Translational Neuroscience

Life Experience and DNA Polymorphisms Influence the Brain Epigenome

Michael O. Poulter

Can J Neurol Sci. 2013; 40: 726-727

Although not strictly fitting the category of translational neuroscience, I believe the implications of this study where it was found that variability in DNA sequence, a single nucleotide polymorphism (SNP), can influence the epigenetic status of DNA and this is influenced by childhood trauma should be of wide interest.

Epigenetics is a burgeoning field of study that seeks to understand how alterations in DNA structure influence a wide range of biological outcomes ranging from cancer susceptibility to behaviour. Across this spectrum, two basic kinds of structure are most often examined. The first is covalent modification of DNA by methylation and second is the interaction between DNA binding proteins (histones for example) and DNA. Both influence the three dimensional structure of DNA and therefore gene expression. Importantly these dynamics are thought to be influenced by environmental conditions that may be positive or detrimental. For example, fetal alcohol syndrome has been shown to alter the methylation status of DNA accounting for the facial/cranial abnormalities that are often observed in these patients. So although, it is well recognized that many neurological and/or psychiatric disorders have a degree of inheritability, it also is clear that life events (severe stress, trauma) do influence the development of morbidity through epigenetic mechanisms. This raises the question whether one could inherit DNA sequences that are prone to epigenetic modification?

Based upon new evidence, the answer appears to be "yes". In a report recently published in Nature Neuroscience, Klengal et al[1] have shown that an allele specific de-methylation event is implicated in the outcomes associated with early child hood trauma. This polymorphism was first identified in the Grady trauma project, which studied a group of individuals who had experienced childhood trauma and developed various psychiatric disorders. The SNP is located in the promoter region of a gene coding for the FKBP5 protein, a regulator for the glucocorticoid receptor element (GRE) complex, which is important for controlling responses to stress and anxiety. FKBP5 reduces glucocorticoid receptor activity by decreasing glucocorticoid binding to its receptor thereby reducing the translocation of the receptor complex to the nucleus. Thus, it enhances glucocorticoid resistance.

First they showed that the SNP strongly increased the expression of the FKBP5 and with it a decrease in GRE activity. Next they showed in those who had experienced childhood abuse and carried the (risk) allele, their DNA was hypomethylated (within intron 7 of the FKBP5 gene) in comparison to carriers with no abuse and in controls. Furthermore, they showed that the severity of the trauma was inversely correlated to methylation (i.e. more trauma less methylation). These data imply a remarkable cause and effect interaction between an inherited DNA sequence, environment (trauma) and DNA structure. To further explore this relationship the authors then asked the question how the de-methylation alters GRE activity. They found no effect on basal gene function (no GRE activation) but upon stimulation with dexamethasone methylation significantly decreased the GRE dependent enhancement of FKBP5 expression.

Next they asked is this really an early life event or could de-methylation occur in an at-risk individual later in life? To answer this question the authors used a human hippocampal progenitor cell line that can be differentiated *in vitro* into mature hippocampal neurons. They treated the progenitors with dexamethasone (i.e. a stressor) which caused de-methylation of intron 7. This persisted after the cells matured. Treatment after maturation had no effect. Thus stress only had an effect during critical times of development which is, of course, consistent with the observation that early childhood exposures to trauma are more critical than those which occur later in life.

What is truly remarkable about the Klengel et al study is that it reveals an extremely complex relationship between sequence variation, DNA methylation and gene function. It is important to note that the SNP is a "long way" from the coding sequence, the

From the Molecular Brain Research Group, Robarts Research Institute, Dept of Physiology & Pharmacology, Faculty of Medicine, University of Western Ontario, London, Ontario, Canada.

Received March 20, 2013. Final Revisions Submitted April 17, 2013.

Correspondence to: Michael O. Poulter, Molecular Brain Research Group, Robarts Research Institute, Dept of Physiology & Pharmacology, Faculty of Medicine, University of Western Ontario, 100 Perth Drive, London, Ontario, N6A 5K8, Canada. Email: mpoulter@robarts.ca.

transcriptional start site and the differential DNA methylation sites. Thus our understanding of the impact of SNPs is challenged by these data as they indicate SNP variation do not necessarily have local effects but may have an impact on DNA structure/function relatively long distances away. From a clinical perspective this means that the way patients are treated and how their treatment outcomes are assessed is going to be increasingly complex: risks factors that include the interaction between inherited attributes (SNPs) and its impact on gene function and life experience will now need to be considered.

References

1. Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 2013;16(1):33-41.

https://doi.org/10.1017/S0317167100014992 Published online by Cambridge University Press