have overlapping functions. RME-6, for example, has a Ras-GAP domain, whereas Rin1 has a Ras association domain, and Rabex-5 has a zinc finger. The role of the Ras-GAP domain in RME-6 is at present unclear, but this domain is conserved in RME-6 homologues from other organisms.

Apart from the immediate question of how broadly RME-6 functions in endocytosis, numerous other questions are raised by the discovery of RME-6. Does RME-6 interact with RAB-5-GDP that is bound to GDI, as indicated by *in vitro* endocytosis assays? Does RAB-5-GTP interact directly with vesicle SNAREs on the coated vesicle to promote fusion? What are

the targets of activated RAB-5 that accelerate endocytosis? Despite these new questions raised by the discovery of RME-6, it is gratifying that the discovery of RME-6 helps RAB-5 fit the classic mould of a regulator of vesicular traffic, because it provides a mechanism to control RAB-5 during the initial stages of endocytosis. It will be exciting to see how this new discovery is used; short interfering RNA of RME-6 could provide a powerful new tool for studying endocytosis in higher eukaryotes. □

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On the bright side of microarrays

The lack of agreement between gene expression studies that use DNA microarrays is a prime example of the kind of problems that are associated with high-throughput data sets. Although the results have been mixed, several studies that directly compare different types of microarray platforms have shown significant variability when comparing across platforms. However, three studies published in the May issue of *Nature Methods* find that with standardized protocols for sample preparation and data analysis, microarray experiments can be reliable, even across platforms, for up to 90% of the genes studied.

Larkin *et al.* (*Nature Methods* 2, 337–343; 2005) performed a careful comparison between Affymetrix GeneChips and spotted cDNA arrays in identifying relative changes in gene expression in response to angiotensin II in a mouse model for hypertension. Using optimized conditions, they found that platform had no significant effect for 88% of the genes tested. One of the keys to obtaining concordant results was to use relative levels of gene expression (ratios) for comparison, because absolute levels of hybridization would be expected to vary between platforms. For the 10% of genes that showed different results between the two platforms, quantitative RT-PCR did not validate either platform, suggesting that the differences are probably due to incorrect annotation of the genes on the arrays, or the presence of splice variants.

Irizarry *et al.* (*Nature Methods* 2, 345–349; 2005) formed a consortium of ten laboratories to assess the contribution of cross-laboratory variability. They found that there could be significant variability between laboratories, even those using the same platform. Data from the best-performing laboratories, however, were consistent even across platforms.

Bammler *et al.* (*Nature Methods* 2, 351–356; 2005) also compared data between laboratories using different platforms, and developed a

Image of a two-colour hybridized microarray. Yellow spots are positions where there are roughly equal levels of reference (green-labelled) and sample (red-labelled) RNA binding to the arrayed DNA probe. Red spots represent RNAs that are increased with respect to the reference and green spots indicate decreased expression. Image courtesy of John Matese, Princeton University.

series of standard protocols for data analysis and sample preparation that could reduce the cross-laboratory variability. These studies show that it is not necessarily the microarray technology itself that is problematic, but more how it is used.

Now that genomics is providing the parts list, a major challenge for cell biology is to understand how networks of genes function together to perform a given cellular function. The first step is to identify the network, and this will require the compilation of large-scale data sets. Although significant hurdles remain, it now seems possible that with standardized protocols and approaches, community-wide gene expression networks can be generated using current DNA microarray technology.

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