CARBOHYDRATES

Inhibitors in an instant

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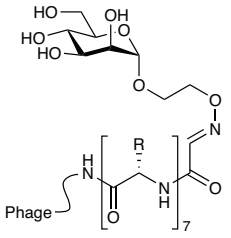
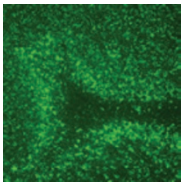


Carbohydrate-binding proteins such as lectins create specific but weak interactions with their glycan ligands using shallow protein surfaces and hydrophilic interactions, features that complicate inhibitor discovery. Previous research has used synergy between a carbohydrate anchoring group and a pendant ligand to develop inhibitors that retain specificity but display improved binding affinity, but generating compound analogs has generally been slow. Ng *et al.* now substantially accelerate this process by combining the diversity of a phage-based peptide library with a chemical modification strategy to quickly survey modified carbohydrates as lectin inhibitors. In their approach, the authors began with an N-terminal serine followed by a variable heptameric peptide; periodate oxidation of the serine group enabled attachment of a modified mannose residue on the phage surface. Panning of the resultant 10^8-member phage library against the lectin target concanavalin A followed by a careful comparison to control experiments led to 86 hits, allowing the authors to define a [WYF]Y[SDEA] consensus motif, which they optimized in a second focused screen to a WYDLF sequence. Biophysical analysis of hits from both rounds confirmed that the monosaccharide, linker and specific peptide sequence were all critical in achieving low-micromolar IC50 values, indicating that these results could not have been achieved by screening a peptide-only library. A crystal structure of the mannose-WYD construct with concanavalin A indicated that the peptide caused conformational rearrangements of the protein surface, opening a hydrophobic site that was not apparent in the structure bound to a three-mannose chain. Finally, testing of a ligand containing a fluorescent probe demonstrated good selectivity, as only 3 of 85 other lectins bound the inhibitor and with lower potency than did concanavalin A. This report offers a new and facile route to creating inhibitors of these challenging protein targets. *CG*

BRAIN CANCER

Staying alive

Nature **520**, 363–367 (2015)

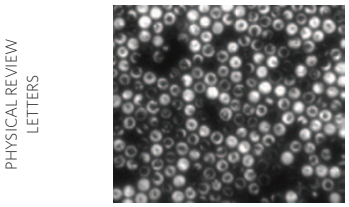


Glioblastoma multiforme (GBM) is one of the most aggressive brain tumors and is characterized histologically by the presence of a necrotic center surrounded by a band of viable tumor cells that make up a structure called pseudopalisades. Despite their lack of access to oxygen and nutrients, these cells are able to thrive and proliferate. To identify the metabolic alterations in GBM tumors that allow survival under these hypoxic conditions, Kim *et al.* compared the expression of metabolic genes between human GBM and normal brain tissues and found that genes involved in glycine metabolism had elevated expression in patients with GBM. In particular, pseudopalisades expressed high levels of mitochondrial serine hydroxymethyltransferase (SHMT2), an enzyme that converts serine to glycine. SHMT2 was confirmed as an essential determinant for hypoxic cell survival, as SHMT2 knockdown in an xenograft model of GBM resulted in cell death. To identity the metabolic changes induced by SHMT2 that allow survival, the authors examined metabolic changes that occur when a GBM cell line (LN229) loses SHMT2 expression. They detected elevated levels of serine and fructose bisphosphate (FBP), which are known to activate pyruvate kinase isoform 2 (PKM2), which stimulates pyruvate production during glycolysis. SHMT2 knockdown boosted PKM2 metabolic activity, resulting in increased TCA cycle activity and oxygen consumption. Treatment of LN229 cells with small-molecule activators of PKM2 decreased LN229 hypoxic survival through increased oxygen consumption. In addition to having reduced PKM2 activity, cells with elevated SHMT2 expression produced large amounts of glycine that needed to be degraded into ammonia and carbon dioxide by glycine decarboxylase (GLDC). Knockdown of GLDC reduced LN229 viability by promoting glycine metabolism by glycine C-acetyltransferase, resulting in the formation of the toxic byproducts amino-acetone and methylglyoxal. Overall, these findings may inspire new ways to modulate glycine metabolism for potential treatment of GBMs. *GM*

CELL MOTILITY

Bigger and faster

Phys. Rev. Lett. **114**, 158102 (2015)



Bacterial communities are dynamic assemblies integrating cell-cell interactions, signaling events and motions. Purely through physical mechanisms, moving cells can influence each other to form coherent structures, such as swarms. Fluid dynamics principles such as compressive forces, shear or pushing effects, and 'surface screening'—the attenuation of collective motions of cells in close proximity to a surface—all contribute to the movements of individual cells and of the group collectively. *Thiovulum majus* are very large, spherical bacteria that generate a large fluid flow to expose all cells to oxygen and nutrients. *T. majus* cells can attach dynamically to surfaces and rotate hundreds of flagella to create this fluid flow. In studying the collective movements of these bacteria, Petroff *et al.* noticed a curious behavior whereby moving cells self-assemble by mutual attraction into a construction with the geometric characteristics of a two-dimensional crystal, specifically a hexagonal lattice studded with vacancies. Within the crystals, each cell pulls the surrounding water towards and around it. Using fluid dynamics principles, the authors derived an equation that explains many aspects of the formation and dynamics of these crystals. They also suggest that crystal formation takes place in two steps involving two different forces. The first is an attractive (normal) component of the flow and is due to force exerted by the flagella. The second is a shear force, generated by the rotation of the cells, which tends to pull cells around one another. The attractive component of the force pulls cells together into a crystal lattice, while the shear forces cause the crystals to rotate and the cells to move past one another. *MB*

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