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In This Issue

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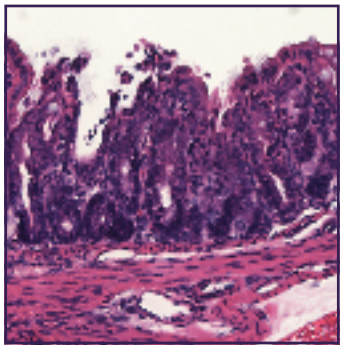
In this issue

Usher syndrome: Mendelian no more Usher syndrome is a genetic disorder characterized by congenital deafness and retinitis pigmentosa, which leads to gradual vision loss; it is the leading cause of deafblindness. Many patients do not have mutations in any of the genes that are known to be linked with Usher syndrome, and patients within a family often present with a variable visual phenotype. So, Ebermann and colleagues set out to identify other genes linked to the condition and found that mutations in PDZ domain–containing 7 (PDZD7), which encodes a ciliary protein, contribute to Usher syndrome (1812–1823). Importantly, PDZD7 mutations were identified only in patients with mutations in other known Usher genes, including Usher syndrome subtype 2A (USH2A) and G protein–coupled receptor 98 (GPR98). In a set of sisters with the same homozygous USH2A mutation, a PDZD7 mutation was present only in the sister with more severe retinitis pigmentosa and earlier disease onset. Further analysis in zebrafish was consistent with the patient data; together, they indicate that PDZD7 modifies retinal disease in patients with USH2A mutations and that digenic inheritance of mutations in PDZD7 and GPR98 contributes to Usher syndrome. This suggests that Usher syndrome is an oligogenic disease and not a single-gene Mendelian disorder, as currently believed. COMM(an)D(ing) role in tumor invasion COMM domain–containing 1 (COMMD1) is the prototypic […]

p120-catenin maintains intestinal barrier integrity



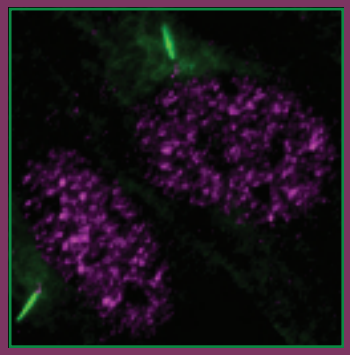
Inflammatory bowel diseases (IBDs) are chronic, remitting inflammatory conditions whose overall etiology is poorly understood and multifactorial. Recent studies have indicated that cadherin adhesion molecules have a role in IBDs. As the function of epithelial-cadherin is regulated in part by p120-catenin (p120), Smalley-Freed and colleagues set out to test the hypothesis that p120 has a role in IBDs by analyzing mice lacking p120 in the small intestine and colon (1824–1835). These mice died soon after birth as a result of massive intestinal bleeding caused by defects in epithelial cell-cell adhesion in both the small intestine and colon. An increase in inflammatory cells in the connective tissue layer beneath the epithelium of the colon was also observed. Further analysis revealed that these inflammatory cells were neutrophils expressing COX-2, an enzyme expressed at elevated levels in most active human IBD samples. These and other data presented in the study indicate that p120 deficiency in the mouse small intestine and colon leads to a loss of epithelial barrier integrity and increased neutrophil accumulation. The data also suggest a role for p120 in IBD.

COMM(an)D(ing) role in tumor invasion

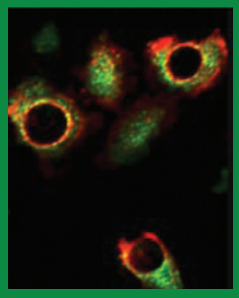
COMM domain–containing 1 (COMMD1) is the prototypic member of the little studied COMMD family of proteins. COMMD1 inhibits NF-κB and HIF, two transcription factors linked to tumor growth, survival, and metastasis. van de Sluis and colleagues therefore set out to test the hypothesis that COMMD1 is inactivated or repressed in tumors (2119–2130). Their initial analysis of the Oncomine database indicated that COMMD1 expression is decreased in a variety of cancers relative to normal tissue controls. Furthermore, the data from the Oncomine database and analysis of both prostate cancer and endometrial cancer patients indicated that decreased COMMD1 expression is associated with increased tumor invasion and worse clinical outcomes. Consistent with these data and a role for COMMD1 in promoting tumor invasion of the tissues and vasculature, decreasing COMMD1 expression in human cell lines increased tumor invasion in a chick xenograft model, while increasing COMMD1 expression in mouse cells decreased lung metastasis in a mouse model. The authors' observation that decreased *COMMD1* expression correlated with increased expression of genes encoding proteins known to promote cancer cell invasiveness provides more evidence to support their conclusion that COMMD1 has a role in tumor invasion.

Usher syndrome: Mendelian no more

Usher syndrome is a genetic disorder characterized by congenital deafness and retinitis pigmentosa, which leads to gradual vision loss; it is the leading cause of deafblindness. Many patients do not have mutations in any of the genes that are known to be linked with Usher syndrome, and patients within a family often present with a variable visual phenotype. So, Ebermann and colleagues set out to identify other genes linked to the condition and found that mutations in PDZ domain–containing 7 (*PDZD7*), which encodes a ciliary protein, contribute to Usher syndrome (1812–1823). Importantly, *PDZD7* mutations were identified only in patients with mutations in other known Usher genes, including Usher syndrome subtype 2A (*USH2A*) and G protein–coupled receptor 98 (*GPR98*). In a set of sisters with the same homozygous *USH2A* mutation, a *PDZD7* mutation was present only in the sister with more severe retinitis pigmentosa and earlier disease onset. Further analysis in zebrafish was consistent with the patient data; together, they indicate that *PDZD7* modifies retinal disease in patients with *USH2A* mutations and that digenic inheritance of mutations in *PDZD7* and *GPR98* contributes to Usher syndrome. This suggests that Usher syndrome is an oligogenic disease and not a single-gene Mendelian disorder, as currently believed.



GRP78: the entry key in mucormycosis



Mucormycosis is a life-threatening fungal infection most commonly caused by *Rhizopus oryzae*, a fungi of the order Mucorales. It occurs predominantly in individuals with diabetes mellitus, in particular those with diabetic ketoacidosis (DKA). As mucormycosis is characterized by fungal invasion of the vascular network, Liu and colleagues set out to identify an endothelial cell receptor(s) for fungi of the order Mucorales (1914–1924). A series of in vitro experiments identified glucose-regulated protein 78 (GRP78) as a receptor for *R. oryzae* on human endothelial cells. Binding of *R. oryzae* to GRP78 induced endocytosis and subsequent endothelial cell damage. Interestingly, increased expression of GRP78 was observed on human endothelial cells cultured in levels of glucose and iron consistent with those seen during DKA and in the tissues that are affected during mucormycosis in mice with DKA, which are susceptible to the infection. Furthermore, mice with DKA were protected from mucormycosis by treatment with GRP78-specific immune serum. These data provide an explanation as to why patients with DKA are highly susceptible to mucormycosis and suggest a new avenue of research for those developing therapeutics for this life-threatening infection.