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Toxicoproteomics: learning to walk before it can run

The genomics revolution has spawned a new lexicon of 'omics' terms, each representing a technology either claiming to be the next 'big thing' or, more realistically, claiming to complement those already in place. Toxicoproteomics can be regarded as the daughter of toxicogenomics and proteomics. It enters an uncertain world, its parents not yet being fully established as high value contributors in the world of pharmaceutical R&D. However, toxicoproteomics has potential; as long as it doesn't claim it can run before it can walk.

The study of proteins, rather than genes or messenger RNA, has appeal because it is the proteins that do most of the work in (and out of) the cell, as well as comprise much of the structural components of cells, tissues and organs. However, unlike DNA and RNA, which are relatively simple chemicals to work with, proteins are highly heterogeneous both in their primary composition as well as their potential for secondary modification (e.g. glycosylation and phosphorylation). This heterogeneity has created many technical hurdles to the study of the 'proteome'. As proteomics (and toxicoproteomics) sets out to understand the biological significance of changes in the proteome it is important that the proteome can first be resolved and then the individual components be characterized. Currently, technologies have been developed that go some way to achieving these objectives. Resolution of the proteome can be achieved through approaches such as two-dimensional (2D) gel electrophoresis. However, the heterogeneity of size and physical properties (the isoelectric point in this case) requires a large number of gels to be run to attempt to resolve the proteome of any biological sample (and this is assuming suitably sensitive detection methods are available). Basically, 2D gels can identify changes in protein composition but cannot address the biological meaning of the changes. To even attempt to do this, the identity of the 'changed' proteins needs to be determined. This can be done by subjecting individual protein spots on the 2D gel to MS to determine protein or peptide sequence followed by the analysis of this sequence against protein databases.

Armed with the knowledge that an identified protein has changed in amount or composition in a sample, compared with other proteins, one might be able to form a hypothesis as to the cause and consequences of such a change. However, in many cases this is going to be a speculative hypothesis that will require the development of much corroborating information. An alternative would be to forego the mechanistic approach (at least temporarily) and focus on associations. Without understanding the biological mechanisms at play, one might be able to associate certain changes with a biological outcome. Although intellectually less satisfying, it is probable that the young field of toxicoproteomics will initially develop along these lines.

Pharmaceutical executives like to see their technology investments pay off (in the short term as well as in the long term). To mature into a hypothesis and mechanism-based science, proteomics and toxicoproteomics will probably have to demonstrate their use in the application of specific phenomenological problems. This will be the walk – the run will come as the technology, databases and analytical tools gain more sophistication.

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The feedback cycle of conventional and virtual screening

Developments in virtual screening methods are helping to establish these computational techniques as an important complement to conventional screening in the drug discovery process [1]. There are, however, several practical aspects to their application.

For the foreseeable future, it seems inevitable that we shall require a biological assay to test compounds. The scoring functions used by the computational methods are not sufficiently reliable to provide accurate predictions of potency. It is also

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