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In This Issue

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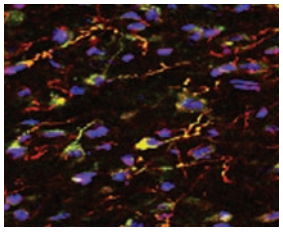
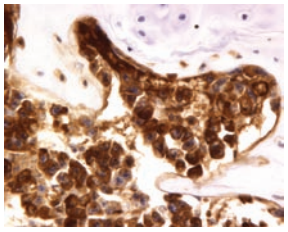
Turning bone into neurons Cell replacement strategies for treating neurodegenerative diseases currently consider the use of ES cells, neural stem cells, and neuronal progenitor cells as potential sources. Bone marrow stromal cells (MSCs) have recently been shown to be inducible into several cell types including osteocytes, chondrocytes, and adipocytes. Mari Dezawa and colleagues now show that MSCs may also be a potential source of cells for neuronal transplantation therapy (pages 1701–1710). The authors successfully induced efficient, exclusive, and specific differentiation of postmitotic neuronal cells from MSCs through gene transfer of the Notch intracellular domain (NICD). Notch is a transcriptional activator that influences the terminal specification of cells such as neurons and glial cells. After NICD transfection, the MSCs were treated with trophic factors and surveyed for neuronal characteristics. Neurite-like processes were evident, and neuronal markers were detected. Voltage-clamp electrophysiological studies demonstrated that these cells also expressed functional voltage-gated ion channels, a sign of neuronal differentiation. The therapeutic potential of these cells was confirmed by their transplantation into a rat model of Parkinson disease and subsequent restoration of neuronal function. See figure Collaborations in carcinogenesis Multiple myeloma, immunoglobulin deposition and heavy-chain diseases, and plasmacytoma constitute plasma cell neoplasms (PCNs). Increased c-Myc expression and deregulated expression of members of the Bcl-2 family of death suppressors, such as Bcl-XL, are common features of […]

Turning bone into neurons



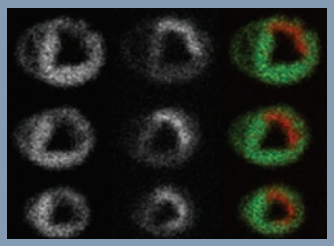
Cell replacement strategies for treating neurodegenerative diseases currently consider the use of ES cells, neural stem cells, and neuronal progenitor cells as potential sources. Bone marrow stromal cells (MSCs) have recently been shown to be inducible into several cell types including osteocytes, chondrocytes, and adipocytes. Mari Dezawa and colleagues now show that MSCs may also be a potential source of cells for neuronal transplantation therapy (pages 1701–1710). The authors successfully induced efficient, exclusive, and specific differentiation of postmitotic neuronal cells from MSCs through gene transfer of the Notch intracellular domain (NICD). Notch is a transcriptional activator that influences the terminal specification of cells such as neurons and glial cells. After NICD transfection, the MSCs were treated with trophic factors and surveyed for neuronal characteristics. Neurite-like processes were evident, and neuronal markers were detected. Voltage-clamp electrophysiological studies demonstrated that these cells also expressed functional voltage-gated ion channels, a sign of neuronal differentiation. The therapeutic potential of these cells was confirmed by their transplantation into a rat model of Parkinson disease and subsequent restoration of neuronal function.

Collaborations in carcinogenesis



Multiple myeloma, immunoglobulin deposition and heavy-chain diseases, and plasmacytoma constitute plasma cell neoplasms (PCNs). Increased *c-Myc* expression and deregulated expression of members of the *Bcl-2* family of death suppressors, such as *Bcl-X_L*, are common features of human PCN. Although several signaling molecules have been manipulated to model PCN formation in mice, the contribution of deregulated *c-Myc* expression and its interplay with members of the *Bcl-2* family remains unclear. Siegfried Janz and colleagues dissect the roles of c-Myc and Bcl-X_L in oncogenesis by characterizing mice that overexpress each gene alone or in concert (pages 1763–1773). Although moderate phenotypes were presented in the single-transgenic mice, the double-transgenic mice displayed severe plasma cell tumors. *Myc/Bcl-X_L* mice harbored significantly more plasma cells in the bone marrow than the single-transgenics, and these plasma cells were capable of continued proliferation that ultimately led to rapid development of PCN. The oncogenic potential of deregulated *c-Myc* expression may be maintained and exacerbated by increased *Bcl-X_L* expression, and thus the two molecules work together to accelerate oncogenesis. These mice provide a new model for PCN formation and will aid in the development of new anti-tumor strategies.

Imaging the healing heart



Following myocardial infarction (MI), the heart undergoes angiogenesis during the healing and remodeling process. Therapeutic strategies for post-MI recovery have targeted angiogenic factors, but evaluation of the efficacy of these strategies is difficult due to the lack of accurate measures for therapeutic effect. Albert Sinusas and colleagues have now developed a noninvasive method for imaging angiogenesis (pages 1684–1691). They demonstrated that an Indium-111–labeled αvβ3-targeted agent (^{111}In-RP748) was useful in tracking angiogenesis in rat and canine models of MI. The αvβ3 integrin is expressed in angiogenic vessels, hence it is present in areas of ischemia-induced angiogenesis. Serial evaluation of changes in myocardial ^{111}In-RP748 uptake showed that increased retention correlated with angiogenesis in areas of decreased perfusion. Since this can be detected by single-photon emission–computed tomography, this method is an ideal tool for monitoring angiogenesis in patients after ischemic injury and during therapeutic trials.

Liver metabolism scores a PTEN

About half of all primary liver cancers show decreased or lost expression of the tumor suppressor *PTEN*. PTEN is a phosphatase that regulates the downstream effects of PIP3, including anti-apoptotic activity, proliferation, and oncogenesis. Akira Suzuki and collaborators now report that *PTEN* deficiency in the liver leads to metabolic dysfunction in addition to tumorigenesis (pages 1774–1783). They generated a hepatocyte-specific *Pten* knockout mouse and found histological, physiological, and molecular pathologies that resembled nonalcoholic steatohepatitis (NASH). Mutant hepatocytes had extensive lipid-filled vacuoles with fibrotic change and infiltration of inflammatory cells, and liver extracts had significantly increased levels of triglyceride and cholesterol ester. The mice showed reduced glucose metabolism and insulin hypersensitivity. These effects were traced to the increased expression of *PPARγ*, a transcriptional activator for adipocyte differentiation. By 40 weeks of age, hepatic tumors were evident in most mutant mice. These results link hepatocellular carcinoma and steatohepatitis and suggest new therapeutic strategies for combating liver disease and cancers.