ACS chemical biology

Spotlight

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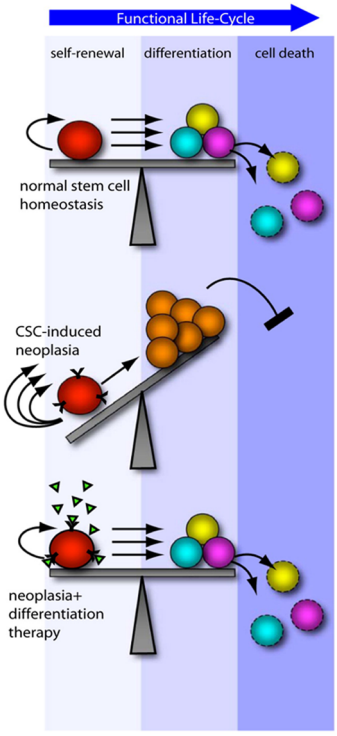
DIFFERENTIATING CANCER STEM CELLS

Approximately 7.6 million people died from cancer in 2008, making it a leading cause of death worldwide. Increasing evidence suggests that unique cells called cancer stem cells are responsible for instigating and nourishing the disease. Though they are tempting anticancer targets, attempts to selectively manipulate cancer stem cells have faced numerous challenges, including difficulties in characterizing such a rare cell population and in developing effective drug discovery screens. Interestingly, in order to realize their tumor-initiating capabilities, cancer stem cells must be able to self-renew and also be resistant to differentiation, and Sachlos *et al.* (*Cell* 2012, DOI: 10.1016/j.cell.2012.03.049) exploit this resistance to develop a screen for small molecules that selectively promote the differentiation of cancer stem cells over their normal stem cell counterparts.

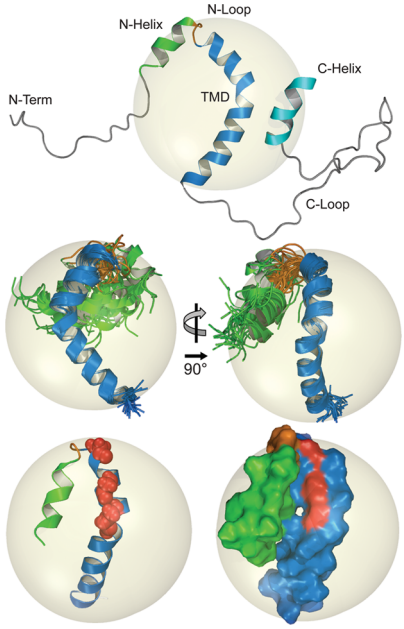


Reprinted from *Cell*, Sachlos, E., *et al.*, Identification of Drugs Including a Dopamine Receptor Antagonist that Selectively Target Cancer Stem Cells, DOI:10.1016/j.cell.2012.03.049. Copyright 2012, with permission from Elsevier.

Because cancer stem cells are difficult to access, the authors use a previously developed variant human pluripotent stem cell line that strongly resembles cancer stem cells, including their resistance to differentiation, to develop the screen. From nearly 2600 compounds screened, the dopamine receptor antagonist thiorazide was identified as a potential cancer stem cell targeting agent. Indeed, when tested with normal blood stem cells and leukemia cells, thiorazide prevented proliferation of leukemia cells but did not affect growth of normal blood stem cells. The authors propose that compounds identified in the screen likely selectively target pathways uniquely hijacked by cancer stem cells for their own survival and propagation. By targeting these pathways and forcing the cancer stem cells to differentiate, they lose their tumor-promoting abilities. This provocative study supports the notion of cell differentiation as a viable anticancer target, and points to dopamine receptor antagonists as potential anticancer agents. **Eva J. Gordon, Ph.D.**

GETTING TO THE HEART OF CHOLESTEROL AND ALZHEIMER'S

Across the globe, it is estimated that over 20 million people suffer from Alzheimer's disease, with 7.7 million new cases diagnosed each year. Formation and aggregation of a peptide fragment of the amyloid precursor protein (APP), called amyloid-β (Aβ), is associated with progression of the disease, as are increased levels of neuronal cholesterol levels. However, the molecular processes that link cholesterol to Aβ generation are unclear. The transformation of APP to Aβ involves generation of an intermediate transmembrane protein called C99, and Barrett *et al.* (*Science*, 2012, *336*, 1168−1171) now use sophisticated structural characterization methods to reveal that C99 forms an avid complex with cholesterol.



From Barrett, P. J., *et al.*, *Science*, 2012, *336*, 1168. Reprinted with permission from AAAS.

Using nuclear magnetic resonance (NMR) and electron paramagnetic resonance spectroscopy, it was determined that C99 is composed of three helices. The N- and C terminal helices are closely associated with the membrane surface and are connected to the middle, transmembrane helix by a short N-terminal and longer C-terminal loop, respectively. Additional NMR and protein mutagenesis experiments illuminated the residues important for cholesterol binding, which were located in the N-helix, N-loop, and the extracellular end of the transmembrane helix. The flexibility of the transmembrane

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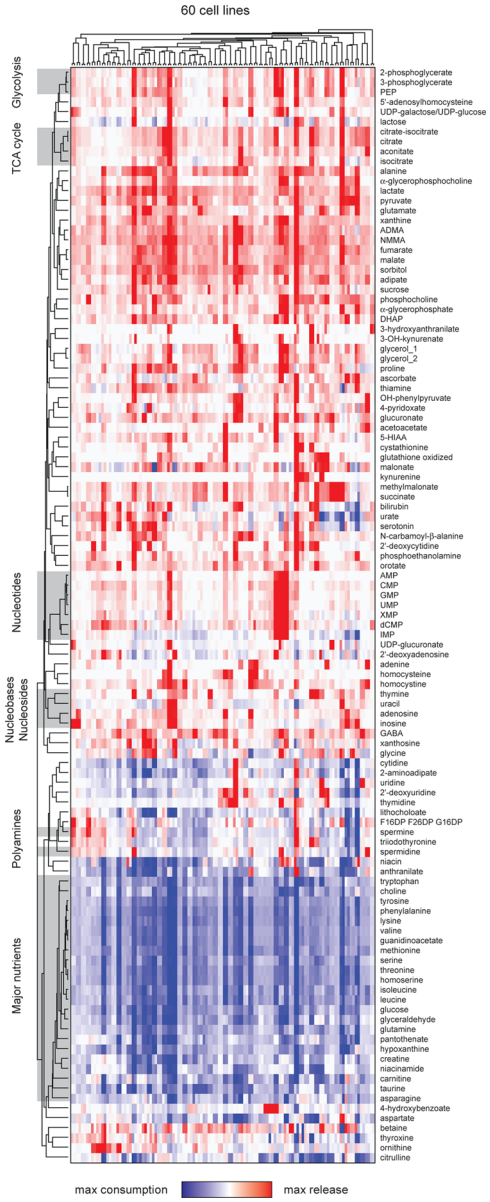
helix likely contributes to its recognition by APP cleaving enzymes. In addition, certain glycine-containing motifs within the transmembrane domain, which have long been implicated in Aβ oligomerization, were also shown to participate in cholesterol binding, with formation of the C99-cholesterol complex likely activating cleavage to form Aβ. These insights into the interaction between C99 and cholesterol may uncover new strategies for the prevention and treatment of Alzheimer's disease. **Eva J. Gordon, Ph.D.**

GETTING TO THE CORE OF CANCER METABOLISM

Reprogramming of metabolic pathways is thought to be a hallmark of cancer, but the molecular underpinnings that link changes in metabolism to the behavior of cancer cells are not clear. Now, Jain *et al.* (*Science*, 2012, *336*, 1040−1044) present an approach called consumption and release, or CORE, profiling, for the systematic characterization of metabolic pathways in cancer cells.

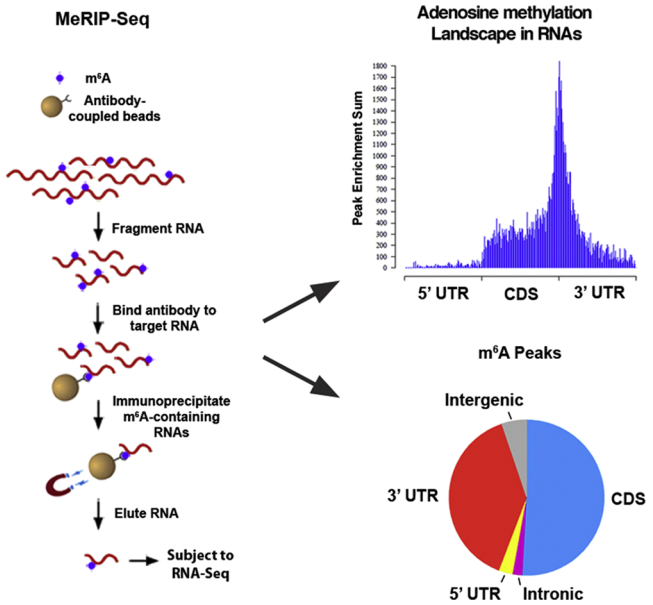


From Jain, M., *et al.*, *Science*, 2012, *336*, 1040. Reprinted with permission from AAAS.

CORE profiling uses liquid chromatography-tandem mass spectrometry to relate metabolite concentrations in spent medium from cells growing in culture to those in fresh medium, enabling a quantitative assessment of metabolic activity during periods of cell growth. Intriguing metabolic phenotypes were uncovered in this analysis of over 200 metabolites in 60 cancer cell lines, such as the discovery that leukemia cells release different metabolites than skin cancer cells, that cancer cells tend to incompletely metabolize nutrients, and that rapidly proliferating cancer cells consume glycine while both slowly proliferating cancer cells as well as rapidly proliferating normal cells release it. When examined in conjunction with known gene expression data from the cell lines, expression of genes associated with the mitochondrial glycine biosynthetic pathway strongly correlated with increased cell proliferation. Mechanistic analysis of the role of glycine in cancer cell proliferation suggested that glycine is used in part for the biosynthesis of purine nucleotides. Notably, examination of gene expression microarray data from over 1300 breast cancer patients demonstrated that patients with increased expression of genes associated with mitochondrial glycine biosynthesis tended to have a worse prognosis. This study exposes glycine metabolism as a potential therapeutic target for cancer, and presents CORE profiling as an exciting technology for the exploration of cancer cell metabolomics. **Eva J. Gordon, Ph.D.**

mRNA GETS DRESSED UP TOO

For decades, scientists have known that tRNAs in all kingdoms of life display an impressive diversity of covalent modifications on the bases and the ribose backbone. In addition, many abundant noncoding RNAs such as ribosomal, small nuclear or nucleolar RNAs can harbor conserved methylation sites that are important for biological function. Now, a new study uncovers a wealth of mRNAs decorated with post-transcriptional methylation on N6 of adenosine. Using an m^{6}A specific antibody to perform immunoblots on cellular RNA, Meyer *et al.* (*Cell* 2012, *149*, 1635−1646) showed that the polyadenylated fraction is enriched in m^{6}A bases.



Reprinted from *Cell*, *149*, Meyer, K.D., *et al.*, Comprehensive Analysis of mRNA Methylation Reveals Enrichment in 3' UTRs and near Stop Codons, 1635−1646. Copyright 2012, with permission from Elsevier.

After proving that the polyA tail itself was not enriched m^{6}A, immunoprecipitation combined with RNA-seq was used to localize where methylations were found in transcripts. The

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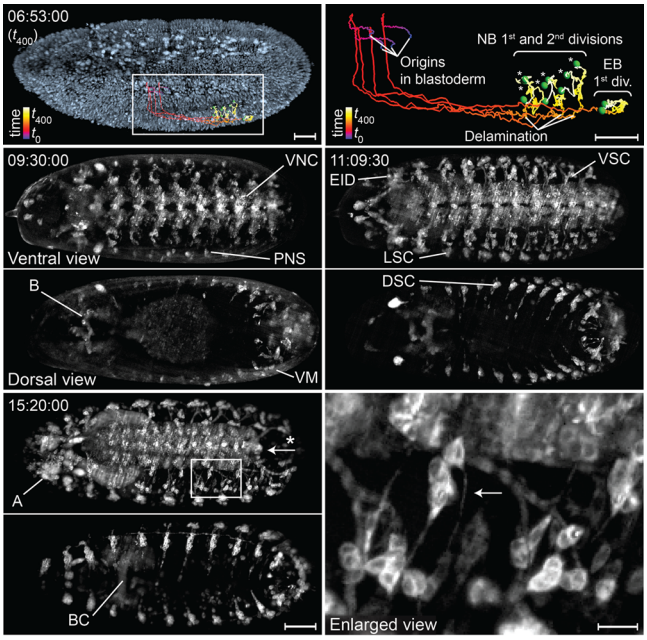
technique, termed MeRIP-seq, for methylated RNA immunoprecipitation sequencing, yielded short tags of RNA sequence that were collectively analyzed to pinpoint the modified adenosine. After applying stringent filters for reproducibility, the researchers settled on a list of 4654 RNAs that harbor at least one methylation peak. Most of these were coding mRNAs, but several hundred also mapped to noncoding RNAs. Most striking was the enrichment for m^6A at the 3′ end of coding regions or within 3′ untranslated regions. Many methylation sites appear to be conserved between human and mouse, and an enrichment for nucleotide context indicates that sequence-specific RNA recognition is probably involved in m^6A genesis. Now, armed with an atlas of where these sites are in the transcriptome, the next questions will certainly probe why these particular RNAs are modified and the biological consequences. Interesting, this study found that the fraction of m^6A in RNAs increases during brain development, so this newest RNA riddle is likely to have fascinating implications. **Jason G. Underwood, Ph.D.**

A 360 VIEW OF EMBRYONIC DEVELOPMENT

Biological imaging comes with a whole host of trade-offs. Light exposure can damage tissues, and following biological processes over time typically means sacrificing spatial resolution. But as researchers attempt to understand more complex features of development, they'd like tools that give them a detailed, view of biological processes in a whole organism. Now Tomer *et al.* (*Nat. Methods* 2012, DOI: 10.1038/nmeth.2062) report a microscopy technique that they use to observe *Drosophila* embryos at 30 s intervals throughout their development.



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Simultaneous multiview (SiMView) imaging and analysis builds on sequential light-sheet microscopy, which uses thin sheets of laser light to image sample layers individually, limiting photodamage. The SiMView microscope places a transparent sample in the center of four optical arms, two that illuminate the sample and two orthogonal arms that detect fluorescence. This optical system is then connected to computer components that support high speed image acquisition and the high level analysis needed to fuse and manage images and track the movement of objects in various imaging frames.

Tomer *et al.* demonstrate the power of this imaging technique through their live imaging of Drosophila embryos. First they compare sequential imaging with SiMView, showing the artifacts and false positives that this new technique avoids. They observe the full development of a Drosophila embryo with fluorescently labeled nuclei and can track the mitotic wave of cell division across the embryo. Using transgenic fruit fly embryos with labeled neurons, they observe the development of the central and peripheral nervous system and the detailed growth of axons.

This technique offers the opportunity to image developmental processes in a whole organism as they occur. The combination of this method with other available techniques and computational tools will expand the detail with which researchers can study complex biology across whole organisms. **Sarah A. Webb, Ph.D.**