11 have been implicated in Joubert syndrome [4–6]. However, it's only with the identification of the *AHI1* gene that the potential for a prenatal genetic screen has been raised.

'Prenatal diagnosis could be offered with existing technology tomorrow, but only for the second child in an affected family,' says Dobyns. He estimates that the *AHI1* gene causes 10–20% of Joubert syndrome and, more broadly, that Joubert syndrome accounts for only about 10% of the cerebellar brain defects observed in prenatal ultrasounds.

As genes for other brain disorders are identified, such as *ZIC1* and *ZIC4* for Dandy-Walker malformation, a broader genetic screen will become feasible [7]. It's also possible that these genes might be involved in more common childhood brain and behavioral abnormalities, says Gleeson, who is currently working with the Cure Autism Now Foundation (http://www.canfoundation.org/) to screen their patient collection for changes in the *AHI1* gene.

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Sugar directly triggers fat formation

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Consume too many carbohydrates in your diet and your liver will convert them into fatty acids for long-term energy storage, evidenced by our burgeoning waistlines. Processed carbohydrates are touted as enemy number one by popular diets, with insulin touted as the key player in the process. However, it's now clear that sugar can act alone in making us fat. Kosaku Uyeda and colleagues at the University of Texas Southwestern Medical Center in Dallas, TX, USA (http://www.utsouthwestern.edu) report that simple sugars can also directly trigger fat formation via the activation of several genes responsible for control of glucose metabolism, as well as fatty acid and triglycercide synthesis [1].

Lipogenesis

Carbohydrate response element-binding protein (ChREBP) is a transcription factor, first discovered by Uyeda's group in 2001, and is responsible for the glucose-induced transcription of the liver pyruvate kinase gene (*LPK*), a regulatory enzyme in the glycolytic pathway. Under low glucose

conditions, ChREBP remains in the cytosol of hepatocytes, and cannot bind to its DNA target due to phosphorylation of multiple sites. In the presence of high glucose, these sites are dephosphorylated and ChREBP can now bind to its targets, triggering fat formation without any help from insulin.

ChREBP promotes lipogenesis enzymes

In findings published earlier this year [2] Uyeda's group described their mouse model in which the *ChREBP* gene is knocked out. Mice unable to produce ChREBP showed a reduced ability to metabolize glucose and store fat, and accumulated excess glycogen in the liver.

Now their latest findings confirm those *in vivo* findings, ruling out indirect mechanisms that could have been involved. Using liver cells from wild-type and *ChREBP*-knockout mice, they show that ChREBP is responsible for glucose-dependent transcriptional activation of LPK and carbohydrate-responsive lipogenic enzyme genes, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), both involved in fatty acid synthesis, among others.[1]

'Not only is it directing regulatory gene expression for LPK, but also these lipogenic enzyme genes, resulting in a

mechanism for coordinating increased glycolysis with increased fatty acid synthesis,' says biochemist Bonnie Miller, coauthor of the study.

'It's really elegant work,' says Richard Veech, a biochemist at the National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, in Rockville, MD, USA; http://www.niaaa.nih.gov). '[Uyeda] has outlined the whole thing – what is controlled and how it is regulating the fundamental thermodynamics of the metabolic pathways.'

Low-carb diets

It's a discovery that has implications for the low vs high-carbohydrate diet debate. 'One of the interesting questions is whether this does play a role in the Atkin's diet,' says Miller. 'It's very interesting to speculate that this mechanism is contributing to a low carb diet.' But controlling fat formation isn't that simple. Miller says that knockout mice lacking ChREBP can still store plenty of glycogen, though less body fat, indicating other control mechanisms in place to ensure necessary energy stores for survival.

'This is a protein that sits at a very intriguing point in controlling metabolic activity,' says Howard Towle, University of Minnesota, Minneapolis, MN, USA (http://www1.umn.edu/twincities/index.php). 'It has real potential to turn out to be a key player in the whole process of what regulates metabolism.'

Although it is too soon to settle the debate, the findings of the Uyeda group are the first to establish a direct link between sugar and fat. 'The more we understand how the pathway is regulated and how glucose promotes its own conversion to fat, will eventually help us to avoid problems,' says Miller.

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Exploiting Toll-Like receptors for designed multiple ligands

Recently, the insightful term 'designed multiple ligands' (DMLs) was conveyed to specify rationally-designed therapeutic agents capable of modulating several targets related to a specific disease or range of disorders, ultimately to achieve superior efficacy or safety [1]. Multiple factors impact on this outcome, with ligand selectivity representing a key parameter. Rational design and evolution of selected pharmacophores or ligands illustrates a popular approach for the pursuit of dual-acting agents, and many examples have been comprehensively detailed [1].

In addition to DMLs, therapeutic approaches capable of altering several clinical disorders have also proven successful by selectively inhibiting a single target. No doubt an extremely effective approach to modify multiple autoimmune diseases can be achieved by antagonizing a single pro-inflammatory cytokine. The interplay and cross-talk existing between immune-cell effectors, such as cytokines and chemokines, imparts a complex cascade of intracellular signaling events that can often result in an exponential or heightened responses. For example, expression of a pro-inflammatory cytokine such as tumor necrosis factor alpha (TNF-α) often triggers the expression of additional effectors, which in turn can perpetuate TNF-α expression and sustain the inflammatory state if left unchecked [2]. Agents capable of neutralizing soluble and membrane-bound TNF-α such as Infliximab™ have demonstrated significant clinical efficacy across a range of autoimmune disorders [3]. In essence, antagonism of a master control cytokine such as TNF-α effectively modulates several downstream targets to confer superior therapeutic activity, and is thus a multiple disease modifier.

The feasibility of discovering and optimizing DMLs having the possibility to be multiple disease modifiers could be improved by selecting closely-related targets, those that are part of a superfamily, or those sharing similar endogenous ligands. To that end, exploring chemical libraries for

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