia and lack one or both copies of p53 (pages 761–769). The mice developed invasive oral-esophageal cancer with the same histopathological characteristics as the human disease. Cell lines derived from the oral cavity of the compound mutants, but not from control mice, induced tumors in nude mice. Rustgi et al. plan to use the mice and cell lines to identify cooperating genetic alterations and to test potential therapeutic agents, building upon the efficacy of sulindac in their model.Closing cranial sutures. Craniosynostosis (CS), the premature closure of cranial sutures, causes cranial dysmorphism in 1 in 3000 infants. Several genes have been implicated in familial CS syndromes, including three FGF-receptor genes. In an earlier quest to understand the molecular pathways involved in suture closure, Kang Ting and colleagues observed upregulation of Nell-1 in abnormally fused sutures of CS patients. They now […]



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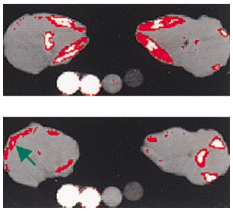
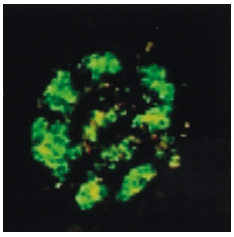
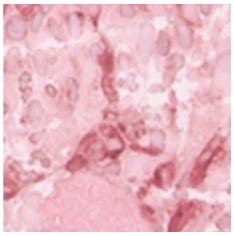


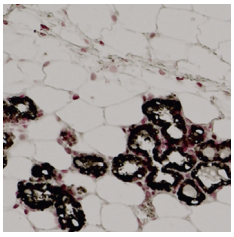
Closing cranial sutures. Craniosynostosis (CS), the premature closure of cranial sutures, causes cranial dysmorphism in 1 in 3000 infants. Several genes have been implicated in familial CS syndromes, including three FGF-receptor genes. In an earlier quest to understand the molecular pathways involved in suture closure, Kang Ting and colleagues observed upregulation of Nell-1 in abnormally fused sutures of CS patients. They now report (pages 861–870) that transgenic mice overexpressing Nell-1 show a phenotype similar to that of humans with CS. Cell culture studies showed that Nell-1 promotes osteoblast differentiation, providing additional support for a direct role of Nell-1 in suture closure.



Mechanisms of glucotoxicity. Chronically elevated blood glucose levels (as are present in patients with type 2 diabetes) impair the function of β cells in the pancreas. Studying the underlying mechanisms, Marc Donath and colleagues previously proposed that elevated glucose levels lead to the upregulation of Fas receptors and subsequent β cell apoptosis. They now present data (pages 851–860) that implicate an inflammatory process in glucotoxicity. Exposure of cultured islets to elevated glucose resulted in increased production and release of IL-1β, followed by NF-κB activation, Fas upregulation, and cell death. IL-1β production in β cells in response to elevated glucose levels was also seen in vivo. These results suggest that inhibition of the IL-1β/NF-κB pathway might preserve β cell mass in type 2 diabetes.



Linking angiogenesis to bone repair. A growing understanding of the molecular mechanism of bone healing in various animal models has revealed the utility of bone morphogenic proteins (BMPs) in bone regeneration and repair. Evidence also suggests a downstream interaction with angiogenesis. Beginning on page 751, Johnny Huard and colleagues report their efforts to potentiate bone formation and repair by simultaneous expression of BMP-4 and VEGF. Using muscle-derived stem cells in an ex vivo gene therapy approach, the researchers observed a synergy between BMP-4 and VEGF, whereby VEGF enhances BMP-4–mediated bone formation in all stages of healing and cartilage formation. This effect was reported at very specific expression ratios for the two growth factors and should aid in the design of new strategies for bone restoration.



PTEN overexpression in mammary glands. The PTEN phosphatase, frequently mutated in tumors such as those found in breast cancer, antagonizes PI3-kinase and inhibits both the Akt and MAPK pathways. These pathways, central to cell proliferation and survival, are implicated in mammary gland development. Seeking to study the role of PTEN in this process, Derek LeRoith and colleagues specifically overexpressed PTEN in mammary epithelium and found inhibition of the Akt, but not the MAPK, pathway (pages 815–825). A comparison of expression profiles of transgenic and wild-type mammary glands using "mammochips" — microarrays enriched for genes expressed in mammary glands — revealed a number of differentially expressed genes including IGFBP5, a known apoptotic regulator of normal mammary development. The presence of an IGFBP5-blocking peptide reduced excessive cell death in mammary cells overexpressing PTEN, revealing IGFBP5 participation in the observed apoptotic response.