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INSIDE LAB INVEST

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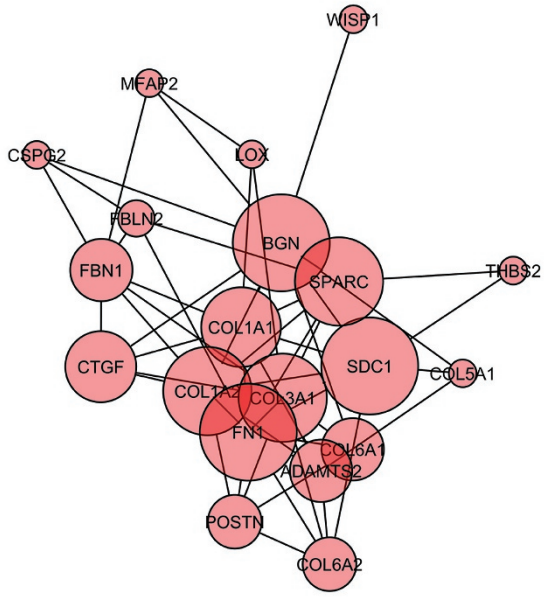

Prognostic significance of stromal expression profile in malignant desmoplasia

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Fibrosis, fibromatosis, and desmoplasia span a pathobiological spectrum from benign reactive conditions to progressive recurrent tumor-like processes, to being a defining feature of many epithelial malignancies. In the last instance, most investigators have focused on the tumor biology of epithelial cells. There have been relatively few studies of the neoplastic stroma, a complex microenvironment that most likely has a profound effect on tumor growth and progression. Beck and colleagues describe a study of gene-expression profiles of breast cancer stromal desmoplasia in which they compared these profiles with those of other fibrosing neoplasms. In a previous paper, this group showed that desmoid-type fibromatoses (DTFs) and solitary fibrous tumors (SFTs) had distinct gene-expression profiles that defined two types of stromal processes. DTFs had profile characteristics of scar formation and profibrotic reactions, whereas SFTs presented an expression pattern consistent with epithelial support stroma and basement-membrane function. The current study examined stromal gene expression in a large series of infiltrating ductal breast carcinomas. One subtype of carcinomas that had a DTF-like stromal expression pattern was associated with a good outcome. Furthermore, immunohistochemical analysis showed that a positive reaction for one DTF stromal protein (SPARC) was also associated with a better prognosis. This study provides evidence that characteristics of the neoplastic microenvironment play a major role in tumor biology and translate directly to important prognostic information about the patient.

The mucus layer in murine colitis

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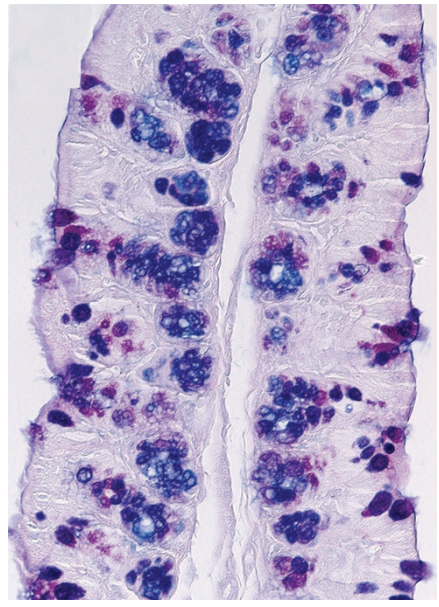
The colonic lumen, which contains an immense population of microorganisms, is considered one of the most complex microenvironments in the biological world. The human proximal colon takes in, on a daily basis, about 14 liters of fluid and all the detritus and debris of food consumed. We eliminate about 250 cm^3 of excrement each day; colonic resorption of fluid constitutes the difference. The mucosal lining responsible for such massive fluid uptake is about 0.03 cm thick and serves as both barrier and functional conduit for exchange of fluid and solutes between the lumen and the bloodstream. The mucosa is covered by an even thinner (about 0.002 cm) layer of mucus. In addition to being a mechanical cushion, the mucus facilitates creation of an even smaller microenvironment: the surface "unstirred layer" immediately above the mucosal epithelium.

The mucus layer is composed of mucins, of which Muc2 is an abundant component in humans and rodents. Intestinal loss of Muc2 leads to colonic inflammation in mice. This fact was exploited by van der Sluis *et al*, who utilized the interleukin-10 knockout (IL-$10^{-/-}$) mouse model of ulcerative colitis to examine the additional role of Muc2 in mucosal protection. Unlike single-knockout mice for IL-$10^{-/-}$ or $Muc2^{-/-}$, which exhibit 100% survival despite the development of colonic inflammation, double-knockout mice (IL$10^{-/-}$, $Muc2^{-}$



$^{/-}$) exhibited a high mortality rate (50% in 5 weeks). The severe colitis manifest in these animals was accompanied by significant upregulation of pro-inflammatory cytokines both in the colon and systemically. This important new mouse model clearly demonstrates that the mucus layer is a key factor in protecting against colitis. The results also point toward a protective effect of IL-10 when the mucus layer is compromised.

Invasive Helicobacter pylori?

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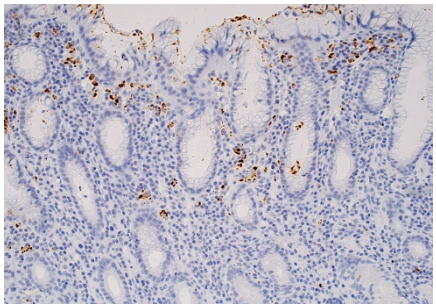

Helicobacter pylori were first described in 1984 as noninvasive bacteria in the gastric mucus. Although occasional studies have reported *H. pylori* within epithelial and immune cells, the organisms were often degenerated and were considered irrelevant to chronic gastritis. A study by Ito *et al* in this issue examined gastric tissue and gastric lymph nodes by immunohistochemistry, quantitative real-time polymerase chain reaction, and microbiological culture. *H. pylori* were commonly found in lamina propria macrophages and occasionally in dendritic cells. These studies suggest that the epithelial damage induced by *H. pylori* infection may allow bacteria to translocate to the gastric lymph nodes, where they stimulate the immune system. Further work is needed to characterize the pathogenic potential of these bacteria within lamina propria macrophages.

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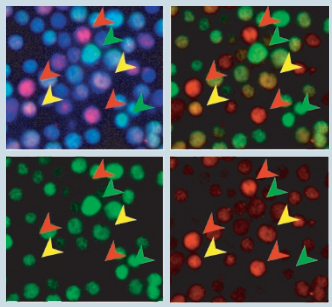
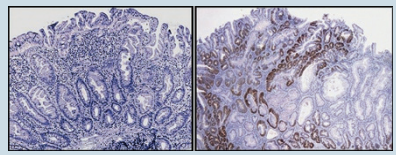


Checks and balances in election of T-cell type during differentiation Regulatory T (T_{reg}) cells are critical to controlling autoimmunity, unlike their pro-inflammatory counterparts, T helper cells that produce interleukin-17 (T_H17 cells), which tend to promote it. Although they have opposing roles, it is becoming clearer that the factors that promote the differentiation of these distinct T-cell subsets overlap, explaining the ease with which immune homeostasis can be thrown off balance. One recent study has found that although both T_{reg} and T_H17 cells require transforming growth factor-β, the concentration of this factor regulates the cytokines present and consequently the transcription factors activated.[1] A separate study has shown that the aryl hydrocarbon receptor (AHR) also regulates the development of both T-cell lineages through ligand specificity.[2] The relevance of the latter observation to disease is emphasized in a study showing that AHR activation during induction of experimental autoimmune encephalomyelitis accelerates disease onset and increases pathology in wild-type mice but not in AHR-deficient mice.[3] Together these data present a more detailed picture of T-cell differentiation and explain how endogenous and exogenous factors can manipulate these processes to prevent or mediate disease.

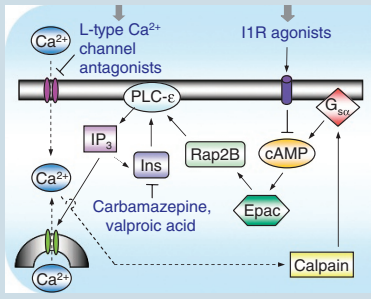
[1]*Nature*, published online 26 March 2008; doi:10.1038/nature06878; [2]*Nature*, published online 23 March 2008; doi:10.1038/nature06880; [3]*Nature*, published online 23 March 2008; doi:10.1038/nature06881



MUCking up mucin expression The morphology, diagnostic criteria, and clinical significance of colonic sessile serrated adenomas (SSAs) are evolving. However, SSAs continue to be confused with hyperplastic polyps because of the morphological overlap between these entities. Given that hyperplastic polyps have no neoplastic potential, this distinction is clinically significant. A recent study in *Modern Pathology* has shown that *MUC6*, a gastric mucin, is expressed in SSAs but not in hyperplastic polyps. *MUC6* expression was retained in SSAs with cytologic dysplasia, but it was absent in serrated adenomas. This study therefore demonstrates that traditional serrated adenomas and SSAs arise through distinct molecular pathogeneses and suggests that immunohistochemistry for *MUC6* may be a useful ancillary procedure in diagnosing some serrated lesions.

Modern Pathology, published online 21 March 2008; doi:10.1038/modpathol.2008.55

New pathway eating away at Huntington's disease Autophagy may be important in clearing pathogenic protein aggregates such as those implicated in Huntington's disease and many other disorders. The autophagy-lysosomal pathway is regulated by mTOR, a protein kinase, and the mTOR inhibitor rapamycin is the only treatment known to induce autophagy in the brain. However, rapamycin is also an immunosuppressant, which prohibits its use in many clinical settings. A recent study published in *Nature Chemical Biology* sought to identify new agents that might induce autophagy without immunosuppression. The screen identified L-type Ca^{2+} channel antagonists and a G_i signaling activator as drugs that induce autophagy via a novel mTOR-independent pathway. The data demonstrated the therapeutic efficacy of these agents and the overall pathway in mammalian cell, fruit fly, and zebrafish models of Huntington's disease, indicating that this discovery has the potential to impact many immunologic, neoplastic, and degenerative diseases.



Nature Biotechnology 2008;26:462–469; doi:10.1038/nbt1392