ACS chemical biology

IN THIS ISSUE

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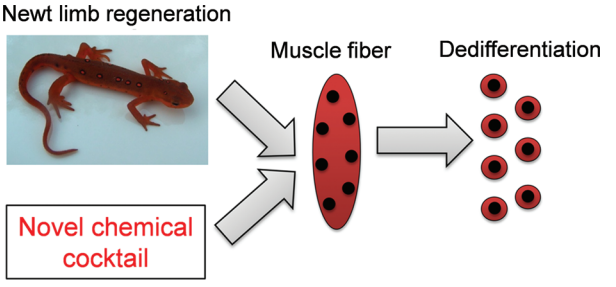
## To Regenerate Like Amphibians Do

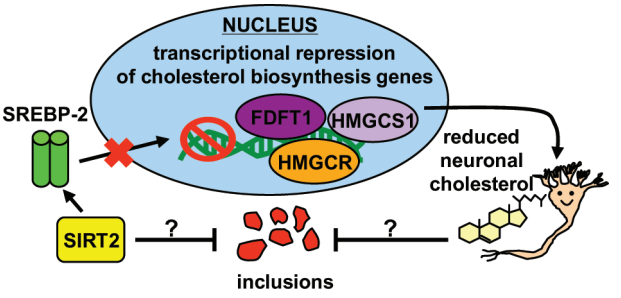
Urodele amphibians, which include salamanders and newts, have the remarkable ability to regenerate their limbs in response to injury. This process requires that skeletal muscle cells undergo a process called dedifferentiation. Dedifferentiated cells are multipotent, meaning they have the capacity to differentiate into one of multiple potential tissue types, which is a key aspect of the regeneration process. Unfortunately, mammalian skeletal muscle tissue does not respond in the same way to injury. To this end, Jung and Williams (DOI: 10.1021/cb2000154) now describe a chemical method to induce dedifferentiation in mouse skeletal muscle, findings that have exciting implications in regenerative medicine.




Mammalian skeletal muscle is composed of multinucleated fibers that must fragment into proliferating mononuclear cells before dedifferentiation can occur. To accomplish this, mouse skeletal muscle fibers were treated with the trisubstituted purine myoseverin, a known tubulin-binding small molecule, and the activity of p21, a cyclin-dependent kinase inhibitor, was suppressed. Subsequent treatment of the resulting proliferating mononuclear cells with another small molecule purine derivative called reversine enabled their differentiation into nonmuscle cells, including fat and bone cells.

## Breakthrough in Drug Development against Parkinson's and Huntington's Diseases

The blood–brain barrier is a major obstacle for the development of drugs against diseases affecting the central nervous system. Novel ways of delivering drugs to the brain hold the key for treatment against debilitating neurodegenerative disorders such as Huntington's and Parkinson's diseases. Taylor *et al.* (DOI: 10.1021/cb100376q) provide a major breakthrough in drug delivery by identifying a compound that can cross this protective barrier and lower cholesterol levels in the brain.

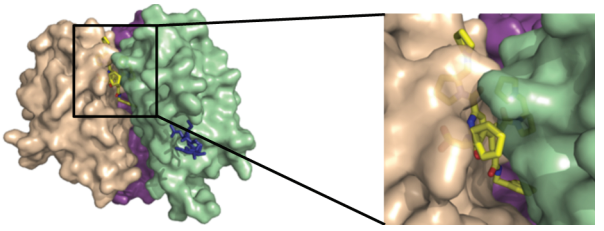



Sirtuin 2 (SIRT2) is a NAD-dependent deacetylase that has recently emerged as a drug target. It is involved in the regulation of sterol biosynthesis, which has been linked to Parkinson's and Huntington's disease progression. Inhibition of this enzyme has been shown to significantly reduce cholesterol levels. The authors performed an arduous screen of a large library of compounds using mammalian-cell-based assays to identify sulfobenzoic acid derivatives as a structural scaffold that inhibits SIRT2 while possessing brain-permeable properties. This scaffold led to the identification of AK-7, a brain-penetrable compound that showed remarkable antineurogenerative properties by reducing neuronal cholesterol levels via SIRT2 inhibition. The identification of this lead compound has significant implications on drug development in treating chronic brain diseases.

## A Classic Example of Protein–Protein Interaction Inhibition

To date, very few examples exist of protein–protein interaction inhibitors. Perturbing the interface of constitutive protein–protein interactions by small molecules is difficult and, as a result, remains a relatively untapped functional methodology for drug development. Exploiting protein–protein interaction inhibition would be an exciting advancement. One potential drug target is the trimeric tumor necrosis factor family, cytokine CD40 ligand (CD40L), which is expressed on several cell types, including activated B cells and T cells. The signaling pathway of this cytokine is mediated through its interaction with membrane receptor CD40. The loss of this important interaction is associated with lupus nephritis and atherosclerosis. In this issue, Silvian *et al.* (DOI: 10.1021/cb2000346) provide a striking example of small molecules inhibition of protein–protein interaction in trimeric CD40L, a target of high therapeutic importance.

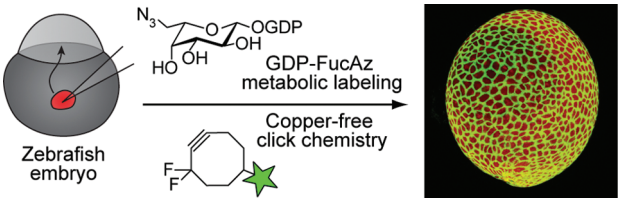
   dx.doi.org/10.1021/cb200148g | *ACS Chem. Biol.* 2011, 6, 528–529



The authors sought to characterize the mode of action of a previously identified CD40L inhibitor, BIO8898. Biochemical assays showed that BIO8898 inhibited CD40L binding to a CD40-Ig fusion protein and reduced CD40L-related apoptosis. X-ray crystallographic studies revealed that one molecule of this inhibitor was bound at the interface between two of the subunits of trimeric CD40L. Additionally, the binding of BIO8898 resulted in conformational changes in the core and a loop at the surface of CD40L. This study provides a valuable example of interrogating protein−protein interactions using small molecules and provides a new target for drug development against this cytokine.

## Monitoring Fucosylation *in Vivo*

Fucosylation is a post-translational modification crucial to cell fate decisions and organogenesis as well as in Notch signaling and brain development. Characterizing the precise function of fucosylation during these vital developmental processes is of great importance. However, monitoring this post-translational modification has been problematic due to the lack of reporters to analyze these modifications *in vivo*. To bridge this shortcoming, Dehnert *et al.* (DOI: 10.1021/cb100284d) report the development of a new imaging tool for studying this process in zebrafish.




The authors "tricked" the metabolism of zebrafish cells into incorporating azide-based fucose analogues (FucAz) on cell-surface glycans by microinjecting embryos with azido fucose analogues modified at the C6 position. The incorporated fucose analogues were then visualized using a fluorophore probe using copper-free click chemistry. However, the incorporation of these unnatural azide analogues was inefficient due to low tolerance by the fucose salvage pathway. To circumvent this problem, GDP-FucAz derivatives were microinjected into zebrafish embryos. Confocal microscopy and flow cytometry showed efficient incorporation of this analogue into cell-surface glycans. Using this approach, the authors were able to follow fucosylation in embryos with stunning clarity. This new imaging tool provides researchers with a much-needed chemical reporter to monitor this crucial post-translational modification in living cells, which will provide a better understanding for the developmental processes involved in the early stages of life.