

# RESEARCH HIGHLIGHTS

## Visualizing tumour propagation and metastasis *in vivo*

Embryonal rhabdomyosarcoma (ERMS) is an aggressive form of muscle sarcoma that arises from myoblasts or satellite cells. Langenau and colleagues now use transgenic zebrafish to image the cells responsible for sustained ERMS growth *in vivo*, and also define a role for non-tumour-propagating ERMS cells in supporting metastatic spread (*Cancer Cell* **21**, 680–693; 2012).

Using elegant *in vivo* imaging techniques, the authors visualized ERMS formation in the tail musculature of fluorescent transgenic zebrafish embryos microinjected with oncogenic transgenes, and identified distinct ERMS cell subpopulations that were fluorescently labelled based on the expression of different myogenic factors. They demonstrated that the cell subpopulation expressing *myf5*, a factor that marks satellite and early muscle progenitor cells, was more proliferative and harboured tumour-propagating capacity *in vivo*. They further showed that cells expressing *myogenin*, a marker of differentiated muscle cells, were not tumour-propagating, but were highly migratory and invaded normal tissue. The authors determined that the migration of *myogenin*-expressing cells to secondary areas of tumour growth precedes the recruitment of tumour-propagating *myf5*-positive cells to those sites, demonstrating that differentiated non-tumour-propagating

ERMS cells facilitate metastasis. Defining the mechanisms by which differentiated, migratory cells promote metastatic colonization by tumour-propagating cells will be an exciting area of future research. AIZ

## Cyclin F keeps dNTPs in balance

Production of deoxyribonucleotide triphosphates (dNTPs) is essential for DNA synthesis during replication and repair, and abnormal or imbalanced dNTP levels increases mutation frequency. Pagano and colleagues now demonstrate that the SCF-cyclin F ubiquitin ligase controls dNTP production during the cell cycle and following genotoxic stress (*Cell* **149**, 1023–1034; 2012).

The authors identify the ribonucleotide reductase subunit RRM2 as a cyclin-F-interacting protein using mass spectrometry, and find that the two proteins interact specifically in the G2 and M phases of the cell cycle. Cyclin F binds RRM2 in a manner dependent on an RRM2 CY motif and on Cdk1- or Cdk2-mediated phosphorylation of Thr 33 in RRM2, and mediates its degradation by the proteasome. Depletion of cyclin F or expression of stable RRM2 mutants increases the amount of dATP and dGTP (but not of dCTP or dTTP). Further, cell clones expressing these stabilized RRM2 mutants show an increase in the mutation frequency of a reporter gene.

RRM2 is known to accumulate in the nucleus following DNA damage, to provide dNTPs for repair. Interestingly, the authors find that various DNA-damaging agents downregulate cyclin F levels (dependent on the ATR kinase), and demonstrate that this is required for efficient DNA repair. These data underscore the importance of maintaining sufficient and balanced dNTP pools, and provide mechanistic insights into how this is achieved. CKR

## miRNAs and cell-cycle control in ESCs

Embryonic stem cells (ESCs) undergo rapid proliferation with shorter cell cycle phases. This depends largely on the activity of the miR-290 and miR-302 microRNA (miRNA) families. A third miRNA, let-7, inhibits self-renewal and promotes differentiation of ESCs, but its activity is kept low in ESCs by the LIN28 protein. Gregory and colleagues have found that the let-7 target TRIM71 represses the expression of a negative modulator of G1–S transition: the cyclin-dependent kinase inhibitor, Cdkn1a (*Nat. Commun.* **3**, 923; 2012). They observe high levels of TRIM71 in murine undifferentiated ESCs, but not in differentiated cell types. Using immunoprecipitation followed by mass spectrometry, they identify Argonaute 2 as a TRIM71 partner. They find that TRIM71 can be found in miRNA-associated catalytic RISC (RNA-induced silencing complex), which is responsible for miRNA-mediated repression and localizes to P-bodies (where this repression is thought to occur). Levels of the known miR-290/miR-302 target Cdkn1a were shown to increase following TRIM71 silencing. TRIM71 effects on Cdkn1a require an intact miRNA binding site, and occur post-transcriptionally. The authors observe that TRIM71 silencing decreases ESC proliferation, whereas overexpression promotes G1–S transition. Thus, the authors have delineated a functional crosstalk between let-7 and miR-290/miR-302. How TRIM71 affects miRNA-mediated effects on Cdkn1a remains to be investigated, as it does not seem to affect levels of miRNA or of the miRNA machinery. NLB

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## Glycine fuels cancer cells

Cancer cells use different metabolic pathways to their normal counterparts; this metabolic switch is necessary to support their rapid proliferation in oxygen- and nutrient-poor conditions. Mootha and colleagues perform metabolic profiling of the NCI-60 cancer cell line collection and report a key role for glycine in supporting rapid cellular proliferation (*Science* **336**, 1040–1044; 2012).

The authors created metabolic consumption and release (CORE) profiles of the individual cancer cell lines to identify metabolites that are taken up or released. Correlating the CORE profiles with known cell proliferation rates revealed that glycine was generally consumed by highly proliferative cancer cells and released by slowly proliferating cells. Tracing radiolabelled glycine in a rapidly proliferating cell line revealed that it was used in *de novo* purine nucleotide synthesis.

Intriguingly, non-transformed, yet highly proliferative, cells also consumed glycine, suggesting that this amino acid supports rapid proliferation. Indeed, depleting extracellular glycine or knocking down the glycine-synthesizing enzyme SHMT2 blocked rapid proliferation by prolonging the G1 phase of the cell cycle. Glycine depletion did not affect slowly proliferating cells. Expression analyses of genes encoding mitochondrial glycine synthesis enzymes revealed that upregulation of these genes correlated with greater mortality and worse prognosis in breast cancer. Thus, the glycine synthesis pathway represents an attractive target for the development of anti-cancer therapeutics. EJC