Plasma peptidome: A new approach for assessing thrombotic risk?

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Svensson et al. (1) report in this issue (see related article beginning page 725) that the proteomic analysis of plasma samples from a large family with type I protein C deficiency was able to discriminate those members who presented with deep vein thrombosis before the age of 40 from those who did not. The analysis was carried out by surface-enhanced laser desorption/ionization (SELDI) TOF (time-of-flight) mass spectrometry (MS), a form of MS in which protein samples are pre-fractionated on a chemically selective metal chip surface (in this particular case, a negatively charged surface) before matrix-assisted laser desorption/ionization (MALDI) analysis.

The SELDI-TOF MS technique has generated intense interest as well as controversy over the last few years in the area of thrombophilia diagnosis. The seminal 2002 article of Petrocoin et al. (2) described how the highly complex mixture of peptides found in one training set of serum samples could be used to generate an iterative searching algorithm that was capable of detecting ovarian carcinoma with 100% sensitivity and 95% selectivity in a masked test set of sera containing 50 women with the cancer and 50 women with benign ovarian disease. The reason Svensson et al. give for their decision to investigate the use of the technique as a biomarker of thrombophilia arose from the notion that the low-molecular-weight serum or plasma proteome (i.e. peptidome) may reflect underlying pathological states. They also hypothesized that the approach may lead to the discovery of unique peptide(s) that would help them identify the unknown gene, which they have previously established in modifying the type 1 protein C phenotype of either the early onset patients or their unaffected kindred. The results appear to support their working hypothesis, since the approach was able to discriminate retrospectively those individuals with covert thrombophilic tendencies from other family members with the same genetic background.

If the potential of this approach is now established, the question then arises as to whether MALDI-TOF-MS or SELDI-TOF-MS may also be useful for detecting the thrombophilic state in the wider, genetically disparate, population in which the predisposing factors may be acquired as well as genetic. One prerequisite for such an approach to be successful is that the plasma peptidome of healthy individuals is stable and unique. Nelsestuen et al. (3) recently reported that this is in fact the case, for which reason they proposed that changes in the characteristics of an individual profile has the potential to be used as a sign of current or future disease, even when these differences remain within the range for healthy individuals. This is important since the algorithm is generated by considering the totality of often slight changes of expression of each of a large number of peptides – one way of looking at this is in differences in pattern when the peptide profiles are viewed as e.g. heat maps (4). Another consideration is the aptness of the mechanism by which the peptidome is generated, namely through proteolytic degradation of larger proteins (5). This mechanism is, of course, in complete harmony with the cascade of proteolytic activation and feedback loops that occur during blood clotting along with the release of low-molecular-weight platelet products. Other contributors to thrombophilia such as inflammation (6) and cancer (4) also generate a distinctive peptidome. In addition, the richness of the peptidome (around 5,000 peptides/proteins with masses less than 20 kDa [7]) gives good reason to believe that the approach has the power to produce a fingerprint profile indicative of thrombotic risk and to merit further investigation.

References