DIABETES

Connectin' through adiponectin

Type 2, or adult-onset, diabetes mellitus is an increasing burden on Western health-care systems, and threatens to reach epidemic levels in developing countries. Adiponectin (also known as 30-kDa adipocyte-related protein (ACRP30)), an established anti-atherogenic protein, has previously been implicated in metabolic disorders such as diabetes, possibly providing a link between obesity and insulin resistance. Now, Yamauchi *et al.*, reporting in *Nature*, have cloned receptors for adiponectin and confirmed its putative functions.

Adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) were cloned, and their expression patterns analysed. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is principally expressed in the liver. On the basis of the sequences of the cloned receptors, they are predicted to contain seven transmembrane domains, but to be structurally and functionally distinct from G-protein-coupled receptors (GPCRs). Yamauchi *et al.* used RNA interference (RNAi) to show that AdipoR1 is a high-affinity receptor for globular adiponectin (but a poor binder of the full-length form), whereas AdipoR2 is an intermediate-affinity receptor for both globular and full-length adiponectin.

Adiponectin has insulin-sensitizing effects in insulin-resistant mice, which seem to result from increased activity of AMP kinase (AMPK) and peroxisome-proliferator activated receptor-α (PPAR-α), leading to greater fatty-acid oxidation. The RNAi experiments confirmed the causal role of AdipoR1 and AdipoR2 in mediating the effects of adiponectin on AMPK and PPAR-α. In particular, the binding of adiponectin to AdipoR1 led to increased AMPK, PPAR-α and p38 mitogen-activated protein kinase activity. As AdipoR1 and AdipoR2 are distinct from GPCRs, and activate unique sets of signalling molecules, the authors suggest that the adiponectin receptors could comprise a new family of receptors.

Adiponectin has already been identified as a potential target for therapeutics to treat obesity-related illness and diabetes, so the cloning of AdipoR1 and AdipoR2 should aid both unravelling the mechanisms by which adiponectin acts, and the design and development of new antidiabetes therapies directed against these receptors. If, in common with GPCRs, these receptors prove to be tractable as drug targets, this could be very good news for patients and drug developers alike.

Daniel Jones

References and links

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HIGH-THROUGHPUT SCREENING

Combine and conquer

Since Loewe described chemical synergism and additivism in 1928, multicomponent therapies whose efficacy exceeds that of their individual constituents have arisen by both design and happenstance, and are now standard treatments for cancer and infectious diseases. Synergistic combinations of drugs already in the clinic might therefore be a rich source of potential therapies, and a relatively unexploited one, due in part to the daunting number of combinations that can be generated. Writing in the *Proceedings of the National Academy of Sciences*, Borisy and colleagues now describe a systematic high-throughput approach to mining this resource.

Dubbed 'combination high-throughput screening' (cHTS), the new technology lies at the heart of the authors' company CombinatoRx, and can be applied to the analysis of two-component and higher-order combinations. The first step is to categorize compounds on the basis of individual activity. Each active compound is then paired with every other compound — both active and inactive — at six different concentrations, and assayed again. By contrast, inactive single entities are pooled in groups of four before testing. Active 'pools' are then deconvoluted to identify the specific pair that confers activity — a more efficient strategy made possible by the lack of overlapping activities and the relatively low frequency at which active combinations form from inactive single agents.

Borisy *et al.* used their cHTS system to find pairs of drugs that are more efficacious than their individual constituents against three disease-causing entities. From a total of about 120,000 combinations, 22 pairs with antifungal activity against fluconazole-resistant *Candida albicans* were identified. Six of these contained a known antifungal and a non-antifungal agent, with the remaining sixteen comprising two non-antifungals — none of the pairs comprised two known antifungal agents. Twenty-six combinations that suppress production of the immunostimulatory cytokine tumour-necrosis factor-α in human blood cells were also discovered.

In their final assay, the authors identified thirteen new synergistic pairs that inhibit the proliferation of tumour cells. When tested in a mouse model of human lung carcinoma, the combination of the antipsychotic chlorpromazine and the antiprotozoal pentamidine was more effective than the anticancer drug paclitaxel, and did not cause the side effects that commonly result from standard chemotherapy. So it seems that, at least in drug discovery, the whole can be greater than the sum of its parts.

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