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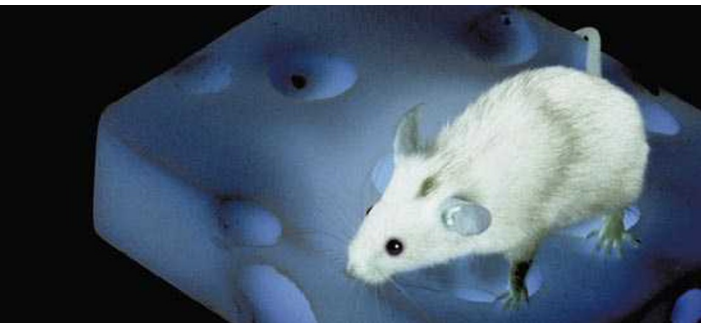
ANIMAL MODELS

Proteomics goes live in the mouse

An important new approach has been added to the range of tools available for studying mouse genetic models. For the first time, comprehensive, quantitative proteomic analysis of tissues from whole animals has been achieved, allowing detailed studies of how genetic alterations affect protein levels *in vivo*.

Because gene expression is regulated at several stages after transcription, monitoring mRNA levels alone does not give a full picture of the effects of genetic alterations on the protein output of cells and tissues. For microorganisms and cultured cells, a method called SILAC (stable isotope labelling with amino acids in cell culture) has been widely applied to allow proteomic analysis using mass spectrometry. Briefly, two populations of cells are compared: one grown in media that contains the natural form of an amino acid — for example, lysine — and the other in the presence of the same amino acid labelled with a stable non-radioactive isotope — for example, $^{13}C_6$-lysine. Protein levels in the two populations can then be compared by mixing them and carrying out mass-spectrometry, which gives a ratio of the levels of the labelled and unlabelled forms of a peptide.



Now, Krüger and colleagues have extended this approach to *in vivo* studies by feeding mice with a $^{13}C_6$-lysine diet. No adverse effects were seen on feeding and growth, fertility, or activity, and development and physiology were normal over several generations of SILAC labelling. By the F2 generation, they saw complete labelling of proteins in all tissues with $^{13}C_6$-lysine, allowing quantitative proteomic analysis in this generation and beyond.

The authors validated their approach by using three mouse models defective for expression of different genes. In each case, following differential labelling of wild-type mice and mice modified for the gene of interest, mass spectrometery accurately confirmed a lack of protein expression in the relevant tissues. Finally, the authors showed that the *in vivo* SILAC approach can be used to make new biological discoveries. By looking at protein levels in red blood cells, they were able to gain insights into how deficiency for the kindlin 3 protein causes anaemia, revealing altered levels of membrane-skeleton proteins in red blood cells.

This approach to *in vivo* proteomics has many potential uses in the study of mouse genetic models, allowing protein levels to be analysed from whole organs all the way down to subcellular compartments and individual peptides. Allowing the effects of transgenic RNAi knockdown to be monitored at the protein level will be another useful application.

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ORIGINAL RESEARCH PAPER Krüger, M. *et al.* SILAC mouse for quantitative proteomics uncovers Kindlin-3 as an essential factor for red blood cell function. *Cell* **134**, 353–364 (2008)
FURTHER READING Peters, L. L. *et al.* The mouse as a model for human biology: a resource guide for complex trait analysis. *Nature Rev. Genet.* **8**, 58–69 (2007)