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The role of the blood transcriptome in innate inflammation and stroke

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Abstract

Cerebrovascular disease is a major cause of death and disability, with a poorer outcome in patients having select risk factors including diabetes and hypertension. Risk factors and the state of cerebral ischemia-reperfusion associated with cerebrovascular occlusion are known to cause inflammatory changes. These events and the inflammatory state are reflected by transcript changes in various components of the blood and can be specifically measured. By defining these changes, new insight into cerebrovascular disease and its therapeutics is being achieved.

Keywords

cerebral ischemia; inflammation; gene expression; transcript; blood

Stroke

Stroke is a leading cause of death and long term disability with the majority of events due to cerebral occlusion.¹ The risk of cerebrovascular disease and stroke is higher in patients with cardiovascular risk factors² which are also strongly related to early brain injury and to poor outcome after cerebral ischemia.³ The mechanisms by which risk factors influence cerebral stroke are still not completely understood. For example, diabetes is associated with a series of vascular changes, including cerebrovascular atherosclerosis, endothelial dysfunction² and, importantly, a chronic state of low-grade inflammation.⁴

Inflammation

Cerebral ischemia initiates a complex process in which inflammation contributes to stroke-related injury with mobilization and activation of leukocytes. This results in excessive production of reactive oxygen species and oxidative tissue damage.⁵ Involvement of inflammatory reactions in the ischemic injury processes has been previously shown.⁶ Specific inflammatory mediators including adhesion molecules and cytokines contribute to the inflammatory cascade. In cerebral ischemia-induced brain injury, cytokines such as TNF- α , IL-1 β , IL-6 are produced by a variety of activated cells types including endothelial cells, neurons, platelets, monocytes, macrophages and fibroblasts.⁷ It has been shown that focal ischemia induces elevated microvascular expression of various inflammatory mediators including TNF- α , IL-1 β , IL-6 and iNOS and this expression is transcriptionally regulated via the MEK/ERK pathway.⁸ Multiple studies have shown that one of the

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Conflicts of interest

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mechanisms of diabetes-enhanced brain injury is oxidative stress caused by hyperglycemia⁹ and that, in this setting, oxidative stress is enhanced by elevation of expression of NAD(P)H oxidase and lipid peroxidation in ischemic cerebral tissue.¹⁰

The blood transcriptome

Developments in the fields of genomics, transcriptomics, and proteomics have the potential to further define complex diseases; however, in the study of stroke, there has been variable data generated. While proteomics holds the promise of large-scale, identification of individual proteins, current knowledge is hampered by limitations including cost of high-throughput analysis and difficulty in identification of low abundant proteins.¹¹ Conversely, the human genome-wide association studies have analyzed 500,000 SNPs in large numbers of subjects and genetically defined diverse diseases and risk factors.^{12–14} There has been more limited studies of large-scale gene expression profiling in comprehensive cohorts focused on risk factors for atherothrombotic disease;¹⁵ but such findings have been reported in oncological studies^{16–19} demonstrating prediction of oncological prognosis and classifications for pre-cancerous disease states.²⁰ While there is less data in vascular disease, there is growing information concerning the transcriptome in this setting. For example, gene expression from leukocytes in patients with sickle cell disease is consistent with increased oxidation and inflammation.²¹ However, a major limitation of previous cardiovascular gene expression studies is their small size and the inherent problem of obtaining the appropriate tissue needed for analysis.

Another area of gene expression that is being directed towards study of blood derived transcripts is the field of micro RNAs (miRNAs); recently discovered small RNAs that play an important role in the negative regulation of gene expression by suppressing protein translation. The expression of many miRNAs is usually specific to a tissue or developmental stage, and the miRNA expression pattern is altered during the development of many diseases.^{22, 23} Specifically, they are miRNAs that participate in the regulation of various biological functions in numerous eukaryotic lineages, including mammals.^{24–26} More than 800 human miRNAs have been cloned with bioinformatic predictions indicating that mammalian miRNAs can regulate approximately 30% of all protein-coding genes.^{27–29} Micro RNAs have been found in whole blood and may reflect disease; they are known to influence redox sensitive enzymes and, hypothetically, could be altered in an inflammatory setting.

Gene expression and neurological disease

Recently, large-scale gene expression profiling has been conducted on stroke and spinal cord injuries.^{30–33} Globally, such studies provide insights into coordinated patterns of gene expression occurring due to injury and provide insight into the relationship between neurodegenerative and neural repair processes after injury. Specific transcript-based molecular signals have shown that, post-stroke, angiogenesis begins within hours of initial cerebral ischemia, followed by message demonstrating vascular growth factors and growth factor receptors and, later combinations that promote endothelial cell division and stabilization.^{30, 31} Importantly, there appears to be overlap in molecular signaling between post-stroke angiogenesis and neurogenesis with inflammatory transcript changes occurring after injury. In addition to defined pathophysiology, aging itself appears to be associated with a specific gene expression profile which could exacerbate initial injury and impair neural reorganization after stroke.³⁰

Stroke and the blood transcriptome

Several studies have linked stroke and gene expression (See Table 1). The monocyte transcriptome is believed to bridge genetic and non-genetic regulators of disease³⁴ and the blood transcriptome has been used to evaluate the outcome of pathophysiology of stroke. In animal models changes in gene expression in cerebral tissue has been compared to blood.^{35, 36} Specifically, blood miRNAs have been studied as biomarkers for brain injury and it has been shown that selected blood miRNAs may correlate with miRNA changes in the brain. In addition, many of the messenger RNA (mRNAs), previously shown to be regulated in brain and blood after brain injury, are related to changes in miRNA expression.³⁵

In clinical studies, gene expression levels in circulating mononuclear leukocytes from acute ischemic stroke patients have been investigated.³⁷ In one study, it was found that while transcriptome analysis did not identify significant changes between circulating mononuclear cells from patients 24 hours after stroke, there were notable changes as compared to healthy control subjects specifically in inflammatory response genes.³⁷ Another study of peripheral blood mononuclear cells demonstrated that, in patients with acute ischemic stroke, there were altered gene expression profiles consistent with an adaptive response to central nervous system ischemia.³⁸

Another small study has shown that genes induced at 2 to 24 h after stroke were expressed mainly by polymorphonuclear leukocytes and to a lesser degree by monocytes.³⁹ These genes included: matrix metalloproteinase 9, S100 calcium-binding proteins P, and coagulation factor V. The fold change of these genes varied from 1.6 to 6.8 and, overall 18 genes correctly classified 10/15 patients.³⁹ Another small clinical study showed that peripheral blood miRNAs and their profiles can be developed as biomarkers in diagnosis and prognosis of cerebral ischaemic stroke.⁴⁰ This study found that dysregulated miRNAs may be detectable even after months from the onset of stroke. Specifically, they found that miRNAs implicated in endothelial/vascular function, erythropoiesis, angiogenesis and neural function were differentially expressed as compared to normal control subjects.⁴⁰

Potential treatment targets for innate inflammation, transcriptome, and stroke

Specifically targeting gene expression to control disease is a field in its infancy but holds much promise. Currently used drugs are already known to regulate transcription. An example are the statins; drugs known to have diverse effects on transcription.^{41, 42} A second example is dipyridamole, an antithrombotic^{43, 44} and vasodilator that has been shown to have antioxidant properties.^{43, 44} The importance of oxidative stress in cerebrovascular disease is well established and dipyridamole suppresses reactive oxygen species (ROS) formation, improving cellular redox status.^{43, 44} As with statins, it has been hypothesized that some of this change may be mediated by transcriptional activity.^{45, 46}

As with oncological studies, the use of the blood transcriptome holds promise in diagnosis and this has begun to be explored. A comparison of different stroke etiologies (cardioembolic vs. atherosclerotic) showed that seventy-seven genes differ at least 1.5-fold, and at least 23 genes differentiate the two types of stroke with at least 95.2% specificity and 95.2% sensitivity for each.⁴⁷ This study found that genes altered in cardioembolic stroke are expressed in neutrophils and modulate immune/inflammatory responses to infectious stimuli.⁴⁷

Conclusion

The pathophysiology involved in cerebrovascular ischemia is complex but the role of inflammation due to innate problems such as cardiovascular risk factors is well established. The major limitation of current and future studies in the area of transcriptomics, inflammation and cerebrovascular disease is the study size coupled with the ease involved in measuring transcripts and problems with multiple testing. In addition, while studies utilizing blood to study gene expression should be larger and more powerful in the future; the source of RNA may also drive the results. Whole blood isolation is simpler than leukocyte isolation and, thus, being widely studied but the assumption that any source of RNA from the blood is equivalent is likely not true.⁴⁸ While it has become clear over the past few years that information obtained from gene expression data is vital to discovering new mechanisms for disease and has aided in the diagnosis and treatment in the field of oncology; far less is known related to cerebrovascular disease. The inherent complexity of cerebrovascular disease makes the vast amount of data available from transcriptomics methods both exciting and daunting in the goals of diagnosis and treatment.

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Figure 1.

The relation between the blood transcriptome and cerebrovascular ischemia. In the setting of stroke/ischemia-reperfusion, cytokines, chemokines, and inflammatory mediators are released leading to transcription of mRNA and miRNA in circulating cells. Some of these cells release exosomes containing miRNA. Gene expression changes due to stroke are reflected in the blood transcriptome and may mediate cerebral inflammatory changes. (PDMP; platelet-derived microparticles, mRNA; messenger RNA, miRNA; microRNA, CNS; central nervous system)

Table 1

Summary of studies: cerebrovascular occlusion and the blood transcriptome

Study	Type of Transcript	Source	Primary Finding
Liu et al ³⁵	Rat miRNA	Brain, whole blood	Correlation between rat and whole blood miRNA in the setting of stroke.
Xu et al ⁴⁷	Human mRNA	Whole blood, platelets, monocytes	Type of stroke reflected in blood transcriptome
Grond-Ginsbach et al ³⁷	Human mRNA	Mononuclear cells	Acute stroke patients have a distinct transcriptome
Moore et al ³⁸	Human mRNA	Mononuclear cells	Stroke is associated with a specific transcript
Tang et al ³⁹	Human mRNA	White cells	Transcript changes are distinct 24 hours after stroke
Tan et al ⁴⁰	Human miRNA	Whole blood	Transcript profile is distinct in a younger stroke population