INVITED COMMENTARY

Invited Commentary on “Potential Circulating Biomarkers for Abdominal Aortic Aneurysm Expansion and Rupture - a Systematic Review” by Urbonavicius et al.

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The systematic review by Sigitas Urbonavicius et al. addresses an important but poorly covered area of vascular research. The identification of biomarkers for AAA would be an important step towards simplifying diagnostic testing, determination of rupture risk, enhancing post-operative follow-up in patients following endovascular repair, and, most importantly, identifying the pathophysiological processes underlying aneurysm genesis and subsequent expansion.

Urbonavicius et al. provides comprehensive documentation of the previous research in this area to date. When examining the data presented it is clear that none of the potential biomarkers reviewed could be used as a diagnostic test for AAA. Some of the papers reviewed give the results of analyses of their biomarkers as diagnostic tests and where these are given they demonstrate the deficiency of the studied biomarker in this area. Often the most informative method for comparing the utility of a biomarker is the area under the receiver-operator characteristic curve and these figures are notably absent in the literature on AAA (and to our knowledge have only been quoted once).¹

Traditionally the hypothesis based research approach adopted by the authors of the studies examined in this review has been considered to be the most valid method for studying disease. Arguably, this ‘hypothesis based’ approach has usually been adopted for reasons of simplicity — until recently it has not been possible to perform studies examining multiple biomarkers at once. However, with recent technological advances it is now possible to examine the entire proteome or selected sub-sections of it at once in more descriptive proteomics experiments. Whilst descriptive research has often been dismissed in the past,² in areas such as biomarkers for AAA where, as shown in this review, hypothesis based approaches have largely failed, descriptive proteomic approaches are an attractive alternative.

Proteomics is the large scale study of proteins. There are multiple different experimental strategies that can be adopted to perform proteomic analyses. Two-dimensional gel electrophoresis³ has traditionally been used but is slowly becoming superseded by mass-spectroscopic profiling. Through laser desorption-ionisation time-of flight mass spectroscopic techniques mass/charge spectra of almost entire proteomes can be determined very quickly. By comparing the spectroscopic profiles seen in those with disease to healthy controls a disease profile can be reconstructed. Often these profiles will utilise multiple mass/charge peaks and can result in impressive diagnostic statistics for a particular...
set of biomarker peaks with areas under ROC curves approaching 1.45. The disadvantage of mass-spectroscopic techniques is the inability to determine the identity of a mass/charge peak directly. Because of this whilst biomarkers based on mass-spectra are relatively straightforward to identify they are therefore of limited clinical utility. Tandem mass-spectroscopy has the potential to directly determine both initial spectra and identify the protein underlying the spectroscopic mass/charge peak6 but there are very few successful reports of biomarkers identified using this technique. Other technologies that may facilitate the search for AAA biomarkers are difference gel electrophoresis.7

An important consideration in the conduct of large-scale descriptive research studies is data analysis. The field of bioinformatics has rapidly expanded in line with recent biotechnological advances. Bioinformatics is the application of computer technology to biological information and permits the application of complex, often iterative analyses to the large amounts of data produced by proteomic techniques. It may also facilitate the analysis of hypothesis based experiments by permitting the analysis of biomarker panels through not only standard multi-variate statistical approaches but alternative methods such as dimension reduction techniques8 and genetic algorithms.9 If proteomic approaches are to be used in the future the need for bioinformatic support must be considered.

In the future it is likely that research in this area will adopt dual approaches of descriptive proteomics studies and hypothesis based approaches. In the near future several genome-wide association studies of AAA are to be completed and the results of these are likely to generate new areas of research and the gene-products associated with the genetic variants associated with AAA are candidate biomarkers to be tested. The generation of proteomic profiles of AAA at different stages of development has the potential to determine whether there are different pathological processes occurring in small and large AAA.

References

2 Marincola FM. In support of descriptive studies; relevance to translational research. J Transl Med 2007;5:21.