WEB WATCH

LocusLink — is there life after death?

By the time you read this, NCBI's LocusLink will be no more. As of 1 March 2005, it will have been replaced by NCBI's Entrez Gene.

Born in 1999, LocusLink has served the genetic community well. It was created to help manage and access increasing amounts of sequence data and web resources. The first publication[1] to describe it refers to it as a "web directory" that "provides a single point-of-access to a variety of gene-specific information sources including web resources and RefSeq".

Throughout its life, LocusLink was continuously updated to inform us not only about the sequence and function of an increasing number of species but also about the correct gene nomenclature. So why did it have to go, and what of its replacement?

In fact, it might be better to view the recent events as the metamorphosis of LocusLink rather than its demise, as Entrez Gene incorporates all of the LocusLink data and can be thought of as its enhanced extension. It provides a unified look and feel for gene-specific information and contains data for many more species, including mitochondrial and plastid genome data for more than a half of them.

Entrez Gene has some important additional functionality — for example, it can display information about splice variants, intron/exon organization and a wealth of data on protein–protein interactions. The 'search' function is much improved — for example, one or more species or taxonomic groups of interest can be used to restrict the queries. Moreover, query parameters can be saved and results sent to you by means of the 'My NCBI' function, as information is updated. The king is dead, long live the king!

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REFERENCE [1]Maglott, D. R. *et al.* NCBI's LocusLink and RefSeq. *Nucleic Acids Res.* **28**, 126–128 (2000)

OBESITY

Low-fat clues to obesity

A new insight into the pathways involved in obesity has come from a surprising source — studies of extremely skinny mice.

Mice that lack a functional *Lpin1* gene develop a condition that is known as lipodystrophy, which is characterized by a severe lack of adipose tissue. The lipin protein that is encoded by this gene is expressed in adipose tissue and skeletal muscle, and the lack of fatty tissue in lipin-deficient mice is caused by a failure of adipocytes to differentiate. Jack Phan and Karen Reue had previously shown that lipin deficiency prevents mice from becoming obese, and that this works both for mice that are overfed and those that are genetically predisposed to obesity. This led them to wonder whether reversing the situation by increasing lipin levels would have the opposite effect and cause mice to become obese.

To test this, they made transgenic mice that overexpressed *Lpin1* either in adipose tissue or in skeletal muscle. In both cases, increased *Lpin1* expression predisposed the mice to obesity. However, whereas the skeletal-muscle transgenics became obese even on a standard diet, mice that overexpressed *Lpin1* in adipose tissue only put on excess weight when they were fed a high-fat diet, indicating an important environmental contribution, which is reminiscent of human obesity.

The authors then showed that the causes of excessive weight gain associated with increased lipin levels were mediated by different pathways in the two types of transgenic mouse. Animals that overexpress *Lpin1* in adipose tissue showed increased activation of genes that are involved in the storage and production of fat. By contrast, the weight-gain mechanism of transgenics with overexpressed *Lpin1* in skeletal muscle was associated with defects in energy expenditure, including an increased efficiency in the conversion of food to body mass and a reduced ability to use stored body fat as an energy source. This was also reflected at the molecular

GENE EXPRESSION

Transcriptional silencing: the third way

Transcriptional silencing has until now been explained by one of two models: the first claimed that RNA polymerase or activating factors are prevented from accessing their targets owing to conformational changes in silenced chromatin; the second placed the transcriptional block further downstream, after the transcription pre-initiation complex has formed. Elegant work by Chen and Widom now shows that neither is likely to be correct. Their results support a third model, in which transcriptional silencing occurs by preventing the formation of stable pre-initiation complexes at silenced promoters.

Driven by a lack of consensus on the molecular mechanisms of transcriptional silencing in yeast, Chen and Widom quantitatively tested the two prevailing models. First, by engineering the yeast chromosome 3 to contain appropriate recognition sites, the authors quantified the accessibility of DNA targets to foreign reporter proteins, including the site-specific DNA-binding protein LexA, *in vivo*. They found no evidence of reduced binding to silenced loci that would indicate involvement of steric hindrance, so discounting the first model.

According to the second model, RNA polymerase II, although present at the promoters of silenced loci, should be absent from their 3′ ends. Chen and Widom used silenced *URA3* to scrutinize RNA polymerase II occupancy; chromatin immunoprecipitation revealed that there was much less RNA polymerase II at either the promoter or the 3′ end of the silenced *URA3* when compared with the euchromatic locus, indicating that transcription is blocked before polymerase is recruited. These results were further confirmed when the transcription factors TFIIB and TFIIE, both of which are recruited to the pre-initiation complex, were