ACS Chemical Biology

Spotlight

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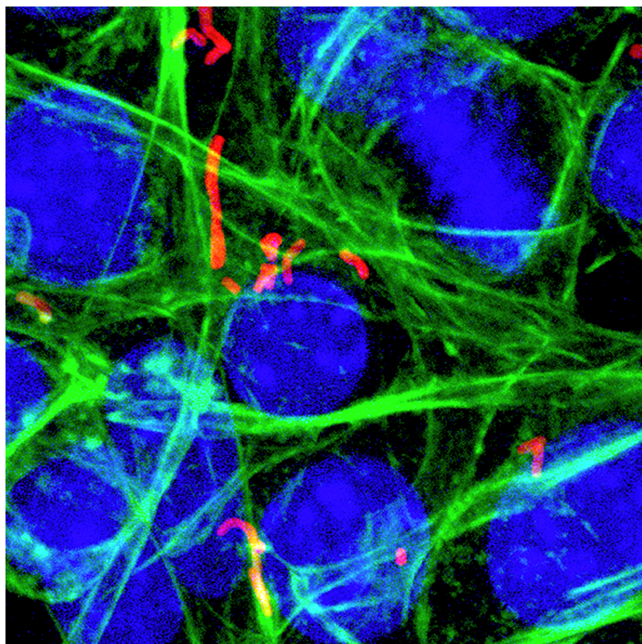
TARGETED ZAPPING OF PANCREATIC CANCER



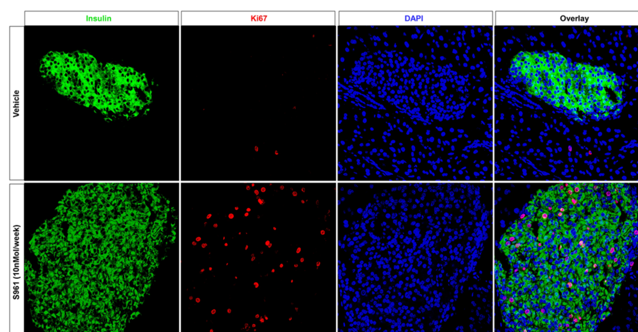
Quispe-Tintaya, W., *et al.*, *Proc. Natl. Acad. Sci., U.S.A.*, DOI: 10.1073/pnas.1211287110. Copyright 2013 National Academy of Sciences, U.S.A.

Across the globe each year, approximately 280 000 individuals are diagnosed with pancreatic cancer, and almost that many die of the disease. Because pancreatic cancer is rarely detected until it has spread to other organs, or metastasized, those diagnosed with the disease often succumb to it rapidly. Thus, there is an urgent need for better treatment strategies for this devastating condition. Now, Quispe-Tintaya et al. (*Proc. Natl. Acad. Sci.*, published online April 22, 2013, doi: 10.1073/pnas.1211287110) report the promising activity of an attenuated, radioactive form of the infectious bacteria *Listeria monocytogenes* (*Listeria*^{at}) in a mouse model of pancreatic cancer.

Based on prior studies demonstrating that *Listeria*^{at} selectively accumulated in tumor cells over normal cells, the authors hypothesized that the infectious agent might serve as an effective delivery agent for therapeutic radionuclides. They created a radioactive *Listeria*^{at} (RL) by coupling a ^{188}Rhenium (^{188}Re)-labeled anti-*Listeria* antibody to *Listeria*^{at}. Mice were injected with pancreatic tumor cells, which resulted in the formation of a primary tumor as well as metastases, and three days later they were treated with RL. Remarkably, those treated with RL exhibited a 90% reduction in the number of metastases compared to control mice. Analysis of various tissues demonstrated that radioactivity accumulated selectively in metastases over the primary tumor and normal organs. Further examination of the biodistribution patterns, pathology, and liver function in mice treated with RL substantiated the therapeutic potential of this strategy, as no obvious safety concerns were apparent. This study sets the foundation for development of a promising new approach for treating metastatic pancreatic cancer.

Eva J. Gordon, Ph.D.

BETATROPHIN: A STRATEGY FOR BEATING DIABETES?



Reprinted from *Cell*, *153*, Yi, P., *et al.*, Betatrophin: A Hormone that Controls Pancreatic β Cell Proliferation, 747−758. Copyright 2013, with permission from Elsevier.

Diabetes is a major global health epidemic, with nearly 350 million people affected worldwide. Though there are various methods for treating diabetes, none are curative nor do they effectively prevent many diabetes-associated complications such as increased risk of heart disease, stroke, and blindness. Both type I and type II diabetes result from decreased function of insulin-secreting pancreatic β cells, which are necessary for metabolizing glucose. Restoring pancreatic β cell activity is a promising treatment approach for diabetes, as it has the potential to be curative by re-establishing normal control over blood glucose levels. Toward this goal, Yi et al. (*Cell* 2013, *153*, 747−758) report the identification of a hormone that promotes the proliferation of pancreatic β cells.

To search for factors that increase β cell proliferation, the authors created a mouse model in which administration of an insulin receptor antagonist leads to a marked increase in β cell proliferation. After determining that the antagonist did not act on β cells directly, they turned to microarray analysis and found a gene, which they named betatrophin, which was elevated in liver and fat cells upon antagonist treatment. Further analysis demonstrated that betatrophin expression correlated with β cell proliferation rates. They determined that the gene encodes a secreted protein, and showed that injection of betatrophin expression constructs into the livers of mice led to a dramatic increase in β cell proliferation. Importantly, mice injected with betatrophin exhibited lower fasting glucose levels and improved glucose tolerance, demonstrating that the increase in β cell production yields functional cells. This exciting discovery paves the way for exploring betatrophin-related strategies for the treatment of diabetes.

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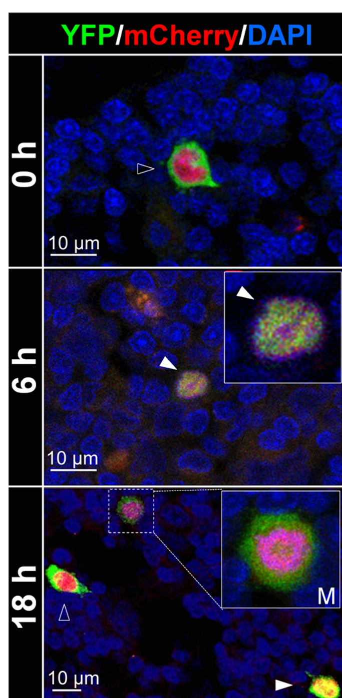
RENEWABLE FOSSIL FUELS



Howard, T. P., *et al.*, *Proc. Natl. Acad. Sci., U.S.A.*, *110*, 7636−7641. Copyright 2013, National Academy of Sciences, U.S.A.

Production of biofuels, which are produced from renewable sources such as plants or microorganisms, is a compelling solution to our alarming dependence on fossil fuels, which come from geologic deposits. Though various types of biofuels are under development, those that are chemically identical to fossil fuels offer a simpler transition to renewable energy sources than would implementation of chemically distinct biofuels such as alcohols and biodiesels. However, renewable sources do not naturally produce the *n*-alkanes, *iso*-alkanes, and *n*-alkenes that make up fossil fuels. Toward circumventing this barrier, Howard et al. (*Proc. Natl. Acad. Sci.*, 2013, *110*, 7636−7641) manipulate the metabolic machinery of the bacteria *Escherichia coli* to produce industrially relevant hydrocarbons.

Using protein engineering methods, the authors created a custom hydrocarbon factory in *E. coli*. They exploited the native alkane biosynthetic pathway in cyanobacteria, which transforms fatty acyl substrates to fatty aldehydes and then to alkanes and alkenes. The engineered hydrocarbon machinery was designed to utilize a variety of free fatty acid substrates, rather than the fatty acid thioester substrates normally used in this pathway, to enable production of saturated and unsaturated hydrocarbons of defined and predetermined chain length. Notably, *E. coli* does not naturally produce branched fatty acids, yet branched-chain molecules are a necessary component of high performance fuels. Thus, the authors also incorporated a branched-chain fatty acid biosynthetic module into the bacteria, and showed that this system could also produce branched-chain hydrocarbons. This proof of principle study demonstrates that fuels that are chemically and structurally identical to fossil fuels can be produced from renewable sources.

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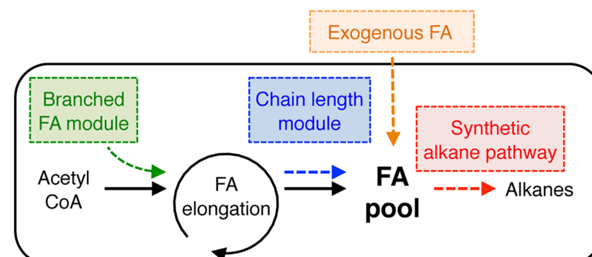
TRACKING MS DISEASE TRIGGERS



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In the autoimmune disease multiple sclerosis (MS), researchers have been trying to understand how autoaggressive T-cells mount their attack against brain tissue. In a new study, Lodygin et al. (*Nat. Med.*, published online April 28, 2013, DOI: 10.1038/nm.3182) report a fluorescent fusion protein based system that they used to follow T-cell activation in an animal model of MS. They show where and when the T-cells that attack brain tissue are activated in the disease process.

The researchers built their fusion protein system by appending a yellow fluorescent reporter to the nuclear factor of activated T-cells (NFAT) and a red fluorescent reporter to the H2B histone protein. They used a retrovirus to express these proteins in myelin-specific T-cells. As these modified T-cells become activated, NFAT moves from the cytosol to the nucleus of the cells. Using intravital (2-photonen laser scanning) microscopy, the researchers could follow the movement of NFAT, and the fluorescence from H2B within the nucleus allowed them to watch the early phase of T-cell activation and monitor cell division.

After testing the system in lymph nodes, they looked at the spinal cords of rats during the development of experimental autoimmune encephalomyelitis (EAE), a disease model for studying MS. As the cells crossed the blood-brain barrier and came in contact with resident phagocytes within the central nervous system that sample, process, and present self-antigens, NFAT moved to the nucleus of the T-cells within minutes and remained there, even though the cells continued to move through the perivascular areas of the brain. As disease progressed, T-cells moved into the white and gray matter within the brain and nervous system, but the numbers of activated cells remained consistently high. In additional experiments, the researchers demonstrated that T-cell activation events that play decisive role in inflammation and clinical outcome occur early during EAE before the onset of symptoms.

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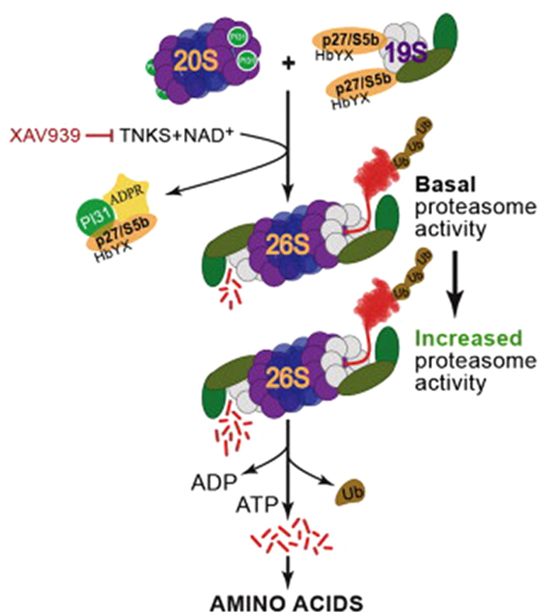
POST-TRANSLATIONAL TINKERING



Reprinted from *Cell*, *153*, Cho-Park, P. F. and Steller, H., Proteasome Regulation by ADP-Ribosylation, 614–627, Copyright 2013, with permission from Elsevier.

In eukaryotic cells, both the making and the destroying of proteins are highly regulated processes. To mark a protein for the trash bin, a peptide tag is added by a selective post-translational mechanism known as ubiquitination. The tiny ubiquitin peptide targets proteins to the 26S proteasome, a large macromolecular protease complex that degrades polypeptides. The proteasome has emerged as an important target for therapeutics with FDA-approved inhibitors currently in the clinic for treating multiple myeloma. Since there can be severe side effects for these drugs, other mechanisms for tinkering with proteasome activities are actively being sought.

To look for new regulators, Cho-Park and Steller (*Cell* 2013, *153*, 614–627) began with an evolutionarily conserved regulator of the proteasome, PI31. Using this protein as bait, the researchers went fishing for binding partners of PI31 in *Drosophila* with the assumption that these partners could play critical roles in regulation. Interestingly, their findings uncovered yet another post-translational modification at work. Among the three identified PI31-binding proteins was tankyrase, an ADP-ribosyltransferase. This enzyme, also known as TNKS, uses NAD as a substrate and transfers an ADP-ribose moiety onto an amino acid side chain of the protein target. In this case, PI31 was the target and the small modification had several consequences leading to increased proteasome activity. First, ADP-ribosylation decreased the binding of PI31 to the catalytic 20S subunit of the proteasome thereby reducing repression. Second, PI31 modification increased binding to the other two binding partners identified in the study, dp27 and dS5b. These two proteins are known assembly chaperones for the regulatory 19S proteasome subunit, so PI31-mediated sequestration of these two proteins actually promoted assembly of the catalytically active 26S proteasome. The researchers went on to show that these same relationships also take place in human cells and that drugs that target TNKS can inhibit the proteasome. These findings unlock a potential therapeutic target in cancer cells via this unexpected enzymatic switch.

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