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Intraneural model of NF1-associated malignant peripheral nerve sheath tumor

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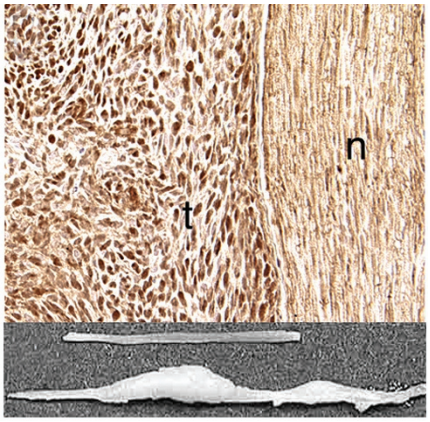
Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive tumors that often occur in patients with neurofibromatosis type 1 (NF1). They typically arise in large to medium-sized nerves, with the sciatic nerve being most frequently affected. Malignant progression from a pre-existing neurofibroma occurs in about 6% of patients with NF1, and the lifetime risk of MPNST in such patients is 8–12%. The overall 5-year survival is 34%, with patients experiencing local recurrence and distant metastasis. Efforts to understand disease mechanisms and develop more effective therapies will be greatly aided by appropriate experimental models. Inside this issue, Perrin *et al* report a successful *in vivo* orthotopic xenograft model of an MPNST that reproduces



characteristics of the human tumor in a relevant intraneural cellular environment. The authors developed and characterized a neurofibromin-deficient cell line that was derived from an NF1-associated MPNST. When engrafted into sciatic nerves of *scid* mice, tumors displayed gross and microscopic features of MPNST, including rapid, bulky growth, nerve invasion, high proliferation rate, angiogenesis, and mast-cell infiltration. The model produced the interesting observation that tumor growth and proliferative rates of MPNSTs in female mice were greater than in male mice. Furthermore, tumor-cell proliferation was reduced in ovarectomized mice, and this effect could be reversed by estrogen or progesterone therapy.

An association between steroid hormones and neurofibromas has been previously hypothesized, on the basis of reports of increased numbers and size of such tumors during puberty and pregnancy. These new results suggest a potential role for steroid hormones in supporting tumor cell growth of this MPNST cell line *in vivo*. Although hormone effects on MPNST growth in NF1 may be tumor specific, the results presented point to an area where further study is warranted. This model system appears well suited for testing therapeutic interventions, including inhibitors of angiogenesis, and for future study of steroid hormone effects on tumor cell growth.

The myriad proteins of Reed–Sternberg cells

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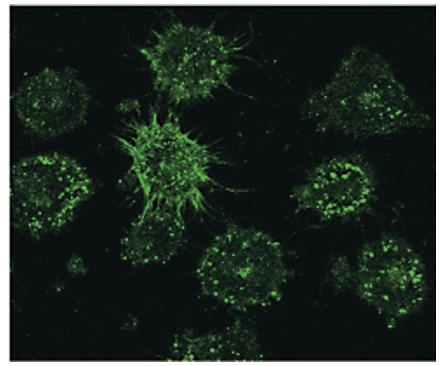
Hodgkin's lymphoma (HL) is characterized by the presence of relatively few neoplastic (Reed–Sternberg and variants) cells admixed with numerous inflammatory cells. The paucity of malignant cells in these tumors and the difficulty of obtaining them in a purified manner have hampered biological studies of freshly isolated malignant cells and required investigators to rely mainly on studies of HL cell lines instead. In this issue, Wallentine *at al* describe a subcellular proteomic approach to identifying proteins expressed by the Reed–Sternberg cells of HL-derived cell lines in an attempt to identify potential biomarkers for these tumors. For this purpose, they utilized liquid chromatography–tandem mass spectrometry, which has been used in the past for biomarker discovery because it enables the identification and cataloging



of large numbers of proteins in complex mixtures. This is important because the identification of biomarkers in HL has been limited to known proteins for which antibodies are available.

From the various subcellular compartments of the HL-cultured cells the authors identified a very large number of proteins that included 785 cytosolic, 305 from the membrane, 441 from nuclei, and 414 released proteins. The functions of these proteins are diverse, but most are involved in cellular differentiation, activation, and cell-cycle control. Many of the proteins found by the authors have previously been demonstrated to be expressed in HL, but others have not been described in this neoplasm and may play a role in its pathogenesis. The authors validated their observations for a few selected proteins using antibody-based technologies, including detecting their presence in tumor samples using immunohistochemistry.

Although further studies on tumor tissue samples would be necessary to confirm these observations, the novel proteins identified in this study may serve as a working inventory of possible biomarkers that could be useful in the diagnosis and monitoring of HL.

ROCKing the matrix

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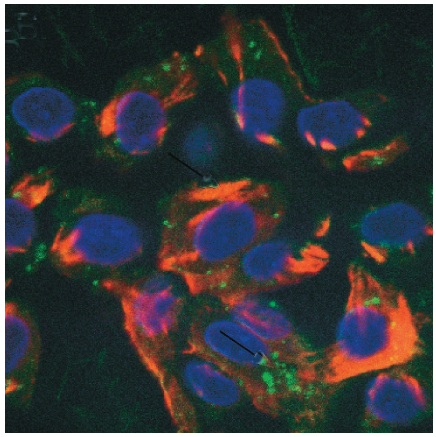
Colon cancer is the third most common cancer and second leading cause of cancer-related mortality in the United States. Effective treatment beyond surgical

excision is dependent on understanding the molecular mechanisms of invasion and metastasis. One of the downstream effectors of Rho, Rho-associated kinase-II (ROCK-II), has been suggested as a contributor to invasion because it is overexpressed at the leading edge of colon cancers, accumulating in podosome-like structures called 'invadopodia,' but this has not been directly tested. ROCK-II affects cell growth, migration, and apoptosis via control of the actin cytoskeleton.

In this issue, Vishnubhotla *et al* use an *in vitro* model to assess invasion into three-dimensional type I collagen scaffolds. They show that ROCK-II contributes to colon cancer invasion through its direct regulation



on matrix metalloprotease (MMP)-2 and MMP-13 at the leading edge of invadopodia. In malignant intestinal epithelial cell lines, ROCK-II localized with MMP-2 and MMP-13 to invadopodia. When ROCK-II expression was knocked down, there was a significant decrease in depth of invasion and a reduction in MMP-2 and MMP-13 activity in malignant cells. However, proliferation continued unabated in the malignant cell lines. Thus, ROCK-II is a critical mediator of colon cancer cell invasion, and this may reflect the effects of ROCK-II inhibition on MMP-2 and MMP-13 activity. These data suggest that ROCK-II inhibition has potential as a novel therapeutic approach to preventing colon cancer invasion.

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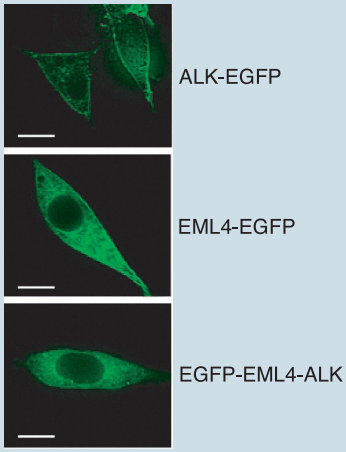
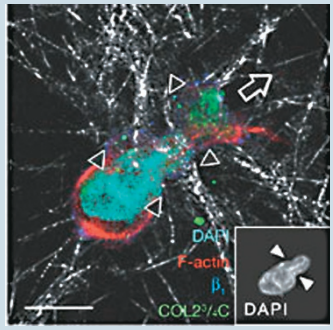


Fusion gene in non-small-cell lung cancer
Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases in Western countries. A small inversion in chromosome 2p was recently shown to result in the formation of a fusion gene comprising portions of the echinoderm microtubule–associated protein-like 4 *(EML4)* gene and the anaplastic lymphoma kinase (***ALK***) gene in NSCLC cells. The expression of the *EML4-ALK* fusion gene in mouse 3T3 fibroblasts caused transformed foci in culture and subcutaneous tumors in nude mice. In NSCLC patients who express the *EML4-ALK* fusion gene, this transforming fusion kinase may be a promising therapeutic target.
Nature 2007;448:561–566; doi:10.1038/nature05945



Control of cancer cell invasion Cell migration is a fundamental process in early morphogenesis and cancer metastasis that requires pericellular remodeling of extracellular matrix (ECM), which is a three-dimensional network that provides physical barriers to advancing cell bodies. ECM remodeling involves multiple sets of proteolytic enzymes, especially membrane-type-1 matrix metalloproteinase (MT1-MMP). A recent article in *Nature Cell Biology* reported the use of time-resolved multimodal microscopy to show how invasive HT-1080 fibrosarcoma and MDA-MB-231 breast cancer cells coordinate mechanotransduction and fibrillar collagen remodeling. Researchers identified two modes of pericellular collagenolysis: first, single-cell migration at selected regions causes fiber reorientation and small tube-like defects, and second, multiple connected cells cause lateral ECM regression by multicellular invasion. This invasive migration and proteolytic ECM remodeling are interdependent processes requiring functioning MT1-MMP that control tissue micropatterning and macropatterning and, consequently, individual and collective cell migration.
Nature Cell Biology 2007;9:893–904; doi:10.1038/ncb1616

Stromally induced hedgehog signaling in B-cell malignancies The interaction of tumor cells with their microenvironment is essential for their growth, survival, and localization. *Nature Medicine* recently reported that the stromally secreted hedgehog ligands indian, in bone marrow, and sonic, in lymph nodes and the spleen, promote the survival of lymphoma and plasmacytoma cells. *In vitro* hedgehog pathway inhibition induced apoptosis through downregulation of Bcl2, while *in vivo* blockage of the hedgehog pathway in a syngeneic mouse model inhibited lymphoma expansion and, at the highest treatment dose, doubled life expectancy. In mice with fully developed disease, hedgehog pathway inhibition decreased lymphoma mass. Inhibition of the hedgehog pathway may provide a new treatment for lymphoma and multiple myeloma.
Nature Medicine 2007;13:944–951; doi:10.1038/nm1614