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GPR55 receptor mediates antiproliferative effects of anandamide in cholangiocarcinoma

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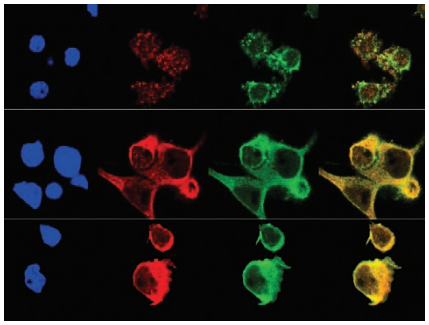

Cholangiocarcinoma, a malignant neoplasm that arises from bile-duct epithelium, has a very poor prognosis—it usually presents with advanced disease and is refractory to chemotherapy and radiation therapy. The incidence of cholangiocarcinoma is on the rise worldwide. Previous work demonstrated that cholangiocarcinoma cells are sensitive to anandamide (AEA), an endocannabinoid that exhibits antiproliferative and pro-apoptotic activities. However, attempts to identify an AEA receptor in cholangiocarcinoma cells failed, suggesting that the anticancer effects seen in cholangiocarcinoma were not receptor-mediated. Recently, GPR55, a Gα12 G-protein-coupled receptor, was identified as an AEA receptor in endothelial cells. This prompted Huang and colleagues to reassess whether the anticancer effects seen previously with AEA in cholangiocarcinoma cells were mediated through GPR55.

The authors demonstrated that GPR55 was expressed in cholangiocarcinoma cells and cholangiocytes. Activation of GPR55 by 0-1602, a GPR55 agonist, resulted in decreased proliferation and increased apoptosis in cholangiocarcinoma cell lines. Depletion of GPR55 by short hairpin RNA abolished AEA's anticancer effects. They also observed that depletion of GPR55 resulted in an inability of AEA or 0-1602 to induce recruitment of Fas death receptor to lipid rafts, which they had previously shown to be required for AEA-induced pro-apoptotic effects. In summary, Huang and colleagues demonstrate that GPR55, a newly identified AEA receptor, is responsible for mediating the anticancer effects of AEA in cholangiocarcinoma cells. This suggests that anti-GPR55 compounds would be useful in treating cholangiocarcinoma.

Therapeutic implications of LAT2 and mTORC1 activation in crescentic glomerulonephritis

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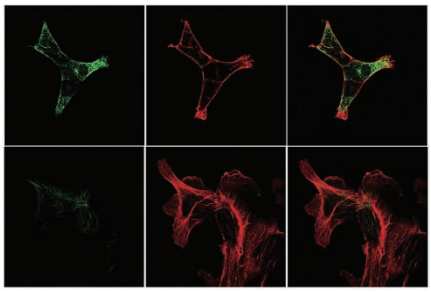

Crescentic glomerulonephritis (CGN) is characterized clinically by rapid loss of glomerular function and progression to renal failure. CGN has a variety of etiologies with a common pathogenetic mechanism of disruption of the glomerular basement membrane, followed by flow of plasma proteins and inflammatory cells into Bowman's space. This leads to proliferation of glomerular epithelial cells and infiltration of macrophages, the main components of cellular crescents. Because mammalian target of rapamycin complex I (mTORC1) signaling plays a prominent role in controlling growth and proliferation, Kurayama and colleagues asked whether mTORC1 signaling might play a role in CGN.

Using a rat model of CGN, the authors identified phospho-S6 ribosomal protein expression—a downstream readout for mTORC1 signaling—in cellular crescents, which was especially prominent at days 5 and 7. Everolimus, an mTORC1 inhibitor, resulted in glomerular necrosis when administered immediately after induction of CGN, whereas treatment with everolimus at day 7 after induction of CGN resulted in a decrease in crescent formation and an increase in intact glomeruli. Additional experiments demonstrated that L-type neutral amino acid transporter 2 (LAT2) was also increased at day 7 after induction of CGN. This suggested a mechanistic relationship between mTORC1 signaling and LAT2 expression. Amino acid deprivation or pharmacological LAT2 inhibition decreased mTORC1 signaling in a cell-line model. Inhibition of LAT2 also resulted in decreased crescent formation in the rat CGN model. In summary, these data suggest that upregulation of LAT2 activates mTORC1 expression, leading to proliferative crescents.

Role of ERK1/2 in repair of intestinal epithelium

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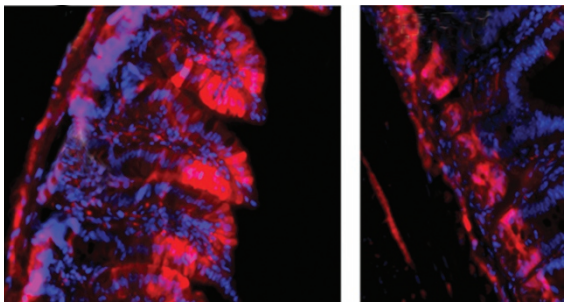
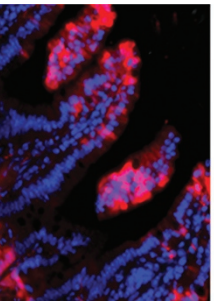
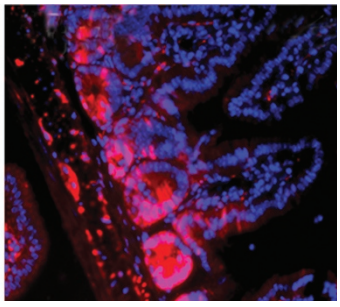
Maintenance of the epithelial barrier is critical to intestinal function. Loss of the receptor exposes the submucosa to toxic substances and pathogens that can cause further injury. In a repair process known as restitution, epithelial cells migrate rapidly to fill in denuded areas. This



process depends exclusively on migration and not proliferation. Previous work has localized chemokine receptor CXCR4 to the intestinal surface and shown that binding of CXCR4 to its ligand plays a role in epithelial restitution. To study its role *in vivo* and further define its mechanism of action, Zimmerman *et al* developed a conditional mouse model that lacks expression of CXCR4 specifically in intestinal epithelial cells.

Homozygous germline "knockout" of CXCR4 die perinatally. However, mice with conditionally inactivated CXCR4 (*CXCR4*$^{f/f}$;vC) within the intestinal epithelium are viable and fertile and exhibit normal intestinal epithelial differentiation and morphology. However, when homozygous *CXCR4*$^{f/f}$;vC mice were subjected to a protocol that induces acute intestinal epithelial damage, there was an absence of *de novo* crypt formation and re-epithelialization by the surrounding enterocytes as compared with *CXCR4*$^{+/+}$ wild-type mice. Ulcers were deeper in mice lacking intestinal CXCR4 in a chronic intestinal damage model as compared with *CXCR4*$^{+/+}$ wild-type mice. Because previous work had shown that extracellular-regulated kinase 1/2 (ERK1/2) signaling plays a role in intestinal epithelial migration, ERK1/2 was examined, revealing that activated/phosphorylated ERK1/2 was markedly decreased in the villus tip of conditional *CXCR4*$^{f/f}$ mice lacking intestinal CXCR4. Overall, the results support the model that CXCR4 activates ERK1/2, leading to migration of intestinal epithelial cells to repair denuded intestinal mucosa.





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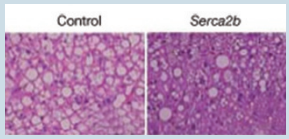
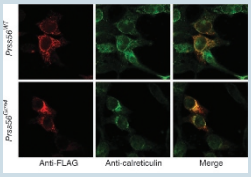


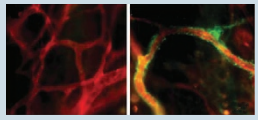
Endoplasmic reticulum stress in obesity It has been assumed that excess nutritional fat could overwhelm the endoplasmic reticulum (ER), leading to ER stress and fat accumulation. However, Fu *et al*, in a recent letter in *Nature*, asked whether *de novo* defects in ER protein synthesis might contribute to ER stress. To get a handle on what might be happening globally in the ER during obesity, they compared the ER proteomes from lean and obese mouse livers, which revealed that proteins associated with protein synthesis were decreased in obese livers while proteins associated with *de novo* lipid synthesis were increased. They found that alterations of ER phospholipid composition and increased sarco/endoplasmic reticulum calcium ATPase (Serca) activity were associated with ER stress. Inhibition of *Serca* expression reduced chronic ER stress associated with obesity.

Nature 2011;473:528–531; doi:10.1038/nature09968



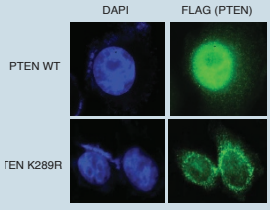
New insight into pathogenesis of angle-closure glaucoma Although some 4 million people are bilaterally blind as a result of angle-closure glaucoma (ACG), little is known about its pathogenesis. To gain insight into ACG, Nair *et al*, as described in a recent letter in *Nature Genetics*, undertook a mouse mutagenesis screen to identify mutants with increased intraocular pressure (IOP). The authors found that a mutation in *Prss56*, a secreted trypsin-like serine protease, could confer an increase in IOP that was associated with posterior microphthalmia. They also analyzed human patients with autosomal recessive posterior microphthalmia and identified two *PRSS56* mutations that segregated with the disease phenotype. Although further analysis is required to understand the precise mechanism by which defects in Prss56 cause IOP ACG, this mouse provides an excellent model for studying its pathogenesis.

Nature Genetics 2011;43:579–584; doi:10.1038/ng.813



Rethinking therapeutic angiogenesis Therapeutic angiogenesis, a strategy for treating patients with occlusive vascular disease, is based on the premise that factors that stimulate endothelial cells might regenerate the vasculature in ischemic tissues. Frontini *et al*, in a recent article in *Nature Biotechnology*, asked whether stimulation of the endothelial cell microenvironment might enhance functional neoangiogenesis. They discovered that *FGF9*, encoding fibroblast growth factor 9 (FGF9), was greatly elevated in a smooth muscle cell line, with features suggestive of perivascular smooth muscle cells. FGF9 by itself did not stimulate neovascularization, but when it was added to FGF2, which stimulates endothelial cells, muscularized blood vessels developed. Furthermore, these vessels were innervated in some cases and responded properly to physiological signals. Finally, FGF9 accelerated functional recovery in an ischemic hind-limb model.

Nature Biotechnology 2011;29:421–427; doi:10.1038/nbt.1845



Ubiquitin ligase for PTEN identified PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a tumor suppressor that negatively regulates phosphatidylinositol 3-kinase (PI3K) activity. PTEN is tightly regulated because of its functional importance. In a recent letter in *Nature Cell Biology*, Maddika and colleagues describe the identification of WWP2 as an E3 ubiquitin ligase for PTEN, which regulates its ubiquitination-dependent degradation. They also showed that phosphorylation of PTEN Tyr 155 regulates WWP2-PTEN degradation although the kinase that phosphorylates PTEN Tyr 155 was not identified. In addition, the authors demonstrated that WWP2 knockdown decreased tumorigenicity whereas overexpression of WWP2 resulted in increased tumorigenicity in a PTEN-dependent manner. Collectively, these studies show that WWP2 is an important regulator of PTEN through its E3 ubiquitin ligase activity and suggest that WWP2 may function as a previously unidentified oncogene.

Nature Cell Biology, published online 1 May 2011; doi:10.1038/ncb2240