WEB WATCH

The rice genome

The Monsanto rice-research.org website provides limited access to the rice genome sequence data, announced with much fanfare earlier this year. Still, limited access is better than no access at all. Access is free to researchers from non-profit organizations, but users must sign a legal agreement before they can get a password. The assembled sequences total 259 Mb, which is roughly 60% of the rice genome, broken into more than 50,000 contigs. The terms of access do not allow users to simply download the sequences; the only way to access it is by BLAST searches, and no user may download more than 25 kb.

Ken Wolfe, University of Dublin, Ireland

Links

FURTHER READING Dalton, R. Cereal gene bank accepts needs for patents. *Nature* **404**, 534 (2000). | Dickson, D. Royalty-free rice arrives on the web. *Nature* **404**, 549 (2000)

Netting homologies

The National Center for Biotechnology Information (NCBI) website has recently posted a new build of its HomoloGene resource, which incorporates the latest UniGene cluster assemblies. HomoloGene allows users to quickly find orthologues among the human, mouse, rat and zebrafish genes represented in NCBI's UniGene clusters and LocusLink site.

Each HomoloGene report consists of a UniGene cluster or LocusLink entry that forms a report's 'base cluster'. To this base cluster are added its published and calculated orthologues. Calculated orthologues are generated by comparing nucleotide sequence in the base cluster with those in clusters from other organisms, and the report lists the best of these alignments.

Fly sequences in LocusLink have now also been added to the reports, providing one more species for comparative analysis.

Jane Alfred

OBESITY

The mouse that eats less but gains weight

Obesity contributes to poor public health in many western populations, underlying illnesses that range from cardiovascular disease to hypertension and stroke. Over the past years, research into animal models of obesity has teased apart some of the endocrinological pathways that mammals have evolved to regulate the body's fat content in times of feast and famine. Now, new insight into the subtle workings of these pathways comes from a paper in the September issue of *Nature Genetics*, which reports the phenotypic effects of inactivating the gene that encodes the mouse melanocortin receptor 3 (Mc3r).

Mc3r functions in a feedback loop that lies downstream of leptin, an adipocyte-derived hormone that circulates in the blood in proportion to body adiposity. In the brain, leptin elicits neuropeptide responses that stabilize the body's fat content by decreasing food intake and increasing energy expenditure. One such neuropeptide is α-melanocyte stimulating hormone (α-Msh), which acts on several melanocortin receptors, including Mc3r and Mc4r. Until now, the relative importance of each receptor in this feedback loop has been unknown, but the study by Chen *et al*. shows that inactivating *Mc3r* has different effects on food intake and adiposity to inactivating *Mc4r*.

$Mc3r^{-/-}$ mice appear to grow normally up to 26 weeks of age but, although at this age they are not overtly obese, their fat mass is almost double that of wild-type and heterozygous littermates. This is because their increased fat mass is initially obscured by a compensatory decrease in lean muscle mass. It is only after 26 weeks that their increased weight gain becomes more obvious (see picture).

Unexpectedly, this increased adiposity is not caused by increased food intake. Instead, $Mc3r^{-/-}$ mice gain more fat per calorie of food consumed, apparently at the expense of their lean body mass. This so-called increased feed efficiency means that the mutant mice store more fat despite eating less than normal mice do, and they become obese if fed a high-fat diet. The mechanism behind these responses is unclear because the $Mc3r^{-/-}$ mice have normal metabolic rates, body temperatures and thyroid function. However, they are less active than wild-type mice, which might contribute to their tendency to obesity, and they also show a transient reduction in neuropeptide Y levels. As this hypothalamic neuropeptide has been implicated in feeding-control mechanisms, Chen *et al*. suggest that its reduction in $Mc3r^{-/-}$ mice may contribute to their reduced food intake.

So how do $Mc3r^{-/-}$ mice differ from $Mc4r^{-/-}$ mice, and what does this tell us about the different functions of the two receptors in the control of food intake and energy expenditure? $Mc4r^{-/-}$ mice eat more than normal mice and are obese. They also have altered metabolic rates and a normal lean body mass. When Chen *et al*. treated $Mc3r^{-/-}$ mice with a non-selective melanocortin agonist, it reduced food consumption in both mutant and normal mice to a similar degree, indicating that α-Msh probably inhibits food intake by acting through Mc4r. Further evidence supporting distinct functions for these two receptors came when Chen and colleagues crossed the two knockout mice to produce doubly homozygous mutants, which were more obese than mice lacking just *Mc4r*. In an accompanying News and Views article, David Cummings and Michael Schwartz speculate

$Mc3r^{+/+}$ $Mc3r^{-/-}$

Courtesy of the Department of Obesity Research, Merck Research Laboratories, Merck & Co., Inc. © Merck & Co., Inc. (2000).

that this phenotype occurs because the double mutants eat excessively, owing to the loss of Mc4r signalling, and store consumed calories more efficiently, owing to the absence of both receptors.

These new insights into the functions of Mc3r could contribute to the development of new diagnostic and therapeutic approaches to treating obesity disorders in humans, and further research should clarify whether drugs that act through Mc3r and Mc4r could be used therapeutically to reduce food intake and its storage as fat.

Jane Alfred

References and links

ORIGINAL RESEARCH PAPER Chen, A. S. *et al*. Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nature Genet*. **26**, 97–102 (2000).

NEWS AND VIEWS Cummings, D. E. & Schwartz, M. W. Melanocortins and body weight: a tale of two receptors. *Nature Genet*. **26**, 8–9 (2000).

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