Progress in gene expression profiling by the introduction of metagenes

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Identification of toxic mechanisms by test compound-induced gene expression alterations is one of the major topics in current toxicological research (Ellinger-Ziegelbauer et al. 2008; Yamauchi et al. 2011; Bolt et al. 2010; Shimada et al. 2010; Adler et al. 2011; Heise et al. 2012). Also, a great deal of effort has been invested to optimize cell systems for gene array analyses in vitro (Godoy et al. 2009, 2010a, b; Zellmer et al. 2010; Hoehme et al. 2010). Recently, Schmidt and colleagues have introduced a technique that substantially facilitated the understanding and biological interpretation of complex gene expression profiles (Schmidt et al. 2008, 2009a, b, 2011, 2012): the metagenes of biological motifs. The authors observed sets of highly correlated genes in breast cancer tissue. Interestingly, these sets belonged to specific biological motifs, for example the proliferation metagene or a metagene of genes associated with the oestrogen receptor. Of particular interest are the newly discovered B- and T-cell metagenes that indicate an infiltration of the tissue with immune cells. However, the presence of normal tissue can also be identified by a ‘normal-like metagene’. Further studies have reported that the mechanoactivity of tumour cells (Martin et al. 2012), stem cell properties (Lee et al. 2010), glycerophospholipid profiles (Cadenas et al. 2010) and apoptosis sensitivity (Petry et al. 2010) can be reflected by specific profiles of gene expression.

Metagenes consist of sets of 30–100 genes and are usually calculated as the normalized mean of these genes. However, the analysis of such relatively high numbers of

genes is laborious and expensive, a fact that becomes particularly relevant when the analysis is not performed by gene array but instead using qRT-PCR. The analysis of such high numbers of genes may not be necessary, as the genes within a metagene are highly correlated and contain redundant information. A recent study that aimed to reduce this complexity showed that analysis of a single gene (IGKC) can be as powerful in diagnosing B-cell infiltration as a metagene contains 60 individual genes (Schmidt et al. 2012). Another recently published study also contributed to metagene analysis by developing tools for statistical analysis of pre-clustered gene sets (Kammers et al. 2011). In addition, the selection of genes with a wide dynamic range or genes with particularly high expression differences has also been described (Hellwig et al. 2010). This offers the advantage that even high analytical variability does not compromise the interpretation of data. Although these developments have been made mostly in the field of cancer research, they may also be helpful for gene expression studies in toxicological research.

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