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In this issue

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IFN-γ tips the balance toward bone resorption IFN-γ has been shown to both promote and inhibit bone resorption, but the mechanisms by which it mediates these opposing effects and which effect predominates in vivo have not been clearly established. In this issue (pages 122–132), Gao and colleagues show that in vitro, IFN-γ inhibits the differentiation of osteoclasts directly but promotes the differentiation of osteoclasts indirectly. Further analysis revealed that IFN-γ increases the activity of APCs and thereby increases T cell activation and production of the osteoclastogenic factors receptor activator of NF-κB ligand (RANKL) and TNF-α. In these experiments, APCs derived from female mice from which the ovaries had been removed generated more osteoclasts than APCs derived from wild-type mice, indicating that, at least in vitro, the overall effect of IFN-γ is to increase the number of bone-resorbing cells. A similar conclusion, that the pro–bone-resorbing effect of IFN-γ predominates, was also reached using three distinct in vivo models of bone loss. The authors therefore suggest that blocking IFN-γ might provide a new approach to preventing both inflammation and bone loss in individuals with osteoporosis caused by inflammation, infection, or estrogen deficiency.TβRIII joins the fight against breast cancer TGF-β functions as a tumor suppressor during the early stages of breast cancer, but high levels of TGF-β during the later stages of disease […]

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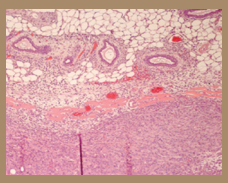
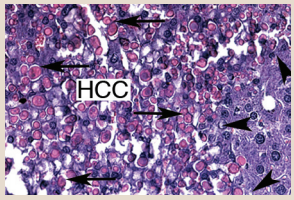
TβRIII joins the fight against breast cancer



TGF-β functions as a tumor suppressor during the early stages of breast cancer, but high levels of TGF-β during the later stages of disease are associated with poor prognosis. Dong and colleagues set out to investigate whether changes in the expression of a TGF-β coreceptor, TGF-β receptor III (TβRIII), which has been described recently as a crucial regulator of TGF-β signaling in mouse development, might provide a mechanism for the distinct effects of TGF-β at the different stages of breast cancer (pages 206–217). Expression of TβRIII by human breast cancer samples was shown to markedly decrease or be lost with disease progression. Loss of TβRIII expression was associated with loss of heterozygosity at the *TGFBR3* locus. In a mouse model of breast cancer, ectopic expression of TβRIII by the tumor cells decreased tumor invasion, angiogenesis, and metastasis. Further analysis revealed that the mechanism behind these protective effects of TβRIII was likely to be TβRIII cleavage at the cell membrane, which releases soluble TβRIII that blocks TGF-β signaling. As low levels of TβRIII were found to be associated with decreased recurrence-free survival of patients with breast cancer and loss of TβRIII was found to begin before tumors became invasive, the authors suggest that analysis of TβRIII levels might help clinicians decide how aggressively to treat their patients.

FoxM1 inhibitor puts the brakes on tumor growth



The transcription factor forkhead box M1 (FoxM1) has been shown previously to be required for tumor initiation in a mouse model of hepatocellular carcinoma (HCC). Using this model of HCC, in which diethylnitrosamine is used to initiate tumor formation and phenobarbital is used to promote tumor growth, Gusarova and colleagues have now shown that FoxM1 is also required for hepatic tumor progression (pages 99–111). Deletion of the gene encoding FoxM1 after tumors had formed but while tumors were still growing caused a substantial decrease in the number of hepatic tumors. A similar decrease was observed for both wild-type mice and *Arf*$^{-/-}$Rosa26-*Foxm1b* transgenic mice (a new mouse model of HCC developed by the authors in which hepatic tumor development is highly dependent on FoxM1) with preexisting tumors following treatment with a cell-penetrating peptide inhibitor of FoxM1, $ARF_{26–44}$. Further analysis showed that $ARF_{26–44}$ treatment increased tumor cell apoptosis and decreased tumor cell proliferation and tumor angiogenesis. $ARF_{26–44}$ treatment affected only the hepatic tumor cells and not the normal liver tissue, leading the authors to conclude that $ARF_{26–44}$ is an effective therapeutic approach to limiting hepatic tumor progression, at least in mice.

Modeling tau-induced neurodegeneration in *Drosophila*

Alzheimer disease (AD) is one of a group of neurodegenerative disorders known as tauopathies because they are characterized pathologically by intracellular aggregates of the microtubule-associated protein tau. Oxidative injury is associated with the neurodegeneration observed in AD and other neurodegenerative disorders, but whether oxidative injury causes neurodegeneration or is a consequence of it has not been determined. Dias-Santagata and colleagues set out to address this conundrum using a *Drosophila* model of human tauopathies (pages 236–245). Neurodegeneration (as assessed by the number of apoptotic neurons) was more extensive in *Drosophila* expressing a disease-related mutant form of human tau and genetically modified to increase levels of ROS than in *Drosophila* expressing only the mutant human tau. Conversely, treatment with the antioxidant vitamin E reduced the number of apoptotic neurons in *Drosophila* expressing mutant human tau. Further analysis indicated that oxidative stress is likely to increase neuronal apoptosis by enhancing tau-induced cell cycle activation. This demonstration that oxidative stress is a factor contributing to the onset of tau-induced neurodegeneration in *Drosophila* led the authors to suggest that targeting antioxidant and cell cycle pathways might provide a new approach to treating individuals with AD and other human tauopathies.