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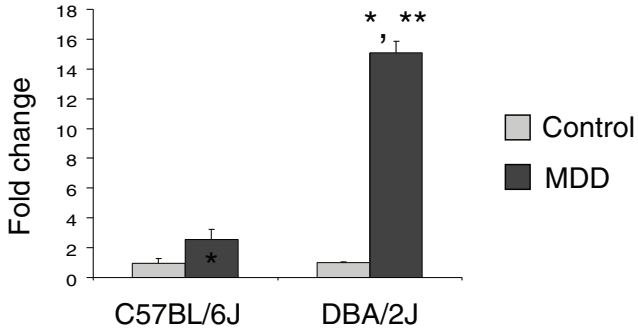

Differential microRNA expression is associated with strain susceptibility to NASH in mice

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Nonalcoholic steatohepatitis (NASH), a common liver disease, is a manifestation of the metabolic syndrome. The underlying pathogenesis is multifactorial and related to derangements of lipid metabolism, insulin resistance, immune response, inflammation, and oxidative stress. NASH can progress to cirrhosis and hepatocellular carcinoma. Recent studies have established that microRNAs (miRNAs) are important in the pathogenesis of NASH, but their various roles have yet to be defined precisely. Interestingly, different strains of mice, much like people, have different natural susceptibilities to developing NASH. Pogribny *et al* took advantage of differences in NASH susceptibilities in different mouse strains to investigate whether miRNAs might be associated with these differences and to better understand the roles of miRNAs in the pathogenesis of NASH.

The authors demonstrated that DBA/2J mice were more susceptible to NASH than C57BL/6J mice and that there was differential regulation of several miRNAs in the different mouse strains, resulting in differential expression of target genes and proteins. Specifically, DBA/2J mice showed a greater magnitude of changes in miRNA expression than did C57BL/6J mice. Moreover, some of the miRNAs that were differentially regulated have previously been implicated in the pathogenesis of NASH. For example, miRNAs controlling lipid metabolism were differentially regulated in the different strains. This study highlights the importance of miRNAs in differences in susceptibility and the pathogenesis of NASH.

Central role for ErbB4 in colon epithelial cell survival

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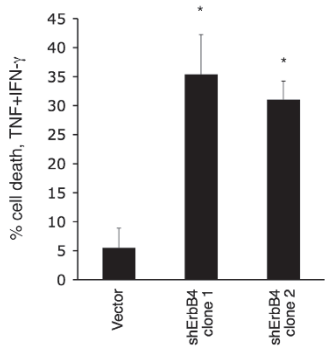

ErbB4 is a receptor tyrosine kinase and a member of the epidermal growth factor receptor–related ErbB family. Studies suggest that ErbB4 controls colonic epithelial cell survival in inflammatory diseases such as Crohn's disease and in colorectal carcinoma. Cyclooxygenase-2 (COX-2), the inducible form of mammalian prostaglandin synthase, is known to promote intestinal epithelial cell survival and to be a key mediator of colorectal carcinoma. On the basis of these data, Frey and colleagues hypothesized that COX-2 might be a target of ErbB4 signaling. They found that overexpression or activation of ErbB4 increased expression of COX-2 in colonic epithelial cells and was dependent on Src and phosphatidyl inositol 3-kinase signaling pathways. Interestingly, epidermal growth factor receptor (EGFR) inhibition ablated ErbB4-stimulated accumulation of COX-2, suggesting that ErbB4 functioned through ErbB4-EGFR heterodimers to induce COX-2 expression. Finally, using celecoxib, a COX-2 inhibitor, the authors showed that COX-2 mediated colonic epithelial cell survival and the ability to form colonies in soft agar, linking ErbB4-COX-2 to potential pathological mechanisms involved in inflammation and colorectal carcinogenesis. Further preclinical studies exploring the modulation of the ErbB4 signaling pathway in specific disease models appear to be warranted to determine whether targeting this pathway might be useful in the treatment of inflammatory bowel disease or colorectal carcinoma.

Inositol-1,4,5-trisphosphate signaling in osteoclast attachment

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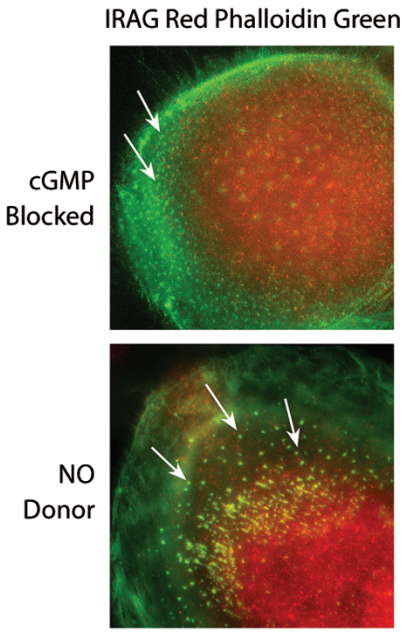
Bone homeostasis is maintained by dynamic remodeling from the opposing forces of osteoblasts and osteoclasts. Osteoblasts make bone; osteoclasts resorb bone. Defects in osteoclasts cause osteopetrosis, a rare disease of abnormal bone mineralization that results in harder, denser bone—'osteopetrosis' literally means 'stone bone'. The ability of osteoclasts to attach to bone is critical in osteoclast motility. Many cases of osteopetrosis are characterized by abnormal attachment, which in some cases occurs despite the presence of normal attachment proteins. Inositol-1,4,5-trisphosphate receptor-1 (IP3R1), an endoplasmic reticulum calcium channel regulates, calcium flux, enabling cell detachment and motility in osteoclasts. The IP3R-associated cGMP-dependent kinase substrate (IRAG) coprecipitates with



IP3R1 and plays an important role in cGMP-regulated calcium release.

On the basis of these data, Yaroslavskiy and colleagues sought to further understand how IP3R1 and IRAG control calcium release and osteoclast attachment. Their data suggest that the β isoform of cGMP-regulated protein kinase I (PKG1β) regulates IP3R1 via phosphorylation of endosome-bound IRAG at serine residues. Phosphorylation of IRAG by PKG1β leads to dissociation of the IP3R1-IRAG complex, promoting calcium release and subsequent detachment. The authors also showed that the process was dependent on Src signaling downstream of activation of nitric oxide or cGMP signaling. Depletion of IRAG expression by small interfering RNA led to increased intracellular calcium and an altered distribution of podosomes. Surprisingly, IRAG localized with membrane attachments and coprecipitated with membrane-associated proteins. This observation will require further studies before its significance is understood. Overall, these studies provide important insights into the regulation of osteoclast motility via IRAG modification by PKG1β, and they suggest possible pathogenetic mechanisms related to osteopetrosis.

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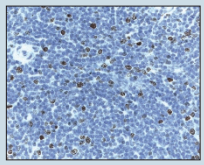
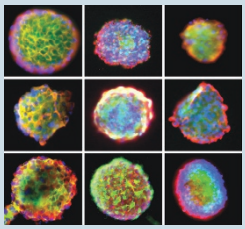
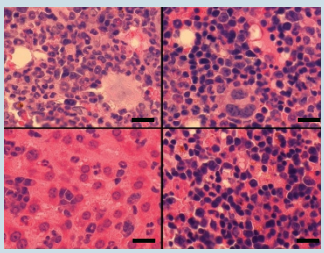


OncomiR addiction in a pre-B-cell lymphoma model MicroRNAs (miRNAs) play critical roles in regulating gene transcription at the posttranscriptional level. OncomiRs are miRNAs that show differential expression in cancers and regulate transformation, carcinogenesis, and metastasis. They can act as either oncogenes or tumor suppressors. Although oncomiRs have been implicated extensively in oncogenesis *in vitro*, relatively few supporting data have been derived from *in vivo* experiments. To generate *in vivo* support for a role of oncomiRs in cancer, Medina *et al*, as reported in a recent letter in *Nature*, generated an ingenious mouse model that achieved tissue-specific and doxycycline-controlled expression of miR-21, which had been shown to be overexpressed in most human tumor types examined. Mice that overexpressed miR-21 developed pre-B-cell lymphomas. Interestingly, when miR-21 expression was turned off by administration of doxycycline, the tumors regressed. Thus miR-21 appears to be involved in both initiation and maintenance of tumors.
Nature, published online 8 August 2010; doi:10.1038/nature09284



Mouse ependymoma model Ependymomas are rare tumors of the brain and spinal cord that have varying clinical profiles and prognosis, suggesting that different subtypes of ependymoma are unique diseases. Approximately 40% of cases are incurable. To better understand the pathogenesis of ependymoma with the overall goal of developing more effective therapies, Johnson *et al* sought to develop a mouse ependymoma model. As explained in a letter in *Nature*, they used a comprehensive genomics approach to identify potential oncogenes and tumor suppressors in ependymoma subtypes. They hypothesized that different subtypes of ependymoma arise from different neural stem cells (NSCs). To match the different types of ependymomas with NSCs, they compared their transcriptomic signatures. Drawing from this analysis, they matched a subtype of ependymoma with embryonic cerebral *Ink4a/Arf*$^{-/-}$ NSCs. When they transduced embryonic cerebral *Ink4a/Arf*$^{-/-}$ NSCs with Ephb2, 50% of mice developed ependymomas with histological and ultrastructural features that were identical to those of human supratentorial ependymomas. The authors plan to use this approach to develop models of other specific subtypes of ependymoma. They also point out that their general approach can be used to develop mouse models of other tumors.
Nature 2010;466:632–636; doi:10.1038/nature09173



Involvement of Musashi-2 in normal hematopoiesis and leukemia Musashi-2 (MSI2), an RNA-binding protein expressed in tissue stem cells, is rarely involved in a translocation with the *HOXA9* locus in blast crisis chronic myelogenous leukemia (CML). Given that little was known about the role of MSI2 in hematopoietic stem cells (HSCs) and cancers, Kharas *et al* embarked on a comprehensive analysis. In a report published in *Nature Medicine*, they demonstrate that MSI2 influences the proliferation and differentiation of HSCs and myeloid progenitors. Furthermore, they show that MSI2 is associated with aggressive myeloid leukemia.

In a related letter in *Nature*, Ito *et al*, using mouse models, demonstrate that NUP98-HOXA9, a chimeric oncogenic transcription factor that is associated with blast crisis in CML, leads to expression of Msi2 during blast crisis. Expression of Msi2 suppresses Numb. They showed that Numb is expressed at high levels during chronic-phase CML and promotes differentiation. Thus, Msi2 promotes blast crisis by suppressing Numb. Finally, they show that MSI2 expression is upregulated during human CML blast crisis and is associated with a poor prognosis.

Together, these papers highlight the roles of MSI2 in HSCs and in myeloid leukemias. These exciting studies suggest that modulation of MSI2 expression/activity in leukemias could be a useful therapeutic strategy in the treatment of both chronic and acute myeloid leukemias.
Nature Medicine 2010;16:903–908; doi:10.1038/nm.2187
Nature 2010;466:765–768; doi:10.1038/nature09171