Galectin-3, an important yet unexplored molecule in drug resistant epilepsy

Epilepsy results in patients experiencing recurrent unprovoked seizures over time. WHO has determined that epilepsy accounts for 1% of the global burden of disease. In about 30–40% persons with epilepsy (PWE), the seizures cannot be controlled with drug management. This epilepsy is referred to as intractable epilepsy or drug resistant epilepsy (DRE).[1] Surgery is one option for such patients; however, about one-third of these patients continue to have seizures even after surgery. Therefore, there is an urgency in trying to understand the mechanisms of epileptogenesis and pharmacoresistance and in finding novel prognostic and diagnostic biomarkers using multiple approaches.[1] Current biomarkers include electrographic and imaging biomarkers but there are no definitive molecular or cellular biomarkers. We still do not have any biomarkers for DRE, which in part could be attributed to our lack of understanding of the mechanisms that separate DRE from drug responsive epilepsies. The potential mechanisms for DRE include wrong drug target, wrong distribution or poor access of drug, the presence of homeostatic mechanisms that may act to overcome the initial effect of the drug, and lastly, the existence of molecules that increase the severity of this pathological condition, thereby making it pharmacoresistant. Epilepsy is multifactorial with different epilepsy syndromes having different pathophysiology, so it cannot have a single common set of biomarkers; however, it is possible that some commonalities exist in the case of DRE. The biomarkers of DRE will include factors that are very sensitive and specific and can be objectively determined and interpreted as indicators of pathological changes related to epileptogenesis, ictogenesis or pharmacoresistance.

Studies using genomics, proteomics, and metabolomics based approaches reported the differential regulation of gene expression and functional modulation of various molecules involved directly or indirectly in biological processes like synaptic alterations, inflammation and neurodegeneration, which are shown to be associated with epileptogenesis and/or pharmacoresistance. Various candidate molecules identified in these studies include kinases like adenosine kinase (ADK), casein kinase 2 (CK2), cyclin dependent kinase 5 (CDK5), inflammatory molecules like interleukin 1-beta (IL-1β), and interleukin 6 (IL-6), cyclooxegenase (COX)-2, molecules of mTOR pathways like vascular endothelial growth factor (VEGF), ribosomal S6 kinase, eukaryotic translation initiation factor (EIF4E) and even microRNAs regulating these molecules like miR-132, miR-34a and miR-146a.[2] Recent studies provided connections between various kinds of brain pathologies and alterations in the peripheral blood transcriptome. Thus, these candidate molecules need further investigations in serum or CSF samples to validate their potential as peripheral biomarkers of DRE.[3] Such peripheral biomarkers will aid in identification and treatment of epilepsy patients at risk. Neuronal death is a significant feature of temporal epilepsy in humans. It has been found that prolonged and frequent recurrence of seizures increases the likelihood of neuronal damage in these patients.[4] Therefore, molecules that are biomarkers for neuronal damage may also have the potential to serve as biomarkers of DRE. Tian *et al*., reported a detectable elevation in serum Galectin-3 (Gal-3) concentrations in patients with intractable epilepsy. Clinical correlation showed significant difference between the generalized epilepsy group and the partial epilepsy group; however, no association was observed with either antiepileptic medications or between male and female patients. These findings suggest that Gal-3 could be a potential biomarker of DRE.[5]

Galectins (Gal) are members of the lectin family and also members of the beta-galactoside-binding protein family, of which 14 mammalian galectins have been identified. They play an important role in cell-cell adhesion, cell-matrix interactions, macrophage activation, angiogenesis, metastasis, and apoptosis. Increased levels of either soluble or cellular Gal-3 have been associated with various diseases, including autoimmune diseases, cancers and neurodegenerative diseases. Galectin-3 is a multifunctional protein and various studies have shown that the expression of galectin-3 is implicated in a variety of processes associated with heart failure, including myofibroblastic proliferation, fibrogenesis, tissue repair, inflammation, and ventricular remodeling. Studies have shown that galectin-3 can also be used as a biomarker to identify at risk individuals, and predict the patient response to different drugs and therapies for cancer, inflammation and fibrosis, heart disease, and stroke. Galectin modulators have been developed that block the binding of

galectins to carbohydrate structures. The galectin-3 inhibitor, TD139 has the potential to treat fibrosis.[6]

The role of lectins in the nervous system is complex and includes both positive as well as negative effects on neurogenesis, cell survival, and axonal elongation. As all of these biological processes are implicated in the development of neurodegenerative diseases including epilepsy, therefore, the role of lectins in epilepsy demands an investigation. Previous studies have reported the potential roles of Gal-3 in neurodegenerative diseases like scrapie, ischemic brain lesions, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and serum Gal-3 was even proposed to be a potential biomarker for the diagnosis of ALS as well as AD. Tian *et al*., studied the role of endogenous lectins in pilocarpine-induced cell death in adult mice, an experimental paradigm extensively used to model temporal lobe epilepsy in humans. These findings provide new insights into its roles as well as in the regulation of endogenous lectins in the adult central nervous system. A surprisingly selective proapoptotic role of Gal-1 has been found in a subpopulation of GABAergic interneurons. They also found that the related lectin Gal-3 was strongly upregulated by pilocarpine in microglial cells with an expression pattern closely matching that of neuronal degeneration revealed by Fluoro-Jade B (FJB) staining in the hippocampus and cortex. They proposed that interfering with the activity of Gal-1 in temporal epilepsy may help in reducing the loss of neurons in humans.[5] Although, it could be speculated that Gal-3 might be contributing to the pathology of epilepsy by causing neuronal loss in humans but the exact role of Gal-3 in epilepsy is still unclear. Is Gal-3 a potential biomarker for the diagnosis of intractable epilepsy? Further research is needed to investigate the role of Gal-3 in the pathophysiology of intractable epilepsy. Finding valuable biomarkers that indicate the existence of unrecognized processes leading to intractable epilepsy are critical for an early intervention.

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