

The Neuroepigenetics of Suicide

Suicide is considered a major preventable public health problem and is the 10th leading cause of death in the United States for all age groups combined. It is generally accepted that suicide marks the tragic endpoint of a highly complex behavior shaped by social, developmental, and neurobiological factors that translate into a predisposition for the act itself. For example, altered serotonergic activity in the prefrontal cortex, which appears to be partially independent of the changes observed in major depression, is thought to play an important role (1, 2). Furthermore, the concordance rate for serious suicide attempts in monozygotic twins has been reported to be up to 17-fold greater than in dizygotic twins, and heritability estimates for serious suicide attempts are estimated to be as high as 55% (2). On the other hand, recent genome-wide association studies of nearly 9,000 individuals diagnosed with a mood disorder, approximately one-third of whom had a history of attempted suicide, effectively ruled out common genetic variants and polymorphisms of large effect (3). Following this approach, much larger cohorts

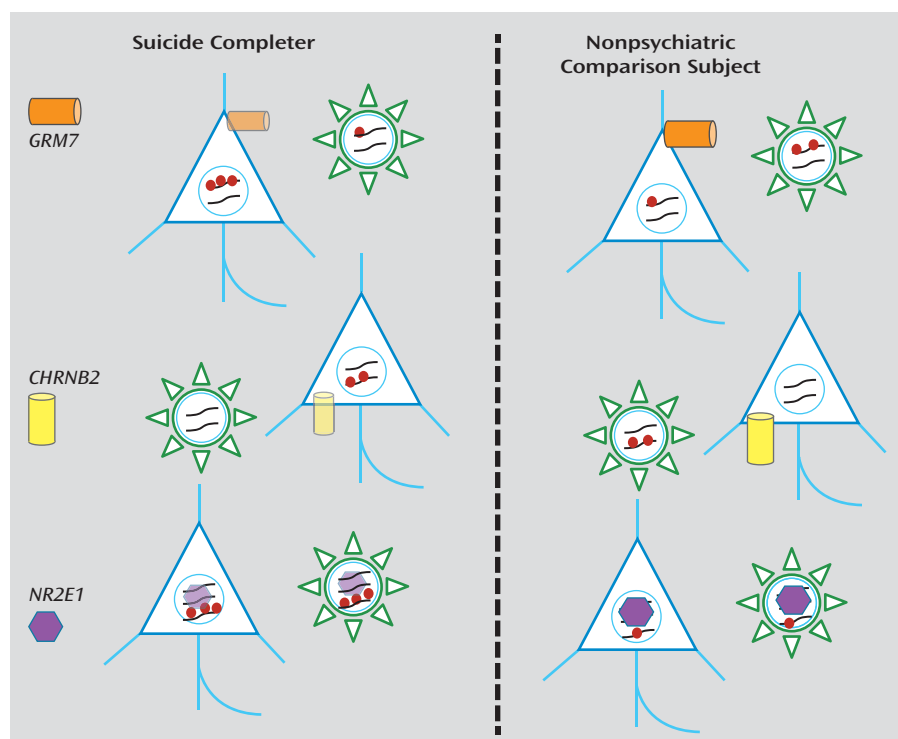
will be required in order to gain insight into what appears to be a highly polygenic risk architecture.

The study findings underscore the fact that suicide and depression are, to a certain degree, disorders of the neuronal genome.

In this issue, Labonté et al. (4) take a different approach by focusing on genome-wide promoter mapping of DNA cytosine methylation as an epigenetic marking that decorates the

human genome and is thought to play a critical role in the regulation of gene expression. Promoters are regulatory DNA sequences adjacent to the start site of a gene, regulating its expression. DNA methylation in promoter sequences is often associated with a repressive chromatin state and lower gene expression activity. Methylation of DNA occurs for different reasons, but life experiences, generally stressful ones, are often associated with changes in methylation of an animal's DNA. Labonté et al. explored DNA methylation changes both in neuronal and nonneuronal chromatin from postmortem hippocampus of 46 individuals who died by suicide and 16 comparison subjects from the Quebec Suicide Brain Bank. Because DNA cytosine methylation and other epigenetic modifications such as histone acetylation are understood as a molecular bridge linking gene expression in brain cells to environment, exposure, and experience, methylation stands at the forefront of mechanisms waiting to be explored to better understand psychiatric maladies such as depression and suicide that are not rooted solely in faulty genetics in the overwhelming majority of cases.

Labonté et al. found that hippocampal DNA from suicide completers showed DNA methylation changes at more than 300 gene loci. Interestingly, this pool of epigenetically altered gene promoters was significantly enriched for genes implicated in cognition, learning, and memory as well as synaptic transmission. In addition, many of the observed DNA methylation changes were specific for the

FIGURE 1. Genome Disorder in Suicide and Depression Is Cell-Type Specific^a

^a Highly schematic illustration of hippocampal tissue with neurons (blue triangles) intermixed with glia and nonneuronal cells (green stars). Red dots inside cell nuclei mark promoter-associated DNA cytosine methylation. Many of the DNA methylation alterations described in Labonté et al. (4) differentially affect the neuronal and glial genomes residing in the same tissue. For example, DNA hypermethylation for metabotropic glutamate receptors, including *GRM7*, and ligand-gated acetylcholine receptor subunits (*CHRNA2*) specifically affect hippocampal neurons of suicide cases, while nonneuronal cells either remain unaffected or show changes in the opposite direction. Other promoters, including the steroid receptor related gene, *NR2E1*, are in a hypermethylated state across the different cell types. Excessive promoter methylation associated with suicidal behavior is therefore likely to affect primarily neuronal gene expression, resulting in down-regulated expression of membrane-bound receptors (*GRM7*, *CHRNA2*) or nuclear signaling proteins (*NR2E1*).

hippocampal neurons and were not observed in glial or other nonneuronal DNA from the same tissue (Figure 1). Therefore, the study findings underscore the fact that suicide and depression are, to a certain degree, disorders of the neuronal genome. From a broader perspective, this study, along with similar work on other psychiatric conditions (5), further emphasizes the fact that genome exploration in brain tissue is ideally done in a cell type-specific fashion, in order to fully capture disease-relevant epigenetic signals that may affect only a subtype of neuron or glia.

The list of genes subject to promoter DNA hypermethylation and decreased hippocampal expression in suicide completers included metabotropic glutamate receptors and nicotinic acetylcholine receptor subunits, and at least one gene, *NR2E1*, encoding a nuclear receptor related to steroid hormone sensors that when mutated in mice results in defective development and hyperaggressive and violent behaviors in both sexes. Tellingly, this mutant mouse line has been named *Fierce* (6). It is encouraging that a subset of epigenetically altered genes in the brains of suicide completers, including *NR2E1*, elicit a congruent behavioral phenotype in a mouse model. Whether this finding will open opportunities to explore radically novel treatment options, or at least increase insight into disease-relevant molecular mechanisms in a preclinical model system, remains unclear. Obviously, suicidal behavior is difficult to model in the animal.

Looking forward, are Labonté et al. (4) pointing us toward an epigenetic risk architecture that reflects a predisposition to suicide, by reporting a large (but by no means infinite) number—300 to 400—of genomic loci? The answer may not be straightforward, because recent work from the same group, using similar approaches in a different sample of suicide completers who had experienced severe abuse in early childhood, yielded again hundreds of epigenetically altered loci (7). However, the overlap of specific loci between these two studies is limited (4, 7), which led the authors to the conclusion that DNA methylation changes in the brains of suicide completers who had suffered childhood abuse may differ from those observed in suicide completers who presumably did not experience early-life adversity (4). Interestingly, the hippocampal DNA methylation studies (4, 7) both reported that epigenetic changes are more prominent in the neuronal as compared with the nonneuronal fraction. Together with a recent transcriptome study of prefrontal specimens from a Hungarian brain collection in which disruption of gene expression networks important for neuronal communication and synaptic signaling was reported (8), these findings contribute to converging evidence that suicide and depression are associated with widespread changes in the molecular architecture of nerve cells residing in key structures of the corticolimbic circuitry.

It will also be important to compare these transcriptome and DNA methylome results from postmortem brain studies with similar data sets obtained from blood samples of individuals with a history of suicide attempts (9). Moreover, most epigenetic markings, including DNA methylation, are now considered to undergo dynamic and reversible changes during life, for example, in response to acute stressors. Therefore, longitudinal studies of tissue or cells easily accessible from living subjects who are able to give consent, complemented by animal work, will be important in order to distinguish between epigenetic changes reflecting an enduring trait triggered by a single early significant stressor or other factors operating earlier in life, as opposed to an acute process reflecting recent or current life events. With the emerging evidence that many neuronal gene promoters are epigenetically dysregulated, novel drugs targeting chromatin-associated proteins surely represent the next frontier for preclinical research in this area (10).

References

- Sequeira A, Morgan L, Walsh DM, Cartagena PM, Choudary P, Li J, Schatzberg AF, Watson SJ, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP: Gene expression changes in the prefrontal cortex, anterior cingulate cortex, and nucleus accumbens of mood disorders subjects that committed suicide. *PLoS ONE* 2012; 7: e35367
- Mann JJ, Brent DA, Arango V: The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. *Neuropsychopharmacology* 2001; 24:467–477
- Perlis RH, Huang J, Purcell S, Fava M, Rush AJ, Sullivan PF, Hamilton SP, McMahon FJ, Schulze TG, Potash JB, Zandi PP, Willour VL, Penninx BW, Boomsma DI, Vogelzangs N, Middeldorp CM, Rietschel M, Nöthen M, Cichon S, Gurling H, Bass N, McQuillin A, Hamshere M, Craddock N, Sklar P, Smoller JW; Wellcome Trust Case Control Consortium Bipolar Disorder Group: Genome-wide association study of suicide attempts in mood disorder patients. *Am J Psychiatry* 2010; 167:1499–1507
- Labonté B, Suderman M, Maussion G, Lopez JP, Navarro-Sánchez L, Yerko V, Mechawar N, Szyf M, Meaney MJ, Turecki G: Genome-wide methylation changes in the brains of suicide completers. *Am J Psychiatry* 2013; 170: 511–520
- Shulha HP, Cheung I, Whittle C, Wang J, Virgil D, Lin CL, Guo Y, Lessard A, Akbarian S, Weng Z: Epigenetic signatures of autism: trimethylated H3K4 landscapes in prefrontal neurons. *Arch Gen Psychiatry* 2012; 69: 314–324
- Young KA, Berry ML, Mahaffey CL, Saionz JR, Hawes NL, Chang B, Zheng QY, Smith RS, Bronson RT, Nelson RJ, Simpson EM: Fierce: a new mouse deletion of Nr2e1: violent behaviour and ocular abnormalities are background-dependent. *Behav Brain Res* 2002; 132:145–158
- Labonté B, Suderman M, Maussion G, Navaro L, Yerko V, Mahar I, Bureau A, Mechawar N, Szyf M, Meaney MJ, Turecki G: Genome-wide epigenetic regulation by early-life trauma. *Arch Gen Psychiatry* 2012; 69:722–731

8. Zhurov V, Stead JD, Merali Z, Palkovits M, Faludi G, Schild-Poulter C, Anisman H, Poulter MO: Molecular pathway reconstruction and analysis of disturbed gene expression in depressed individuals who died by suicide. *PLoS ONE* 2012; 7:e47581
9. Murphy TM, Mullins N, Ryan M, Foster T, Kelly C, McClelland R, O'Grady J, Corcoran E, Brady J, Reilly M, Jeffers A, Brown K, Maher A, Bannan N, Casement A, Lynch D, Bolger S, Buckley A, Quinlivan L, Daly L, Kelleher C, Malone KM: Genetic variation in DNMT3B and increased global DNA methylation is associated with suicide attempts in psychiatric patients. *Genes Brain Behav* 2013; 12:125–132
10. Covington HE 3rd, Vialou V, Nestler EJ: From synapse to nucleus: novel targets for treating depression. *Neuropharmacology* 2010; 58:683–693

SCHAHRAM AKBARIAN, M.D., Ph.D.
TOBIAS HALENE, M.D., Ph.D.

From the Division of Psychiatric Epigenomics, Friedman Brain Institute, and Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York. Address correspondence to Dr. Akbarian (schahram.akbarian@mssm.edu). Editorial accepted for publication February 2013 (doi: 10.1176/appi.ajp.2013.13020235).

Work in the authors' laboratory is supported by NIH, the Brain Behavior Research Foundation, and the Department of Defense. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.