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Regulation of adipogenesis by KLF15

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Because of its role in obesity and the metabolic syndrome, which have reached epidemic proportions throughout much of the world, there is increasing interest in adipocyte biology, especially in controlling adipocyte differentiation. Currently, it is thought that CCAAT/enhancer-binding protein (C/EBP) β and C/EBP α activate transcription of peroxisome proliferator-activated receptor γ (PPAR γ) and C/EBP α to unleash an adipocytic-specific differentiation program. Glucocorticoids such as dexamethasone are used to suppress inflammation. They act as ligands for the glucocorticoid receptor (GR), which functions as an important transcription factor. One of the major off-target effects of dexamethasone is induction of adipogenesis, leading to the “buffalo hump” and central obesity that are hallmarks of patients receiving this therapy. Asada and colleagues studied the mechanism of action in dexamethasone’s ability to induce adipogenesis.

The authors focused their attention on Krüppel-like factor 15 (KLF15), which is known to regulate adipogenesis through induction of PPAR γ . Using bioinformatics analysis, they identified two GR binding sites (GREs) within the first intron of KLF15 and further demonstrated that GR induced KLF15 promoter activity through binding of the GREs. Moreover, they showed that knockdown of KLF15 impaired the ability of mouse embryonic fibroblasts to undergo adipocytic differentiation. Their results highlight a

novel pathway whereby GR stimulation leads to activation of KLF15, which induces expression of downstream targets such as PPAR γ and C/EBP α . This strongly suggests that endogenous GR activation plays an important role in adipocytic differentiation, indicating that modulation of GR activity could be used to control adipocytic differentiation therapeutically.

Exploiting glucose transport to attenuate complications of intestinal ischemia/reperfusion injury

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Intestinal ischemia/reperfusion (I/R) injury can occur in a variety of situations, e.g., mesenteric artery embolism, trauma, or as a result of intra-abdominal surgery. Complications of I/R include the development of sepsis, systemic inflammatory response syndrome, and multiorgan system failure, with mortality rates of 60–80%. One of the major pathogenetic mechanisms of I/R injury

involves disruption of epithelial barrier function with resultant migration of commensal bacteria across the gut lumen into the blood, where various organs are seeded. Thus, therapies that support epithelial barrier integrity after I/R injury could reduce the severity of complications due to I/R. Huang *et al* hypothesized that epithelial apoptosis results in epithelial barrier disruption and that luminal glucose uptake by sodium/glucose transporter 1 might prevent or reduce epithelial apoptosis.

The authors demonstrated that apoptosis decreased by caspase inhibition attenuated the loss of epithelial barrier function as compared with controls, both *in vitro* and *in vivo*. Furthermore, they showed that enteral administration of glucose alleviated I/R-induced epithelial damage, maintained epithelial barrier integrity, and decreased bacterial translocation and mucosal inflammation. To better understand how increased glucose prevented I/R complications, Huang and colleagues examined phosphatidylinositol 3-kinase/Akt signaling after I/R. They found that Akt activity decreased after I/R. Further investigation showed diminished cell survival signals, which were reversed by enteral glucose administration. Because enteral glucose administration appears to attenuate I/R injury in mouse models, additional studies are warranted to determine the efficacy in humans.

Matrix metalloproteinases are involved in acute kidney injury due to ischemia/reperfusion

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Ischemia/reperfusion (I/R) acute kidney injury (AKI) can be caused by a number of factors and is a major contributor to morbidity and mortality. Various molecular mechanisms involving intracellular pathways have been suggested to cause I/R AKI. Recently, however, attention has

turned to the extracellular world of matrix metalloproteinases (MMPs), a family of zinc-dependent proteases responsible for extracellular matrix turnover and protein degradation. MMP-2 and MMP-9 have been shown to play important roles in the pathogenesis of I/R injury in several organs and tissues. Previous studies in the kidney have implicated MMP-2 and MMP-9 in modulation of renal microvascular permeability. To determine

whether either of these MMPs is involved in the pathogenesis of I/R AKI, Kunugi *et al* investigated whether inhibition of MMP-2 and/or MMP-9 attenuated AKI after I/R.

The authors found that MMP-2 and MMP-9 accumulated in the renal cortex of mice after I/R and preceded the onset of tubular necrosis and renal dysfunction. Interestingly, there were two waves of MMP-2 and MMP-9 expression, corresponding to the initial ischemic insult and the period after reperfusion. When I/R was performed in MMP-2^{-/-} knockout mice, AKI was less severe than in MMP-2^{+/+} mice, confirming that MMP-2 is involved in AKI. Finally, pharmacological MMP-2 and MMP-9 inhibitors also diminished the severity of AKI in mice after I/R. Overall, these results suggest that MMP-2 and MMP-9 are attractive targets for pharmacological intervention in cases of I/R. Kunugi and co-workers plan to perform a preclinical study using nonhuman primates to test the efficacy of MMP-2 and MMP-9 inhibition in preventing I/R AKI.

LMO1 is a neuroblastoma oncogene Examination of sporadic neuroblastomas has identified several chromosomal rearrangements, such as amplification of the *MYCN* oncogene. Recently, however, attention has been turned to the identification of germline variations that predispose to neuroblastoma. Genome-wide association studies (GWASs) have already identified common single-nucleotide polymorphisms associated with neuroblastoma. To identify additional genetic risk factors, Wang and colleagues, as reported in a recent letter in *Nature*, expanded their previous GWAS to analyze 1,627 neuroblastoma patients and 3,254 genetically matched controls. They observed a significant association between neuroblastoma patients and LIM domain only 1 (*LMO1*) at 11p15.4, which was also associated with aggressive neuroblastoma. *LMO1* mutations appeared to deregulate expression of *LMO1*, leading to increased expression. Subsequent examination of sporadic neuroblastomas revealed that the *LMO1* locus was duplicated in 12.4% of cases and was associated with an aggressive phenotype and decreased survival. *Nature*, published online 1 December 2010; doi:10.1038/nature09609

An *in vitro* organotypic neoplasia model To obtain a model of epithelial tumorigenesis that would be amenable to high-throughput drug screening and other high-throughput studies and that would recapitulate the salient features of epithelial tumorigenesis, Ridky and colleagues devised a method to generate three-dimensional squamous cell carcinoma models that utilize primary epithelial cells from the epidermis, oropharynx, esophagus, and cervix. In the study, described in a recent technical report in *Nature Medicine*, they expressed oncogenic Ras and cyclin-dependent kinase 4 in primary squamous cells from different anatomical regions and cultured them on an acellular derivative of dermis that contained extracellular matrix proteins and basement-membrane elements, leading to invasion across the basement membrane. Stromal fibroblasts from the various regions facilitated epithelial cell invasion. Preliminary analysis indicates that these models more faithfully evaluate the ability of cells to invade across the basement membrane and are amenable to high-throughput drug screening. *Nature Medicine* 2010;16:1450–1455; doi:10.1038/nm.2265

An immunological mechanism to disseminate postoperative ileus

Postoperative ileus, a common complication of intestinal surgery, is characterized by bowel dysmotility that can disseminate away from the operative site to involve the entire bowel—the “gastrointestinal field effect.” Memory T cells have recently been increasingly implicated in a variety of processes within the bowel. In a recent article in *Nature Medicine*, Engel *et al* hypothesized that memory T cells might play an important role in disseminated ileus. They demonstrated that dendritic cells at the site of surgery within the small bowel, residing within the bowel wall, induce T helper type 1 (Th1) cells via interleukin-12. Th1 cells amplify local inflammation and, more importantly, migrate via the bloodstream to the colon, where they induce ileus by activating macrophages to produce inducible nitric oxide synthase. This inhibits smooth muscle function, thus neatly explaining the gastrointestinal field effect. *Nature Medicine* 2010;16:1407–1413; doi:10.1038/nm.2255

Mechanism of persistent STAT3 activation during oncogenesis Activated interleukin-6–Janus kinase–signal transducer and activator of transcription-3 (STAT3) signaling has emerged as an important mechanism in the pathogenesis of many types of tumors. An important question has been how STAT3 remains persistently elevated in cancer cells given that STAT3 expression is normally tightly regulated. In a recent article in *Nature Medicine*, Lee *et al* report that *S1pr1* expression is strongly induced by Stat3 expression and that STAT3 is a transcription factor for *S1pr1*, thus creating a feedback loop that mediates persistent activation of STAT3. Interestingly, the authors also showed that S1pr1-mediated STAT3 expression in stromal cells was also critical for tumor progression. *Nature Medicine* 2010;16:1421–1428; doi:10.1038/nm.225