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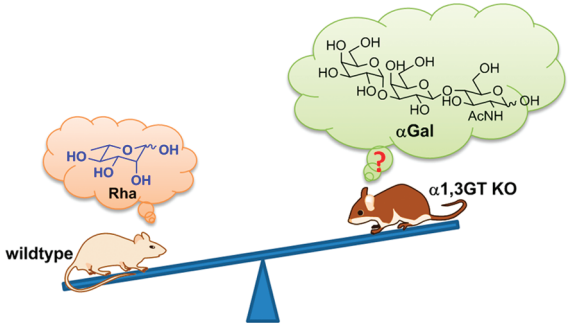
A Sweet New Alternative in Cancer Therapy

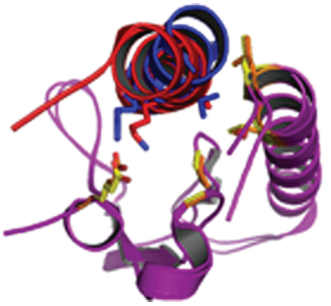
Carbohydrate antigens, especially α-Gal, are important immunogenic molecules in humans. Approximately 1% of serum IgG consists of antibodies toward α-Gal; this abundance makes it attractive as a tool for immune complex formation and the sequential recruitment of other immune cells. Thus, vaccine development to antigen-presenting cells through *in vivo* complexing of anti-Gal/α-Gal has been a promising cancer immunotherapy with enhanced immunogenicity. Unfortunately, research using α-Gal as an immunogen in cancer therapy suffers from the lack of an animal model due to the presence of α-Gal synthases in several nonprimate mammals. In this issue, Chen *et al.* (DOI: 10.1021/cb100318z) offer a superior new alternative carbohydrate antigen, L-rhamnose (Rha) in developing cancer immunotherapies.



The presence of high titers of anti-Rha antibodies in human serum makes these antibodies attractive replacements to anti-α-Gal antibodies in immunotherapy. Using a simple synthetic Rha-protein conjugate, the anti-Rha antibodies were boosted to high titers in wild-type mice, which lack a natural Rha synthase, providing an easily accessible preclinical trial animal model. Thus, this study shows that a powerful combination of synthetic Rha-conjugate immunogens and wild-type mice could provide an exciting new alternative in the development of cancer immunotherapies.

A Weighty Antagonist

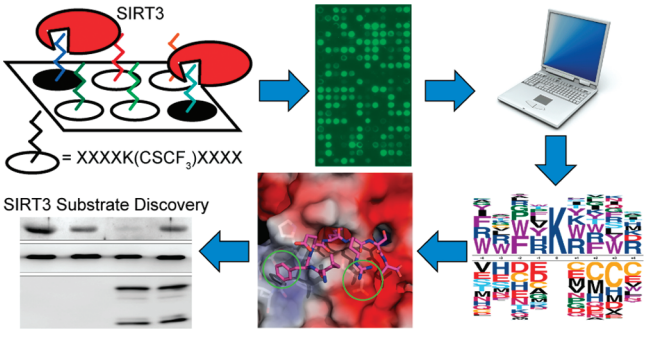
Metabolic syndrome is a term that encompasses the medical factors leading to an increased risk of cardiovascular disease and diabetes. It affects one in five people globally. A group of gastrointestinal hormones, incretins, are important determinants in controlling metabolic syndrome by increasing insulin production, thus regulating blood glucose levels, while inhibiting glucagon release. Two main incretins are known to exist in humans; glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide. The activation of GLP-1 receptor leads to increased secretion of insulin, and therefore the development of GLP-1 antagonists has therapeutic utility in treatment of hypoglycemia. Patterson *et al.* (DOI: 10.1021/cb1002015) report the development of a potent new GLP-1 receptor antagonist that increases appetite, body weight, and glucose levels in mice.



Exendin-4 (Ex-4) is a well-characterized antagonist of GLP-1 receptor but lacks potency as a result of its nonhuman amino acid sequence, which elicits an immune response, and its short duration of action within the cell. To develop a more potent GLP-1 receptor antagonist, a series of GLP-1/Ex-4 hybrid peptides were generated to identify the structural determinants for GLP-1 receptor binding. The simultaneous substitution of three specific amino acids in the Ex-4 portion resulted in a 3-fold increase in potency. Site-specific acylation further enhanced potency and produced a superior antagonist for *in vivo* subcutaneous administration. The antagonist was administered daily to diet-induced obese mice and resulted in increased appetite and body weight and decreased glucose tolerance. The development of a potent and sustained antagonist supports the importance of GLP-1 in the regulation of body weight.

The Expanding Roles of Sirtuins

Sirtuins are a family of NAD^+-dependent protein deacetylases that are involved in critical cellular processes such as genome maintenance, metabolism, and cell survival. They play a role in the reversible acetylation of proteins, a major regulatory mechanism in the cell. Recent studies have implicated the involvement of SIRT3, the central deacetylase in the mitochondria, in the regulation of central metabolic pathways. Additionally, polymorphisms in human SIRT3 have been linked to age-related phenomena. In order to identify SIRT3 substrates, Smith *et al.* (DOI: 10.1021/cb100218d) have developed a screening strategy to evaluate sirtuin substrate specificity leading to valuable insights into their role in cellular metabolism.



Recent studies showed that more than 20% of all mitochondrial proteins are acetylated on one or more lysine residues.

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Although there are multiple sirtuins in the human mitochondria, only SIRT3 has shown high levels of deacetylation activity. The authors focused in on identifying the protein targets of SIRT3 using a screening strategy comprised of a novel acetyl-lysine analogue (thiotrifluoroacetyl-lysine), SPOT-peptide libraries, machine learning, and kinetic characterization. The unbiased screening strategy suggested potential SIRT3 substrates are involved in major metabolic pathways such as the urea cycle, ATP synthesis, and fatty acid oxidation. This novel screening strategy provides a much needed approach for the quick and efficient identification of substrate identification for sirtuin isoforms.

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