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# INSIDE LAB INVEST

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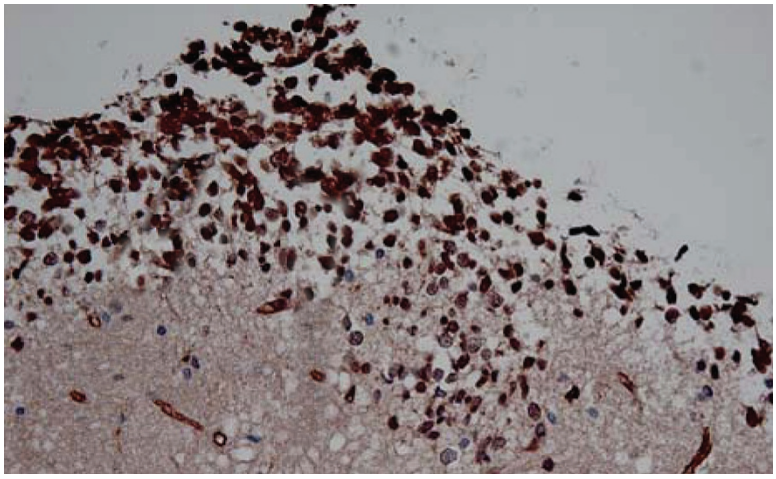

## Understanding leptomeningeal dissemination in medulloblastoma: just stick to it!

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Medulloblastoma is the most common malignant pediatric brain tumor. With an estimated annual incidence of 0.5–0.8 per 100,000 children under 19 years of age, it accounts for 16% of all pediatric brain tumors and 40% of childhood cerebellar tumors. The propensity of these tumors to spread within the subarachnoid space of the spine and brain remains a significant therapeutic challenge. About 30% of patients will have cerebrospinal fluid metastases at presentation, which places them in a high-risk group with poor prognosis. Although much emphasis has been placed on understanding molecular genetic pathways of tumorigenesis, the pathobiology of medulloblastoma dissemination has not been extensively studied.

In this issue, Fiorilli *et al* present data that suggest a role for integrin-mediated adhesion in the process of leptomeningeal metastasis. First of all, D283 medulloblastoma cells that preferentially express integrins α9 and β1 strongly adhere to extracellular matrix that is enriched with tenascin. The latter binds to α9β1 heterodimer. Adhesion was blocked by antibodies to α9 and β1 integrins. Immunohistochemical studies of primary medulloblastomas showed strong reactivity for these two integrins, and for tenascin, at the interface of the brain and leptomeningeal tumor. Adhesion of medulloblastoma cells to tenascin-rich extracellular matrix promoted their survival and proliferation as well as activation of the MAPK pathway in a growth factor–deficient environment. *In vitro* cell survival was also inhibited by antibody blockade of α9 and β1 integrin binding. These data suggest that the adhesion of medulloblastoma cells to the meninges promotes the survival and proliferation of tumor at this secondary site, and that future therapies may be designed to target this process.

## Regulating *Helicobacter pylori*–induced pathology

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Gastric *Helicobacter pylori* infection induces epithelial apoptosis. Although it is well known that apoptosis is regulated by BCL-2 family proteins, remarkably, the expression pattern of these proteins in gastric epithelia has not been characterized. This question is important, because *H. pylori* infection appears to induce apoptosis differentially in various gastric epithelial cell types. In this issue, Hagen *et al* present the first comprehensive study of cell-specific apoptotic protein expression before and during *H. pylori* infection. BCL-2 family proteins expressed in surface and pit cells are consistent with the presence of classic apoptosis pathways; however, the BCL-2 protein expression in chief and parietal cells suggests a contribution of unconventional pathways in regulating survival and death. For example, BAD, a pro-apoptotic protein, was the only BCL-2 family protein detected in parietal cells. In contrast, chief cells express high levels of BCL-$X_L$ and BCL-2, a combination that strongly inhibits apoptosis. Thus, gastric epithelial cells use cell-specific pro-survival and pro-apoptotic pathways. The data presented here will form an important foundation for future studies of the pathobiology of gastric *H. pylori* infection.

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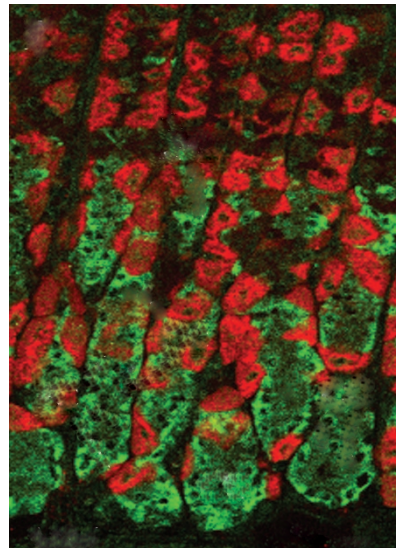

## Intestinal nanoparticle transcytosis following *Yersinia* exposure

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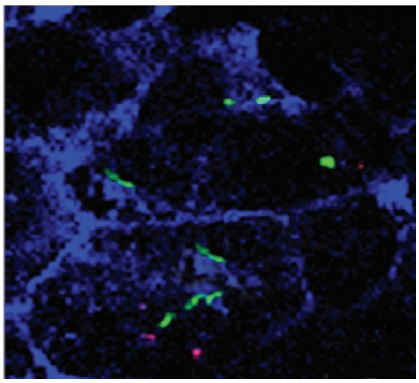
The surface area of the small intestine, including the villi, is about 27 $m^2$, the size of a medium-sized conference room. This surface is bathed in the rich mixture that is our partially digested food, digestive secretions, and innumerable foreign antigens and inanimate materials. The fact that the 20-μm-thick intestinal epithelial barrier

keeps these foreign items from suffusing our circulation is one of the miracles of life. However, transepithelial movement of antigens—whether as individual peptides or as particulate matter—occurs via direct

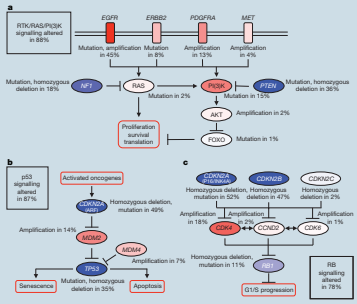


transit through epithelial cells or through the paracellular pathway. In the first scenario, transcytotic pathways can play a key role. In the second, intercellular tight junctions regulate both transepithelial resistance and the passage of fluid and solutes. Compromise in intestinal epithelial barrier function is thought to be a key causative event for Crohn's disease. Small intestinal infection with enteropathogenic bacteria may be an inciting factor in epithelial compromise, and infection-induced changes in intercellular tight junctional function have been well studied.

In this issue, Ragnarsson *et al* examine the short-term effects of *Yersinia pseudotuberculosis* exposure on the transcellular pathway in intestinal enterocytes. Using both monolayers of human colon epithelium–derived Caco-2 cells and biopsies of human ileum, they demonstrated that 2 hours of exposure to *Y. pseudotuberculosis* expressing (inv+), the bacterial adhesion molecule, increased transepithelial transport of fluorescein nanoparticles. Further experiments suggested that this transport was mediated by macropinocytosis. The authors hypothesize that bacterial factors may initiate transcytosis of luminal exogenous particles across human small intestinal mucosa, representing an additional mechanism of intestinal barrier dysfunction.

# nature.com/pathology

**From networks to individualized therapy** Although a single mutation is generally insufficient to drive carcinogenesis, the 'single gene' (or gene product) approach has endured because of a lack of tools enabling simultaneous study of multiple genes. A recent article in *Nature* describes an attempt to overcome this obstacle by integrating nucleotide sequence, DNA copy number, DNA methylation, and gene expression data from a large group of primary glioblastomas. Overall, the genetic events identified mostly confirm previous data, but the authors used these data to map the genetic alterations present in each tumor onto known signal transduction pathways. Three of these—p53 tumor suppressor, phosphatidylinositol-3-kinase–receptor tyrosine kinase, and retinoblastoma tumor suppressor pathways—were mutated in 78%, 88%, and 87% of tumors, respectively, and 74% of tumors included at least one mutation in each pathway. Interestingly, tumors tended to have only one mutation in each pathway. These data suggest that deregulation of one component in a pathway relieves the selective pressure for additional mutations in that pathway and also indicate that dysregulation of all three of these pathways is required for glioblastoma tumorigenesis. Because multiple genetic events were identified in each pathway, it stands to reason that therapy must be directed against the altered component(s) and that individualized therapy might include a validated target in each pathway. Thus, in addition to traditional surgical pathology diagnosis, ancillary molecular analysis of tumors may guide therapeutic decision making and, finally, improve the prognosis for this lethal cancer.

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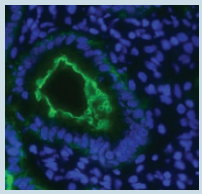

**Up, up, and away** Microvillus inclusion disease (MVID) is an autosomal recessive disorder characterized by intractable, life-threatening, watery diarrhea. The disease is usually fatal because of the associated malabsorption and dehydration. Given the nonspecific clinical features, diagnosis requires evaluation by transmission electron microscopy and demonstration of microvillus membrane inclusions and shortened or absent apical microvilli. A recent communication in *Nature Genetics* presents a homozygosity mapping approach to identifying the genetic basis of MVID. The gene identified, myosin Vb (*MYO5B*), has been extensively studied and shown to be necessary for *in vitro* polarization of cultured hepatocytes and trafficking to and from the apical membrane. Thus, by virtue of previous work on the cell biology of epithelial polarity and membrane traffic, this study has been able to leap from gene association to functional defect in a single bound and may pave the way for a rapid (faster than a speeding bullet?) transition from electron microscopy to immunocytochemistry for diagnosis.

*Nature Genetics*, published online 24 August 2008; doi:10.1038/ng.225

**Every breath you take** Cockayne syndrome (CS) is a rare autosomal recessive disorder characterized by growth failure, neurological defects, photosensitivity, and premature aging. Although the CS B protein (CSB) that is mutated in CS has been identified, its function as a chromatin remodeler does not appear to explain the phenotype of CS patients. The observation that Purkinje cells and oligodendrocytes, which are particularly sensitive to hypoxia, are often damaged in CS patients caused the authors of a recent study in the *EMBO Journal* to hypothesize that CS may be due to a failure of hypoxic response pathways. Their data show that cells with mutant CSB are unable to activate hypoxia-inducible factor-1 (HIF-1)-dependent gene expression following hypoxia. This is explained by the discovery of a role for CSB in recruitment of p300, a transcriptional cofactor/histone acetyltransferase that is required for HIF-1-dependent gene expression, to the transcriptional apparatus. In the absence of functional CSB, p300 remains associated with p53, allowing transcription of pro-apoptotic genes and enhancing hypoxia-induced cell death. Although it is too soon for therapeutic use, this suggests that enhanced oxygen delivery may lessen CS pathology.

*The EMBO Journal*, published online 11 September 2008; doi:10.1038/emboj.2008.180