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Neurosci Lett. Author manuscript; available in PMC 2012 June 27.

Published in final edited form as:
Neurosci Lett. 2011 June 27; 497(3): 213–217. doi:10.1016/j.neulet.2011.03.019.

Use of peripheral blood transcriptome biomarkers for epilepsy prediction

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Abstract

There are currently no predictive methods to identify patients who suffered an initial brain injury and are at high risk of developing chronic epilepsy. Consequently, treatments aimed at epilepsy prevention that would target the underlying epileptogenic process are neither available nor being developed. After a brain injury or any other initial precipitating event (IPE) to the development of epilepsy, pathological changes may occur in forms of inflammation, damage in the blood brain barrier, neuron loss, gliosis, axon sprouting, etc., in multiple brain areas. Recent studies provide connections between various kinds of brain pathology and alterations in the peripheral blood transcriptome. In this review we discuss the possibility of using peripheral blood transcriptome biomarkers for the detection of epileptogenesis and consequently, subjects at high risk of developing epilepsy.

Biomarkers of epileptogenesis

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. From the genetic perspective, epilepsy is a complex of neurological disorders characterized by similar phenotype (seizures). Epilepsy may be divided into *familial epilepsy* caused by intrinsic genetic factors such as mutation in a particular gene or combination of certain genetic traits; and *acquired epilepsy* originating from an initial precipitating event (IPE) often resulting in status epileptics (SE) and a high likelihood of recurrent seizures or chronic epilepsy. Some of the common causes of acquired epilepsy are hypoxic-ischemic encephalopathies during the neonatal period and/or early infancy, febrile seizures during late infancy and early childhood, stroke and degenerative diseases in older adults, central nervous system (CNS) infections, drug use and traumatic brain injuries in all ages. Perhaps the major cause of acquired epilepsy is a traumatic brain injury (TBI) characterized by a high occurrence of residual deficits. While primary brain damage occurs immediately due to external forces, secondary damage develops over the subsequent hours and days, and involves multiple mechanisms including glutamate and excitatory amino acid release, free-radical generation,

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calcium-mediated damage, gene activation, mitochondrial dysfunction, and inflammatory processes [45].

After initial precipitating injuries (such as trauma), up to 25% of the patients develop posttraumatic epilepsy with the latent (silent) period varying in duration [1, 26, 27]. The foregoing suggests that the development of epilepsy involves both IPE and a genetic predisposition to developing epilepsy. Numerous studies of the epileptic brain indicate that when clinical seizures occur, the brain has already undergone multiple irreversible changes, and most physicians accept that current treatment of epilepsy is mostly symptomatic. Therefore, there is a critical need for treatments that arrest epileptogenesis. The clinical challenge is in identifying the subset of patients with ongoing epilepstogenesis that will benefit from interventions designed to block adverse plasticity leading to epilepsy (antiepileptogenic treatment). At the present time, no clinically accepted biomarkers predictive of the likelihood of developing epilepsy after IPE are available. Well-recognized histopathologic markers of epilepsy become discernible only after the epileptic state is already established.

Early diagnosis and intervention are critical for efficient treatment of any disease, including epilepsy. Previous clinical trials have failed to provide positive recommendations for preventive therapy and they used a traditional approach of splitting patients with treatment and without treatment, disregarding the selection of patients at high and low risks of developing epilepsy [42, 63]. Finding valuable biomarkers that indicate the existence of unrecognized processes leading to the occurrence of disease are critical for early intervention. The necessity for earlier treatment of epileptic patients was raised in several recent publications [16, 63]; however, the absence of valuable biomarkers permitting the identification of subjects at high risk of developing epilepsy after IPE and the prediction of seizure occurrence hampers the progress of these studies.

Currently, there are electrographic and imaging biomarkers of epileptogenesis. One of the electrographic markers of epileptogenesis at the network level is the occurrence of EEG spikes which represents paroxysmal discharges of neuronal populations [15]. Interictal spikes are widely accepted diagnostically as a sign of epilepsy, but little is known about the reasons for the presence of interictal activity in the epileptic brain. As it was described in kindling and other models of epilepsy, EEG spikes appear in multiple brain regions before the occurrence of spontaneous seizures [2, 6, 28, 34] and may be a valuable biomarker of epileptogenesis. It is hypothesized that spikes may guide sprouting axons, increase and sustain the strength of the synapses formed by sprouted axons, and alter the balance of ion channels in the epileptic focus, ultimately provoking seizures [60]. However these data have not yet been proven in humans after an insult to the brain and prior to development of chronic epilepsy.

Pathological high frequency oscillations (pHFOs) represent another possible marker of epileptogenesis. pHFOs were described more than ten years ago in hippocampal-entorhinal circuitry in epileptic patients and animals [7, 8]. It was hypothesized and later supported by experimental evidences that these brief (15–30 ms) high frequency (250 to 500 Hz) oscillations are generated by local clusters of pathologically interconnected neurons (PIN-clusters) [9, 11]. The size of the area of pHFOs generation depends on at least two conditions: strength of local excitatory connections and strength of recurrent inhibition. Small discretely localized areas of interictal pHFOs generation remain fixed, and the electrophysiological pattern of pHFOs is unchanged over several weeks to months, indicating that pHFOs reflect abnormal discharges from a fixed pathologic substrate imbedded within less epileptogenic tissue [10]. pHFOs are generated in local brain seizure generating zones [32, 59, 68] that indicates their potential role in seizure genesis making

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them a useful and highly predictive marker of epileptogenesis and recurrent seizure occurrence. However, the necessity for implantation of electrodes into the brain limits clinical application of electrographic biomarkers of epileptogenesis.

Magnetic resonance imaging (MRI) methods may provide an additional means of detecting epileptogenesis. Studies of thalamus temporal evolution after pilocarpine induced SE revealed a blood-brain barrier (BBB) breakdown two hours after the status that began disappearing by six hours [51]. Longitudinal MRI studies of the intrahippocampal kainic acid (KA) model detected both an immediate neurotoxic effect of KA injection and a follow up gliosis occurring 2 weeks later [5]. In the kindling model of epileptogenesis, the increased signal was observed in the rostral ipsilateral regions of CA1 and dentate gyrus in kindled but not in control rats [33]. However, although imaging and electrographic biomarkers predictive of the likelihood of developing epilepsy after IPE have been described, their implementation into routine clinical practice to evaluate patients at risk is hampered for at least two reasons. These are the high costs of imaging tests and the invasive nature of the procedure for identification of existing electrographic biomarkers. This again emphasizes the need for the identification of reliable and robust peripheral biomarkers of epileptogenesis. If available, such biomarkers would be a convenient tool for non-invasive identification of patients at risk of developing chronic epilepsy.

As defined, peripheral neurological disease biomarkers should reflect disease-specific changes of biological processes that can be consistently applied to different individuals with that specific condition. Thus, biomarkers should provide comprehensive information with regard to predicting specific features of a disorder, evaluate risk for individual subjects, aid diagnosis in clinically similar/overlapping conditions, and help with the development of new treatments. Furthermore, biomarkers should be inexpensive and easy to apply.

Highly inclusive methods of investigations such as studies of the whole genome and proteome are most promising when attempting to identify such biomarkers. In particular, microarray-based technology permitting the analysis of whole transcriptome in a single experiment may be an efficient approach to discover biomarkers associated with the disease [38].

Peripheral blood transcriptome as a source of biomarkers of neurological diseases

Recently published data support the idea that blood gene expression profiling can provide surrogate markers for neurologic diseases. The feasibility of this approach was demonstrated at several levels [47]. The method of choice in these studies is a microarray-based technology that proved to be an efficient tool for the analysis of brain function in health and disease (refer to Karsten, et al. 2008 [38]). Its main principle is based on the reversed hybridization of fluorescently labeled experimental and control total RNA to oligonucleotide probes representing near whole transcriptome immobilized on the surface of a microarray glass slide.

An emerging application in this field targets identification of early disease biomarkers based on gene expression profile from peripheral blood transcriptome mainly represented by leukocytes [4, 48, 61, 62]. More than 20% of brain transcripts were found to be co-expressed in the peripheral blood monocytes of both human and rats when Affymetrix microarrays were used [52]. Such remarkable overlap in gene expression response of the blood and brain cells may be due to the genetic component or injury leading to the disruption of BBB. An example of the genetic constituent may be a mutation in a specific gene leading to a cascade of regulatory events affecting expression of the same downstream genes in both tissues.

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Injury evoked transcriptome response may be explained by the exposure of the blood cells to the local tissue damage, pathological changes in BBB permeability due to SE and/or inflammatory response. Continuous blood flow ensures that a large number of blood cells will be exposed to the environment of the local damage, further increasing specific gene expression response in the whole blood transcriptome. Although mechanisms of blood-brain transcriptome co-regulation still remain speculative, the phenomenon itself was illustrated by several recent findings that some of the "traditionally brain specific" and disease-associated genes may also be altered in the blood transcriptome in a similar pattern.

Coppola et al. [13] identified significant alterations in progranulin expression level in the leukocytes of patients with sporadic and familial neurodegenerative dementias. Progranulin was originally identified as a gene responsible for some cases of familial frontotemporal dementia (FTD; [3, 14]. While highly elevated expression of Progranulin was found in the blood of patients with clinically diagnosed FTD and Alzheimer disease [13], low expression in the blood predicted the presence of Progranulin mutations [13, 22]. Patients with Friedreich's ataxia, a rare neurodegenerative disease caused by the mutations in Frataxin gene, demonstrate significantly reduced Frataxin expression in the peripheral blood that was proposed as a diagnostic test [50]. Our recent study identified multiple gene expression changes specifically present in the motor neuron surrounding glial cells in the mouse models of Amyotrophic Lateral Sclerosis [41]. Surprisingly, some of these changes were also found in the blood of presymptomatic SOD^{G93A} mice suggesting that prognostic tests for motor neuron disease using peripheral blood transcriptome are feasible [41].

Second, multiple studies have established a direct link between neurological disease and changes in the blood transcripome. Some of the examples include identification of disease relevant genes in the blood of patients with Alzheimer's disease [25, 35, 46, 48], Parkinson's disease [54], Hungtington disease [4], Amyotrophic Lateral Sclerosis [43, 53], multiple sclerosis [23], migraine [29], autism [24, 64], schizophrenia [49, 66], bipolar disorder [31, 39], post-traumatic stress disorder [55], chronic fatigue [67], Tourette syndrome [44, 61], and various types of acute brain injury such as ischemic stroke and seizures [58, 64, 69]. In addition, although a large number of genes regulated in the peripheral blood might be common to many types of injury (e.g. stress related genes), there are sets of genes specific to a particular type of brain injury [56, 57, 62]. Robust gene expression changes in peripheral blood monocytes were identified in adult rats as soon as 24 hours after ischemic stroke, intracerebral hemorrhage, kainate-induced SE, hypoxia, and insulin-induced hypoglycemia [56, 57]. This combined evidence demonstrates that an altered state of the central nervous system is associated with specific profiles in the peripheral blood, and this association clearly depends on the disease stage, particular etiology, genetic component and other factors.

Nevertheless, most gene expression changes identified in blood are associated with a fully developed disease phenotype and almost no studies of blood transcriptome in presymptomatic animal models or patients have been reported, raising the issue of whether the identified genes may be useful as clinical predictive biomarkers of the disease. Indeed, in spite of these multiple efforts, often inconsistent results point to only potential use of peripheral blood biomarkers mainly applicable to the prediction of disease progression or therapeutic response [12, 65]. No clinical peripheral blood transcriptome (PBT) biomarkers currently exist for early neurological disease diagnosis that can be used prior to any notable clinical phenotype. Consequently, this prevents any attempts of early treatment using disease modifying drugs.

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Epilepsy, BBB and peripheral blood

Mounting evidence suggests that inflammation is an important contributing factor of epileptogenesis. CNS inflammation is often associated with a disruption of BBB, exposing neuronal and astrocytic cells to blood cells and environment [20, 21, 40]. Recent studies in the mouse models of chronic seizures point to the direct pathogenic link between leukocytes and seizure generation [21, 40] making it plausible to speculate that global profiles of gene and protein expression in the peripheral blood may be altered by inflammatory processes in epileptogenic brain. In addition, pathological lymphocyte accumulation was noticed in the patients with refractory epilepsy [21, 30], further supporting the hypothesis of seizure and blood co-regulation. Indeed, several recent publications [56, 57] and the data from our ongoing projects [36, 37] point to the presence of global gene expression changes in the peripheral blood transcriptome in response to the underlying epileptogenic processes.

Many experimental models of SE exist in which a significant fraction of animals develop spontaneous seizures and pathology resembling human temporal lobe epilepsy (TLE, [17–19]. While the onset of epilepsy following the IPE occurs months or years later in humans, it takes several weeks to months in rodent models. Even in a homogeneous population of rodents, not all develop epilepsy after SE or TBI. These observations point to possible changes in the gene expression profile of animals during the latent period of epileptogenesis when the mechanisms leading to epilepsy are at play immediately following the IPE. The sequence of events somehow differs in those animals that do not eventually develop epilepsy and may possibly reflect silent but more aggressive epileptogenesis in the subjects with later occurring epilepsy. This observation became a main premise of our ongoing attempt to identify peripheral blood transcriptome changes associated with silent epileptogenesis during the latent period [36, 37]. To avoid identification of the potentially biased model-specific gene expression changes, both local seizures (KA) and systemically (pilocarpine) induced epilepsy models were used. In our experiments, peripheral blood transcriptome was investigated prior to the injection (base line), 24 h, 48 h, 72 h and 1 week after SE but prior to the development of chronic seizures. Animals with seizures are identified several months later using 24 h video monitoring and electrophysiological measurements. Accumulated samples from two different models and several time points permit various types of microarray data analysis. The following questions can be asked: are there any global differences in the peripheral blood transcriptome between the animals developing seizures and animals that fully recovered after initial SE? Does the transcriptome profile changes significantly before and after SE? Is it associated with later occurring seizures? What is the time course of these differences? Are identified gene expression differences present in both models or represent specific mechanisms of induced seizures? Is there transcriptome profile normalization at later time points? These and other equally important questions demand detailed and lengthy examination, though preliminary analyses appear hopeful. The obtained microarray data point to distinct groups of genes associated with animals that later develop seizures [36, 37]. This supports the hypothesis that the molecular signature preceding the development of epilepsy is present in the peripheral blood transcriptome, and this in turn may allow the development of a prognostic test that can be used to both screen and diagnose potential epilepsy patients, and to prospectively evaluate the effectiveness of antiepileptogenic therapy. However, more work is required in order to fully demonstrate the usefulness of this approach.

Acknowledgments

Supported by NINDS R43NS060476.

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