

Epigenetics of Stroke: A Promising Avenue

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Stroke, a multi-factorial disease, is known to be the prime cause of disability in adults and the second most leading cause of death all over the world having an annual incidence of around 250 to 400 in 100,000 people. Genetics and epigenetics are thought to play an important role in stroke disease pathophysiology. However at present, therapeutic options available for the treatment of stroke are very less. The only known and approved pharmacological treatment for acute ischemic stroke till date is the use of intravenous recombinant tissue Plasminogen Activator (tPA) [1]. Besides tPA only reduces the disability in six per 1000 ischemic stroke patients and has no effect on the mortality rates [2]. There is clear need to identify new drug targets. Current studies have suggested the role of epigenetic factors in the pathological mechanisms leading to an increased risk of cardiovascular diseases and stroke. Epigenetics can be defined as a set of complex and interrelated molecular processes which modulate the gene expression and function within every cell inside the body, by the environmental influences, with no change in the genetic code of DNA. Epigenetic changes are known to be long lasting and heritable through successive cell generations [3]. The cellular and molecular mechanisms underlying the stroke recovery and pathogenesis are employed in epigenetic processes. Epigenetics may serve as a valuable field in generating biomarkers for the risk identification and prognosis of stroke. Various epigenetic

mechanisms are found to be involved in ischemic stroke pathogenesis like DNA methylation, Histone code modifications and chromatin remodelling and RNA mechanisms. Among these mechanisms, DNA methylation is widely studied in association with stroke. It is one of the key epigenetic mechanisms linked with genome stability and regulation of gene expression. It is thought to play a crucial role in cell identity, by preventing unwanted mutations which could be caused by the instability of genetic elements. It has been observed that global DNA methylation changes over time in response to different environmental exposures. Thus an association of global DNA methylation has been suggested with ageing process as well as with modulation in the risk of several pathologies of many diseases including stroke [4]. A significant increase in the overall level of DNA methylation has been observed after the ischemic stroke in the infarcted tissue as compared to the contralateral hemisphere [5]. The role of epigenetic factors in ischemic stroke has been examined by numerous candidate gene association studies and genome wide association studies. These genetic factors involved in stroke are directly linked to the epigenetic mechanisms. For e.g. Methylenetetrahydrofolate Reductase (MTHFR) is an essential factor for DNA methylation and is used for the formation of cellular reservoirs of S-adenosylmethionine (a methyl group donor) and in folate metabolism. Hyperhomocysteinemia resulting from the deficiency of MTHFR leads to an increased risk of stroke and cardiovascular disease as shown in several studies [6,7]. A study confirmed the association of LINE-1 hypomethylation with Vascular Cell Adhesion Molecule (VCAM-1) in a population free of ischemic heart disease or stroke [8]. Several single nucleotide polymorphisms have been discovered by

genome wide association studies which are linked to the stroke pathophysiology. For e.g. a study showed the association of BDNF val66met polymorphism with acute and long term poor stroke outcomes and also showed that BDNF promoter methylation is related to long-term [9]. X chromosome inactivation and genomic imprinting are carried out by DNA methylation and are related to other inherited causes of stroke. After the studies on ischemic stroke heritability were conducted, it was proposed that women are expected to have a family history of stroke than men from their mothers than from their fathers which is not dependent of traditional vascular risk factors. This could occur as a result of the effects of genomic imprinting [10]. The DNA methylation levels are expected to be varied after stroke, and may play a crucial role in recovery and injury process.

The Era of Epigenetic Medicine

Preclinical studies investigating epigenetic agents have been performed which target the stroke syndromes; however, they are still in their initial stages. Many epigenetic drugs have been classified such as 5-azacytidine, 5-aza-2-deoxycytidine (or decitabine), and zebularine, whose function is to act as an analog of the nucleoside cytosine and carry out non-specific inhibition of the function of DNMT enzymes. A variety of drugs that target histone modification pathways are present, in conjunction with the agents that affect the DNA methylation. A wide array of these drugs are HDAC inhibitors which are used in preclinical studies in the stroke models, including trichostatin A, suberoylanilidehydroxamic acid, sodium butyrate, sodium 4-phenylbutyrate, and valproic acid. Their role is to decrease the level of neuronal injury and improve the functional outcomes [11]. Promising results have been obtained for the treatment of ischemic stroke by using the RNA-based therapies and other epigenetic strategies. Gene silencing approaches using ncRNAs (which include miRNAs) and related short interfering NAs (RNA interference) have also been studied for the treatment of ischemic stroke [12,13].

Studies have been conducted on the effect of different medications on epigenetic mechanisms involved in

susceptibility and/or development of cardiovascular diseases. Certain medications like folic acid and vitamin B-12 which target DNA methylation are extensively being used for cardiovascular disease management. A meta-analysis suggested that protective role of folic acid supplementation in ischemic stroke prevention in regions of low folate fortification [14]. A non-significant and 11% reduction in the risk of stroke was observed due to folic acid supplementation in another meta-analysis carried out by Clarke et al [15]. These studies point out the effects which medications and supplements can have on the epigenotype, but also indicate the need for further work to be done in this field, as till date only a few studies have been conducted.

Future Directions

Studies detailing the role of epigenetic mechanisms in ischemic stroke are still in their primary stages but have shown immense potential for role in stroke pathology and discovery of novel methodologies for its treatment. Histone modification inhibitors are found to be neuroprotective in animal models of cerebral ischemia and intracerebral hemorrhage. Also, the function of miRNAs in neuronal, glial, and endothelia responses to ischemic stroke have been found to be varied. Future therapeutic methodologies for locus specific and genome-wide regulation of genes are being constructed. DNA methylation is mitotically stable and through cell division it is transmitted in such a way that the acquired changes are passed onto the cell progeny. Well designed epigenetics studies are required to understand the how epigenetic factors play role for disease pathophysiology which can be used for development of novel therapeutic target for treatment of stroke.

References

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