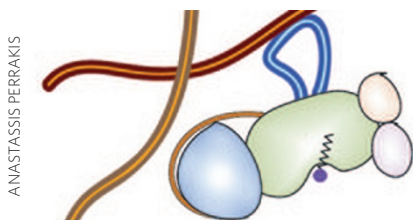# research highlights

GLYCOBIOLOGY

Telling twins apart

J. Biol. Chem., published online 13 November 2012, doi:10.1074/jbc.M112.358416

ANASTASSIS PERRAKIS

The secreted lysophospholipase autotaxin (ATX) is responsible for synthesizing lysophosphatidic acid (LPA), with numerous cellular outcomes. Most ATX research has focused on the β isoform, but three other isoforms are known to be produced, depending on which of the gene's 27 exons are translated. ATXα includes a polybasic 52-residue insert, thought to confer proteolytic instability to the protein. Houben *et al.* now demonstrate that although the insert is cleaved, most likely at a furin consensus site, this cleavage neither has an impact on protein stability nor affects enzyme activity. The authors also show that ATXα has similar kinetics to ATXβ and is equally sensitive to an ATX inhibitor, raising the question of why this inserted domain is present. Further inspection of the inserted sequence pointed to the presence of potential heparin-binding motifs; these were validated by the strong interaction of ATXα with unfractionated heparin, with an apparent K_d of 10 nM according to surface plasmon resonance, whereas ATXβ showed almost no binding. This effect was mirrored by the ability of ATXα, but not ATXβ, to bind the surface of glycosaminoglycan-expressing cells in a heparinase-sensitive manner. Surprisingly, heparin also increased ATXα activity by up to two-fold. Though ATX is known to be targeted to the cell membrane by integrin binding, these results point to a second, isoform-specific targeting mechanism that both localizes and activates ATXα to optimize LPA signaling.   *CG*

CANCER

Feeding forward and back

Cancer Cell **22**, 585–600 (2012)
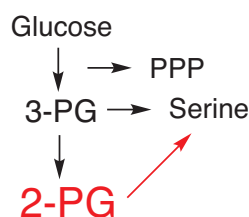
Cancer cells rely on an elevated glycolysis rate for their increased biosynthetic needs. The glycolytic enzyme phosphoglycerate mutase 1 (PGAM1) catalyzes the conversion of 3-phosphoglycerate (3-PG) to 2-PG downstream of most glycolytic reactions that yield biosynthetic precursors. Hitosugi *et al.* demonstrate that stable knockdown of PGAM1, an enzyme commonly misexpressed in cancer cells, leads to elevated 3-PG and reduced 2-PG in addition to decreasing the rate of glycolysis, flux through the pentose-phosphate pathway (PPP) and anabolic biosynthesis. Using biochemical and structural approaches, they showed that 3-PG can directly bind the active site of the PPP enzyme 6-phosphogluconate dehydrogenase (6PGD) and that 3-PG can compete with 6PGD's substrate for binding. Treatment with methyl-2-PG, a compound converted to 2-PG in cells, rescues glycolytic rates and flux through the PPP in cells with stable knockdown of PGAM1, indicating that 2-PG feeds back on upstream steps. Indeed, they found that treatment with methyl-2-PG also decreased 3-PG. Because 3-PG is a precursor for serine biosynthesis, the authors evaluated the effects of 2-PG on 3-phosphoglycerate dehydrogenase (PHGDH), which converts 3-PG to 3-phosphohydroxypyruvate. 2-PG can promote PHGDH activity *in vitro* and in cells but only at concentrations higher than those detected in PGAM1 knockdown cells. Taken together, these data indicate that PGAM1 expression controls the amount of 3-PG, which promotes PPP and biosynthesis, and 2-PG, which indirectly controls the amount of 3-PG by regulating PHGDH activity.   *AD*

NUCLEAR TRANSPORT

Bicycle built for two

Science **338**, 666–671 (2012)

Ribosome biogenesis occurs in the nucleolus and involves the ordered assembly of rRNA transcripts with ribosomal proteins synthesized in and imported from the cytoplasm. Kressler *et al.* now show that two ribosomal proteins, Rpl5 and Rpl11, which bind near each other on the 5*S* rRNA of the 60*S* ribosomal subunit, are brought into the nucleus together by a newly defined transport system. Using tandem affinity purification, the authors showed that a new protein, symportin 1 (Syo1), purifies together with Rpl5 and Rpl11. Syo1 contains ARM and HEAT repeat domains typically found in nuclear transport proteins and is conserved in eukaryotes. Knockout of yeast *syo1* results in lowered 60*S* ribosomal subunit abundance, supporting its role in ribosome assembly. Yeast two-hybrid and *in vitro* reconstitution experiments revealed that Rpl5, Rpl11 and Syo1 form a heterotrimeric complex. Crystallography and hydrogen-deuterium exchange MS defined Syo1 interactions with Rpl5 and Rpl11, respectively. Though Syo1 readily transits the nuclear pore complex, the Syo1–Rpl5–Rpl11 complex requires Kap104, a nuclear transport receptor, for efficient nuclear import and Ran-GTP for release of the complex from Kap104. Released Syo–Rpl5–Rpl11 binds efficiently to 5S rRNA. Taken together, the data support a potentially general model in which coordinated transport of ribosomal proteins can be used to order the assembly of preribosomal complexes.   *TLS*

STRUCTURAL BIOLOGY

E2 loader

Nat. Struct. Mol. Biol. published online 11 November 2012, doi:10.1038/nsmb.2451

Nat. Struct. Mol. Biol. published online 11 November 2012, doi:10.1038/nsmb.2415

Autophagy, a cellular process whereby a double-membrane vesicle engulfs a portion of the cytoplasm and fuses with the lysosome, leading to the degradation of the engulfed contents, is mediated in part by noncanonical ubiquitin-like protein cascades. Atg7, an E1 enzyme, activates the E2 enzymes Atg3 and Atg10. Kaiser *et al.* and Yamaguchi *et al.* report crystal structures of the E1–E2 complexes, Atg7–Atg3 and Atg7–Atg10, demonstrating that Atg7 binds both E2 enzymes via the same surface but that the specific amino acids driving the interactions are distinct between the complexes. Both groups also demonstrate in biochemical assays that Atg7 can mediate unexpected conjugation of ubiquitin-like proteins (UBLs) Atg8 and Atg12, transferring them to both E2 enzymes rather than specifying Atg8–Atg3 and Atg12–Atg10 conjugations. Kaiser *et al.* further confirmed that amino acids essential for Atg7-Atg3 interaction were also necessary to rescue autophagy in Δ*atg7* or Δ*atg3* yeast cells. Taken together, these data indicate that E1 enzymes can use the same surface to bind distinct elements from disparate E2 enzymes and that specificity for selective loading of UBLs onto Atg3 and Atg10 observed *in vivo* might be mediated by elements in addition to Atg7.   *AD*