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In This Issue

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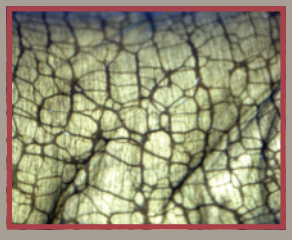
Inducing macrophages to protect against effects of obesity Diet-induced obesity (DIO) triggers the accumulation of inflammatory macrophages in white adipose tissue (WAT), a process that is key to the development of insulin resistance and diabetes. Using mice overexpressing the triacylglycerol (TG) synthesis enzyme acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) in both macrophages and adipocytes, Koliwad and colleagues have now determined that inducing macrophages to store increased amounts of TG is sufficient to protect mice from diet-induced inflammatory macrophage activation, macrophage accumulation in WAT, and insulin resistance (756–767). Further evidence to support the hypothesis that increasing DGAT1 expression in mouse macrophages enhances their ability to store TG and reduces the inflammatory and metabolic consequences of DIO was provided by in vitro analysis of bone marrow–derived macrophages: Dgat1 mRNA levels correlated directly with TG storage capacity and inversely with inflammatory activation by saturated fatty acids. Of clinical interest, the ability of antidiabetic agents known as PPARγ agonists to suppress saturated fatty acid–mediated inflammatory activation of bone marrow–derived macrophages was abrogated if the cells were DGAT1 deficient. The authors therefore suggest that modulating DGAT1 levels in human macrophages might be a crucial mechanism underlying the antiinflammatory (and thereby antidiabetic) effects of PPARγ agonists. RET's role in development deciphered Mutations in the protooncogene rearranged during transfection (RET), which encodes two major alternative isoforms of a […]

Rab25: a tumor suppressor in the intestines?

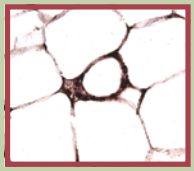
A loss of cell polarity is thought to play a critical role in the development of epithelial neoplasias. As the small GTPase Rab25 regulates polarized trafficking to the cell membrane and is expressed throughout the gastrointestinal mucosa, Nam and colleagues set out to investigate whether it has a role in neoplastic transformation of intestinal epithelial cells (840–849). Initial analysis indicated that expression of Rab25 was substantially decreased in human colon adenocarcinomas compared with normal colon, independent of stage, and that lower Rab25 expression predicted shorter patient survival times. To follow up on these data, which suggested that Rab25 functions as a tumor suppressor in intestinal epithelial cells, the authors analyzed Rab25-deficient mice. Although these animals showed no gross abnormalities, when they were crossed with $Apc^{Min/+}$ mice (a model of a hereditary syndrome that predisposes to colon cancer), the Rab25-deficient $Apc^{Min/+}$ mice developed increased numbers of intestinal polyps and colonic tumors compared with parental $Apc^{Min/+}$ mice. The demonstration that Rab25-deficient $Smad3^{+/-}$ mice developed more colonic tumors than did control $Smad3^{+/-}$ mice provided further confirmation of the probable tumor-suppressive role of Rab25 in intestinal epithelial cells.

RET's role in development deciphered



Mutations in the protooncogene rearranged during transfection (*RET*), which encodes two major alternative isoforms of a receptor tyrosine kinase (RET9 and RET51), underlie several diseases and developmental defects, including Hirschsprung disease (HSCR) and congenital anomalies of kidneys or urinary tract (CAKUT) syndrome. It is not clear, however, how *RET* mutations lead to such a range of diseases, which can occur in isolation or combination. To address this issue, Jain and colleagues set out to characterize enteric and autonomic nervous system development in mice expressing RET9 or RET51 isoforms mutated at different tyrosine residues that act as docking sites for the adaptors Plcγ, Src, Shc, and Grb2 (778–790). Analysis of these mice indicated that mutation of RET51 at Y1062, a docking site for multiple adaptor proteins, caused distal colon aganglionosis reminiscent of HSCR, whereas this mutation in RET9, which lacks the Grb2 docking site present in RET51, produced severe abnormalities in multiple organs. Other analyses indicated that mutations that abrogate RET-Plcγ binding, previously shown to produce CAKUT syndrome–like abnormalities, produced only minor abnormalities in the nervous system. The authors conclude, from their analysis of ten strains of mutant mice, that different RET-stimulated signaling pathways control the development of the genitourinary system and the enteric and autonomic nervous systems.

Inducing macrophages to protect against effects of obesity



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Transporter's role in kidney stones and hepatotoxicity

Kidney and urinary stones and liver toxicity are linked to alterations in oxalate and sulfate homeostasis, respectively. Sulfate anion transporter–1 (Sat1; also known as Slc26a1) mediates epithelial transport of oxalate and sulfate and is localized to the kidney, liver, and intestine. Dawson and colleagues therefore generated Sat1-deficient mice to investigate whether Sat1 has a physiologic role in oxalate and sulfate homeostasis (706–712). $Sat1^{-/-}$ mice excreted excess amounts of oxalate in urine (a common symptom in individuals with calcium oxalate kidney stones), exhibited high levels of oxalate in blood, and had calcium oxalate stones in renal tubules and bladder. Further analysis indicated that these mice also excreted excess amounts of sulfate in urine, had markedly reduced levels of sulfate in blood, and exhibited enhanced acetaminophen-induced liver toxicity — all of which are consistent with the fact that sulfate is required for detoxifying xenobiotics such as acetaminophen. The authors therefore conclude that Sat1 regulates oxalate and sulfate homeostasis and may be critical to the development of calcium oxalate kidney and urinary stones and liver toxicity.