MOUSE MODELS

A double hit for diabetes

Diabetes is one of the fastest growing diseases in the western world, and so finding a cure is a pressing need for the millions of familes worldwide that are affected by the various defects in sugar metabolism that this disease encompasses. Individuals affected by lipoatrophic diabetes mellitus, for example, have high levels of sugar in the blood due to insulin resistance. The genetic predisposition to diabetes is probably as varied as the disease itself, therefore, animal models offer an opportunity to understand the molecular and physiological basis of this class of disorder as well as providing a testbed for possible cures. Laustsen, Michael and colleagues have now created a mouse model of lipoatrophic diabetes and have investigated a fruitful route for its cure by gene therapy.

The study stemmed from the authors' interest in four mouse proteins — the insulin receptor substrates (IRS) 1-4 — which relay the insulin signal within cells. Single knockout mice for each Irs gene had shown that Irs1 and

Irs2 have important and non-redundant roles in post-natal growth and glucose homeostasis, respectively; by contrast, Irs3 and Irs4 knockout mice had few abnormalities. But the Irs3 and Irs4 null phenotypes could have been compensated for by Irs1 and Irs2 or, conversely, the Irs1 and Irs2 mutant phenotypes could have been ameliorated by Irs3 and Irs4. Double knockout mice showed no redundancy between Irs1 and *Irs4*; however, the phenotype of *Irs1*,3 double knockout mice bore a striking resemblance to the features of lipoatrophic diabetes in humans: the mice had high levels of glucose and insulin in the blood, had reduced white adipose tissue (lipoatrophy) and developed non-insulin-dependent diabetes. Furthermore, the diabetes phenotype could be reversed by injecting the *Irs1*,3^{-/-} mice with an adenoviral vector carrying the leptin gene, which had previously been shown to alleviate the insulin resistance of the other mouse models of lipoatrophic diabetes.



Irs1 and Irs3, therefore, have complementary physiological roles. So, what promise does this hold for human diabetes sufferers? As humans lack the IRS3 protein, they might be more dependent on the function of IRS1, and so sequence variants of this gene should be worth a closer look.

References and links

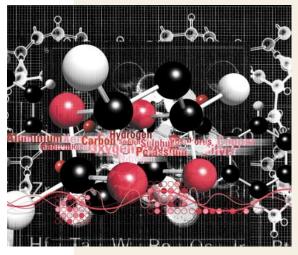
ORIGINAL RESEARCH PAPER Laustsen, P. G., Michael, M. D. et al. Lipoatrophic diabetes in Irs 1-/-, Irs 3-/- double knockout mice. Genes Dev. 16, 3213-3222 (2002)

WEB SITE

Gustav Leinhard's laboratory: http://www.dartmouth.edu/~biochem/lienhard

CANCER GENETICS

Molecular signatures



Large-scale microarray analysis is almost ubiquitous in biological research. Recent papers in Nature Genetics illustrate the power of this technique to enhance our general understanding of cancer, and, specifically, to aid in diagnosis and in the identification of targets for the development of new therapies.

In order to shed light on the molecular basis of metastasis, Ramaswamy and colleagues used microarrays to compare the geneexpression profiles of metastatic and primary tumours from a range of human tissues, and found that the expression of 17 genes differed between the two classes of tumour and, therefore, provided a molecular signature for tumour-type.

Interestingly, some primary tumours shared the same gene-expression profile as metastatic nodules. Primary lung tumours that had the metastatic molecular signature were associated with worse prognoses compared with tumours that lacked such a signature. Furthermore, primary tumours from breast, prostate and brain with this signature were more likely to develop distant metastases, indicating that the molecular signature is biologically significant and that the basis of metastasis could be shared by different tumour types.

The authors argue that the propensity for a primary tumour to metastasise is linked to its genetic state as indicated by the geneexpression profile. This is in contrast to the

current model, according to which the probability of a primary tumour becoming invasive depends mainly on its size — the bigger the tumour the more likely it is that a somatic mutation will occur that confers the metastatic phenotype.

With further refinement and testing, this work could be used to develop diagnostic tools that predict the clinical outcome of primary tumours on the basis of their geneexpression profiles at diagnosis. Microarraybased gene-expression profiling could also be used to provide detailed cancer diagnosis, as illustrated by Dyrskjøt and colleagues in the same issue of Nature Genetics. Their results showed that each class of bladder cancer has a distinct gene-expression profile that could be used in diagnosis or to generate new therapies targetted at specific stages and types of the disease. It is clear that microarray analysis will be invaluable in many aspects of cancer research. We will have to wait and see how long it takes for the practical application of these results to reach the clinic.

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References and links

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WEB SITE

Whitehead Institute Cancer Genomics:

http://www-genome.wi.mit.edu/cancer