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EDITORIAL

Where Do Omics and Markers Go Next?

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This special issue includes articles that are beginning to use emerging new technologies to address mechanisms of injury in stroke and that can potentially provide biomarkers for those injuries. The new technologies have become very powerful, and the best uses of each need to be carefully considered and applied thoughtfully to the clinical problems of stroke.

Though genetics has revolutionized many areas in medicine, it has yet to provide new insights into the pathogenesis of stroke. A number of genes have been associated with cardiovascular disease, including important ones for hypertension, atrial fibrillation, aortic aneurysms and others. One is hopeful as suggested by Markus that ongoing GWAS studies will provide new insights into the pathogenesis of ischemic stroke, cerebral aneurysms, and other cerebrovascular diseases; however, it seems likely that stroke is a multi-factorial, polygenic disease which will require precise clinical phenotyping to yield associated genes that will challenge the need to obtain large numbers of samples for each phenotype.

Phenotyping might be helped by clinical syndromic classifications, but it might also be helped by using blood biomarkers. One should consider each tissue source of a biomarker since it is likely to give different information depending upon the question asked. For example, Foerch suggests that rapid release of glial GFAP and S100B may provide a serum/plasma marker of intracerebral hemorrhage because of rapid astrocyte injury compared to slower astrocyte injury with ischemic stroke. This is an intriguing idea and one wonders whether hemorrhages associated with hypertension and hemorrhages due to amyloid angiopathy might be associated with different biomarkers. Thus, a variety of proteins released from astrocytes might provide ancillary or even better markers as addressed in the Feener study that might be specific for different diseases or mechanisms of injury. Thus, the cell source as well as temporal course may be helpful in understanding pathogenesis.

It is important to remember that astrocyte, neuronal, microglial, oligodendrocyte, and brain endothelial proteins can probably be detected in serum and could point to specific cellular injury. This degree of sophistication will certainly require state of the art proteomic approaches as addressed in part by the Kennedy article. A novel aspect of protein metabolism is addressed in the study of Ning and Lo who examined the degradation patterns of proteins following stroke treated or untreated with tissue plasminogen activator (tPA). They find that the proteomic degradation pattern is altered by tPA and thus points to a new field where a potential therapeutic effect can be assessed using virtually any biomarker including protein degradation. Protein degradation is of particular interest not only for the actions of tPA but also for MMP9 and other proteolytic enzymes that might be released following a stroke or activated within the blood during and following a stroke. This may be an extremely promising biomarker approach and also suggests that measuring downstream effects of possible treatments might help provide surrogate measures of drug efficacy that could then be correlated with clinical response.

The above idea is also strongly supported by the Montaner study. They found that tPA-treated patients had lower serum interleukin (IL)-6 and IL-8 levels compared to non-tPA-treated patients, whereas there were no changes in TNF-alpha or intercellular adhesion molecule (ICAM)-1. They noted that the patients who improved and those who

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re-canalized had the lowest IL-6 levels. These are extremely important findings since they show cytokine differences related to a treatment and clinical outcome. Such measures will help understand the effects of treatment and its mechanism. The data are interpreted to mean that tPA may decrease inflammation, but it could be that a smaller infarct produced lesser inflammation. The source of the IL-6 is of particular interest since it certainly is related to inflammatory cells, but one also wonders whether ischemic endothelium and brain might also account for the decrease in IL-6 related to tPA, which should decrease endothelial injury and decrease brain injury. Whatever the source, this cytokine could prove to be a valuable biomarker not only for tPA treatment but possibly others. This study also points to the fact that cytokines, chemokines, proteins, and other molecules measured in serum/plasma can come from one or multiple sources: the brain (all cells therein); endothelial cells; other organs including the liver, kidney, lung, GI organs, and others; and can come from inflammatory cells in the blood, platelets in blood and even the red blood cells. Measured levels are affected by the rate of secretion and uptake back into cells, rates of removal from the blood, and proteolysis within blood as pointed out by Ming and Lo. All of these factors, including the uncertain cellular sources make the measurements difficult to interpret. The bottom line is, however, if the findings are consistent, they can always be used as a biomarker for injury and/or treatment and/or mechanism.

The field of biomarkers has recently been expanded by the availability of array technology to assess mRNA, microRNAs, and other newly discovered RNA species. Measurements of RNA, however, are unique among the biomarkers since RNA biomarkers in blood almost certainly only reflect the intracellular contribution from inflammatory cells (like neutrophils, monocytes, lymphocytes), platelets (which is found in immature platelets), red blood cells (also in immature red blood cells) and any other circulating cells which could include progenitor cells (for endothelium and other organs), tumor cells, and possibly cells from various organs depending upon the disease state. The preponderant RNA, however, is from inflammatory cells, platelets, and red blood cells. This has led our group to pioneer the measurement of RNA in peripheral blood with the finding that panels of RNAs can be shown to correlate with the occurrence of ischemic stroke and the cause of ischemic stroke. This work has been extended by Jeyaseelan in this special issue as well as by others in the field like Vemuganti and colleagues who find specific microRNAs induced in the brain or blood following brain ischemia. The importance of these microRNAs is that they must be expressed within cells in the blood and likely play a role in RNA expression and protein synthesis by the inflammatory and immature platelets in the blood and could be useful biomarkers for specific mechanisms and possibly treatment targets themselves.

Inflammation, inflammatory cells, and Toll-like receptors (TLRs) are the topic of the Stenzel-Poore review. As pointed out, modulating TLRs can acutely worsen or improve stroke. In addition, pre-conditioning with TLR acting agents can also protect the brain against stroke. These studies are very important not only for the potential role of pre-conditioning to protect against stroke prior to surgery or other anticipated injury, but they also suggest that the status of TLRs before stroke could be important in determining whether a stroke will occur and how severe it might be. That is, TLR status could be a biomarker for the risk of having a stroke, a field unexplored in humans at least. Moreover, it is important to know which TLRs on which cells are mediating acute injury and pre-conditioning induced neuroprotection. If they are mainly on the inflammatory cells, this again points to the very important role of inflammation in potentially causing or worsening ischemic stroke. As the anti-ICAM trial showed, stimulating the immune system in humans unequivocally worsens stroke in humans. It is still unclear whether downregulating the immune system in humans with stroke will improve outcomes and, if so, what would be the safest and most likely method of immune system modulation to work?