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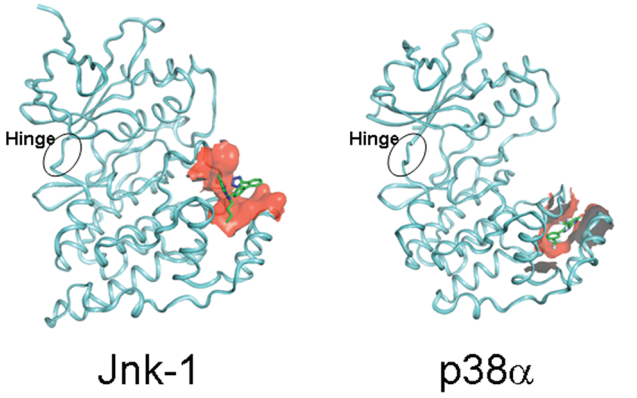
An Alternative Approach to Protein Kinase Inhibition

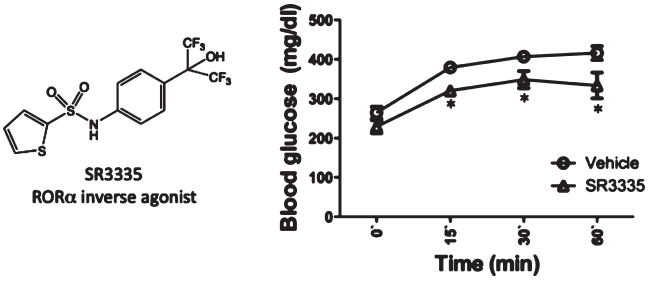
Protein kinases play an important role in cellular signaling. Given their significance in several diseases, they are also considered attractive drug targets. It is estimated that over 200 kinase inhibitors are currently under clinical development. An overwhelming majority of these potential drugs are small molecules that inhibit binding to conserved ATP-binding site. However, an inherent drawback of this strategy is nonspecificity, which often results in unexpected toxicity and side-effects. Comess *et al.* (DOI: 10.1021/cb1002619) present a unique approach to identifying new compounds that specifically inhibit a target protein kinase by binding a novel allosteric site on two different target kinases of high therapeutic importance.



The authors focused on serine/threonine protein kinases c-Jun N-terminal kinase 1 (Jnk-1), implicated in type 2 diabetes, and p38α, associated with the inflammatory response in rheumatoid arthritis. Using an affinity-based, high-throughput screening technique, compounds that bound to all sites on the protein kinases were studied. In addition to compounds that bound the ATP site, the screen identified several compounds that bound kinases in an allosteric manner. Allosteric ligands that bound to a previously unknown allosteric site distant from the active site of Jnk-1 and p38α were characterized using NMR spectroscopy, X-ray crystallography, surface plasmon resonance and activity assays. One of the allosteric inhibitors to Jnk-1 was used as a lead compound to develop a synthetically superior ligand, which specifically inhibited Jnk-1 activation in human adipocyte and hepatocyte cells. Thus, the identification of a novel druggable site and associated inhibitor in kinase enzymes has significant implications for drug discovery.

A Promising New Compound in Diabetes Treatment

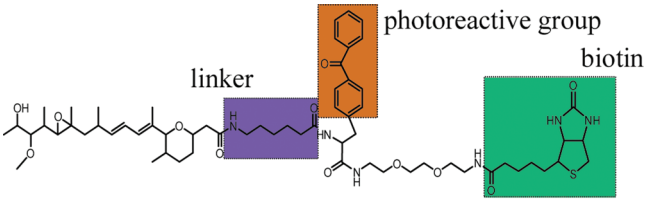
The retinoic acid receptor-related receptors (RORs) are transcription factors belonging to the nuclear receptor superfamily. Receptors for steroid hormones, thyroid hormones, bile acids, *etc.* are some of the members of this family. However, the ligands of several of the nuclear receptor family have yet to be characterized and are termed orphan receptors. RORα is one such receptor, which has previously been implicated in regulation of glucose levels. Kumar *et al.* (DOI: 10.1021/cb1002762) have synthesized a highly selective inverse agonist for RORα that suppresses glucose production in the liver.



Using a previously identified benzenesulfonamide scaffold, the authors synthesized an inverse agonist, SR3335, that directly binds RORα. Importantly, this compound had no effect on other receptors such as RORβ or RORγ, demonstrating specificity. SR3335 suppressed RORα target genes involved in hepatic gluconeogenesis. This observation was confirmed using intraperitoneal injections into diet-induced obese mice where lower plasma glucose levels were detected. Thus this report identifies the first specific RORα inverse agonist that could be used as a tool to study RORα function. This promising compound could be relevant to the pharmaceutical industry in the treatment of type 2 diabetes.

The Spliceosome, a Target for Anti-Cancer Drug Development

GEX1A (herboxidiene) is a natural product with antitumor activity. This compound causes cell cycle arrest at the G1 (major period of cell growth) and G_2/M (DNA damage checkpoint) phases in different human cell lines. Several factors, including cyclin-kinase inhibitors such as p27, regulate the cyclin-dependent kinases that drive the mammalian cell cycle. In this issue, Hasegawa *et al.* (DOI: 10.1021/cb100248e) focused on the effects of GEX1A on p27 and found an important link between GEX1A and the splicing machinery of the cell.



The authors studied the effects of GEX1A on the cyclin-dependent kinase p27, a key inhibitor in the G1 transition of the cell. GEX1A caused a time- and dose-dependent accumulation of truncated p27, which was caused by the retention of an intron

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with a premature stop codon. GEX1A variants with different photoreactive groups showed that this compound binds SAP155, a subunit of Splicing Factor 3b, a major component of the spliceosome. GEX1A is thus one the few known small molecules to interfere with pre-mRNA splicing. Additionally, it implicates the spliceosomal machinery as a novel and unique target for anticancer drug development.