Laboratory Investigation (2009) 89, 610-611

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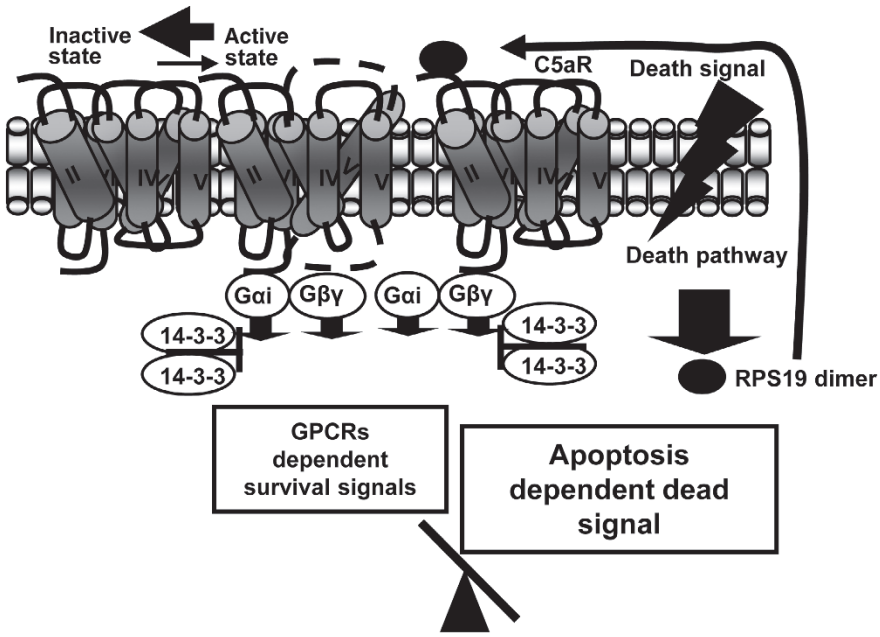
doi:10.1038/labinvest.2009.44



A cellular switch for life and death

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RP S19 and C5a both act as ligands for the C5a receptor and are known to function in chemotaxis. However, they have recently also been found to elicit pro- and anti-apoptotic effects by binding to C5aR. Nishiura and co-workers have found that different apoptotic stimuli all result in upregulation of C5aR expression, which is not restricted to monocytes and neutrophils but also occurs in NIH-3T3 cells, HL-60 promyelocytic leukemia, and AsPC01 pancreatic cancer cell lines. The two ligands have opposite effects. RP S19 stimulates apoptosis, whereas C5a decreases apoptosis. The authors suggest that these opposing effects may regulate the life span of inflammatory cells during the inflammatory process. However, many questions remain, such as how the different ligands lead to different signals from the same receptor, and why this appears to be a generalized phenomenon, possibly common to many cell types. Future work will surely focus on this interesting new cellular switch involved in life-and-death decisions.

What is the function of Syt?

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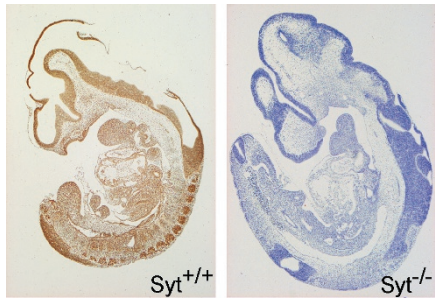
Cloning the breakpoints of cancer-specific translocations often leads to more questions than answers. This has certainly been the case with the *SYT-SSX* gene fusion that is characteristic of synovial sarcoma. Scientists had hoped that identification of the fusion genes would answer critical questions about synovial sarcoma, such as the line of differentiation. However, this did not turn out to be the case. Most synovial sarcomas were originally identified around the knee, and the histological features were thought to recapitulate primitive synovium. However, over time, it has been realized that synovial sarcoma can occur pretty much anywhere, including within parenchymal organs, and therefore synovium does not appear to be the line of differentiation. Although the *SYT-SSX* gene fusion is useful diagnostically, progress in understanding the function of the SYT-SSX chimeric protein has been slow. SSX is assumed to be a transcriptional regulator based on sequence homology with other transcription factors. However, SYT does not share homology with proteins of known function. At present, SYT is thought to regulate transcription through global chromatin structural modifications.



To try and unravel the physiological function of SYT, Kimura and colleagues generated a mouse *Syt* knockout model. The knockout results in embryonic lethality at day 9.5, around mid-gestation, and exhibits embryologic defects, including failure of neural tube closure and cardiac defects. Many genes that are important for neuronal development are downregulated by *Syt* knockout. A defect in cell growth appears to contribute to the cardiac phenotype. In an attempt to understand the functional basis of the embryonic phenotypes, $Syt^{-/-}$ mouse embryonic fibroblasts (MEFs) were cultured, revealing defects in cytoskeletal organization and functional deficits in cell motility. Although a definitive function for SYT has not been identified, the $Syt^{-/-}$ MEFs and the phenotypes of the *Syt* knockout mouse have brought us one step closer to the goal of understanding Syt function.

Moderating the acute-phase response

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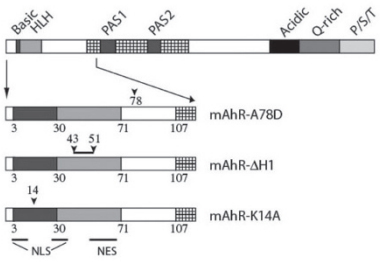
The acute-phase response (APR) is an important physiological response mechanism to various environmental stresses, such as infection, inflammation, chemical stress, and cancer. Acute-phase proteins (APPs), secreted by the liver, mediate the APR by signaling various body

tissues. However, chronic activation of the APR can have unwanted consequences on immune signaling, catabolism, cachexia, and amyloidosis.

Much of the APR is driven by cytokine signaling and activation of transcription factors such as nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3, and CCAAT-enhancer binding protein-β. Aryl hydrocarbon receptor (AHR), also known as dioxin receptor, is a ligand-activated transcription factor belonging to the basic helix–loop–helix PAS protein family, which is known to promote the expression of detoxification enzymes such as CYP1A1. Based on a recent report that AHR was implicated as a modulator of NF-κB activity, Patel and



colleagues asked whether AHR might be involved in regulating the APR. They showed that AHR was able to suppress APP expression. Normally, upon activation, AHR binds to AHR-nuclear translocator (ARNT), which migrates to the nucleus and binds DNA dioxin response elements (DREs). Analysis of several AHR mutants revealed that suppression of APP expression was dependent on ARNT binding and translocation to the nucleus but not DRE binding. This suggests an alternative, nonclassical mechanism involving multiple protein–protein interactions, such as binding and preventing RELA, the p65 subunit of NF-κB, from binding and activating transcription at APP promoters. The authors emphasize that suppression of different APPs might be dependent on the AHR ligand. Therefore, potential therapeutic strategies could be designed based on ligands that selectively suppress the APR.

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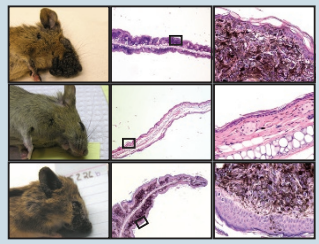
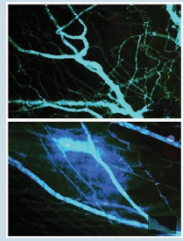
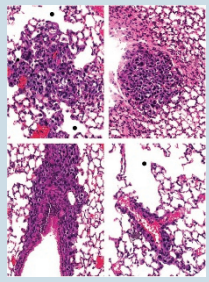


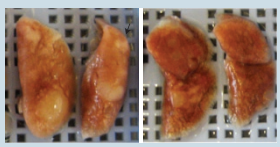
New mouse melanoma model Genetically engineered mice offer the possibility for building cancer models that faithfully recapitulate the salient findings of human cancers. In a recent article in *Nature Genetics*, Dankort and colleagues reported a recently developed mouse melanoma model. Using an elegant design, they achieved melanocyte-specific deletion of *Pten* and simultaneous activation of oncogenic $Braf^{V600E}$, two common genetic findings in human melanoma, resulting in aggressive melanomas that metastasize widely. Activation of $Braf^{V600E}$ alone causes only benign-appearing melanocytic proliferations akin to nevi. Evaluation of potent inhibitors of either mTorc1 (rapamycin) or MEK1/2 (PD325901)—downstream effector molecules of Pten and Braf, respectively—resulted in growth cessation, whereas a combination of the two drugs not only stopped tumor growth but led to tumor regression. This model will allow these research teams to dissect several interesting aspects of melanoma biology and will likely become a key tool for the preclinical evaluation of melanoma therapies.
Nature Genetics, published online 12 March 2009; doi:10.1038/ng.356



Good intentions gone bad! Migrating neutrophils roll through the circulation until they receive signals from endothelial cells to stop. The stop signal appears to be mediated by the expression of neutrophil integrins that adhere to endothelium and put the brakes on the neutrophils. However, this process may have unintended consequences. In a recent article in *Nature Medicine*, Hidalgo and colleagues have shown that activated $\alpha_M\beta_2$ integrins not only bind to endothelium but also "grab" other cells in the area, which may include platelets and red blood cells. In mouse models, these interactions contribute to the pathology seen in transfusion-related acute lung injury and sickle cell disease. Since these interactions are promiscuous, they may contribute to virtually any thromboinflammatory disease, which has broad pathogenetic and therapeutic implications.
Nature Medicine 2009;15:384–391; doi:10.1038/nm.1939



Global assessment of MMP mutations in melanoma Matrix metalloproteinases (MMPs) are proteolytic enzymes widely believed to play important roles in cancer. In a recent brief communication in *Nature Genetics*, Palavalli and co-workers sequenced the exons of all 23 MMP genes in a cohort of melanoma samples. Using this approach, they identified somatic mutations across eight different MMP genes, affecting 23% of the tumors analyzed. They focused additional attention on MMP8, showing that it functioned as a tumor suppressor in melanoma with the ability to inhibit growth of melanoma cell lines in soft agar and aggressive behavior, including metastasis, in a mouse xenograft model. This analysis demonstrates that MMPs play important roles in melanoma and highlights the need for further analysis of MMPs across the spectrum of human cancer.
Nature Genetics, published online 29 March 2009; doi:10.1038/ng.340



Putting cancer on a diet Dietary restriction (DR) has long been known to have anti-cancer effects. However, the mechanism of the anti-cancer properties of DR has remained a mystery. In a recent article in *Nature*, Kalaany and Sabatini report the discovery of the mechanism underlying this long-standing observation. It turns out that cancers that do not respond to DR possess constitutive activation of the phosphatidylinositol-3-kinase (PI3K) pathway, whereas those that do respond to DR lack constitutive PI3K activation. In a convincing demonstration of this finding, a DR-sensitive cancer cell line was converted to being DR resistant by transfecting it with a constitutively active PI3K allele. These provocative results are sure to whet the appetite for further investigations into this interesting area.
Nature 2009;458:725–731; doi:10.1038/nature07782