

### In This Issue

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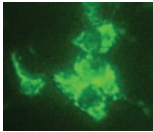
**Survivin' apoptosis** As cancer progresses, cancer cells acquire the ability to become resistant to apoptosis. Understanding the molecular mechanisms involved in the regulation of apoptosis is key for developing proper cancer therapies. Survivin is a member of a family of proteins that are inhibitors of apoptosis (IAPs), but the means by which it inhibits apoptosis remains largely unknown. Dario Altieri and colleagues investigated the subcellular compartmentalization of survivin to see whether the cellular location is directly involved in the regulation of apoptosis and the establishment and progression of tumors (pages 1117–1127). The authors identified a specific mitochondrial pool of survivin that is released into the cytosol in response to apoptotic stimuli. There, survivin inhibits caspases and blocks apoptosis. The researchers showed that selectively targeting survivin to the mitochondria enhanced soft agar colony formation. In vivo, such targeting resulted in increased tumor growth and ablation of apoptosis in immunocompromised mice. The data here demonstrate a novel pathway for apoptosis inhibition and tumor progression. See figure

**Tethered activation binds obesity** The most frequent genetic cause of obesity in humans is melanocortin-4 receptor (MC4R) mutations. MC4R activation by  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MHC) results in appetite suppression, while MC4R inhibition by agouti-related protein (AGRP) enhances appetite. In addition to having ligand-stimulated or -inhibited activity, MC4R also has a basal level of activity. Given its pivotal [...]

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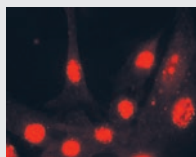


### Survivin' apoptosis

As cancer progresses, cancer cells acquire the ability to become resistant to apoptosis. Understanding the molecular mechanisms involved in the regulation of apoptosis is key for developing proper cancer therapies. Survivin is a member of a family of proteins that are inhibitors of apoptosis (IAPs), but the means by which it inhibits apoptosis remains largely unknown. Dario Altieri and colleagues investigated the subcellular compartmentalization of survivin to see whether the cellular location is directly involved in the regulation of apoptosis and the establishment and progression of tumors (pages 1117–1127). The authors identified a specific mitochondrial pool of survivin that is released into the cytosol in response to apoptotic stimuli. There, survivin inhibits caspases and blocks apoptosis. The researchers showed that selectively targeting survivin to the mitochondria enhanced soft agar colony formation. In vivo, such targeting resulted in increased tumor growth and ablation of apoptosis in immunocompromised mice. The data here demonstrate a novel pathway for apoptosis inhibition and tumor progression.

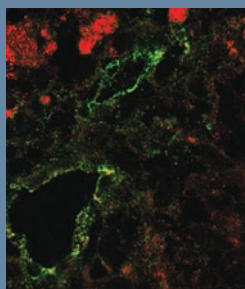
### Tethered activation binds obesity

The most frequent genetic cause of obesity in humans is melanocortin-4 receptor (MC4R) mutations. MC4R activation by  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MHC) results in appetite suppression, while MC4R inhibition by *agouti*-related protein (AGRP) enhances appetite. In addition to having ligand-stimulated or -inhibited activity, MC4R also has a basal level of activity. Given its pivotal role in energy homeostasis, MC4R is considered a viable therapeutic target for combating obesity. The domains in MC4R for  $\alpha$ -MHC activation are well known, but those required for its constitutive activity and the biologic importance of this activity remain uncertain. To further understanding in these areas, Christian Vaisse and colleagues made a systematic study of naturally occurring MC4R mutations in obese patients (pages 1158–1164). They transiently transfected HEK293 cells with wild-type or mutant receptors and defined a cluster of N-terminal mutations that impaired the constitutive activity of MC4R. Deletion of the N-terminal domain demonstrated that it is required for this basal activity. Further analysis proved that this domain functions as a tethered intramolecular agonist that does not mimic the action of  $\alpha$ -MHC. The work here suggests that a ligand that provides a low, sustained level of MC4R activation may be a better therapeutic agent for combating obesity than a more powerful ligand that results in receptor internalization and desensitization.



### The unkindest cut of all

Poly(ADP-ribose) polymerase-1 (PARP-1) is activated following DNA damage and catalyzes poly(ADP-ribose) chain formation by transferring ADP-ribose from NAD<sup>+</sup> onto itself and other nuclear proteins. If left unregulated, this process can deplete cellular NAD<sup>+</sup> pools. When cells undergo programmed cell death, caspases cleave PARP-1 at a conserved site and generate 24-kDa and 89-kDa fragments, which together are a hallmark of apoptosis. Mice lacking PARP-1, however, have a normal apoptotic response, but inactivation of PARP-1 genetically or by chemical means can protect mice from several disease models for inflammation. Zhao-Qi Wang and colleagues investigated the biological significance of PARP-1 cleavage by generating a PARP-1-knock-in transgenic mouse (*PARP-1<sup>KI/KI</sup>*) that carries an uncleavable form of PARP-1 (pages 1072–1081). These mice develop normally, but when treated with LPS, they were significantly more resistant to endotoxic shock than wild-type mice. The authors found that the amount of proinflammatory cytokines was greatly reduced in the sera of the *PARP-1<sup>KI/KI</sup>* mice. NF- $\kappa$ B transcriptional activity was impaired as well, despite the fact that NF- $\kappa$ B binding was normal. The data here suggest that PARP-1 cleavage itself may be important for generating an NF- $\kappa$ B-mediated inflammatory response, which may be useful for developing therapeutic strategies for inflammatory diseases.



### Vital for vasculature

Tumor growth and metastasis require new blood vessel growth. There are many factors involved in the normal growth and stabilization of new blood vessels. One of these, sphingosine 1-phosphate receptor-1 (S1P<sub>1</sub>), is required during embryonic development to stabilize nascent blood vessels. Timothy Hla and colleagues investigated the importance of S1P<sub>1</sub> in angiogenesis in tumors (pages 1082–1089). The authors implanted mice with Lewis lung carcinoma cells and, using  $\beta$ -gal directed from the S1P<sub>1</sub> promoter as a marker for S1P<sub>1</sub>, examined tissue sections for  $\beta$ -gal expression. S1P<sub>1</sub> expression was found in the vasculature only in the areas around the implanted tumor. The researchers then developed a multiplex RNA interference technique that specifically silenced the S1P<sub>1</sub> transcript in endothelial cells and blocked the cellular migration and the growth of neovessels into Matrigel subcutaneous implants. Injection of the S1P<sub>1</sub> small interfering RNA into tumors repressed S1P<sub>1</sub> expression. In conjunction with loss of S1P<sub>1</sub> expression, neovascular stabilization and angiogenesis were compromised and tumor growth suppressed in vivo. This study indicates both that S1P<sub>1</sub> is vital for vascular growth in tumors and that siRNA technology may be of great use in anticancer therapies.