ARTICLE ADDENDUM

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Addendum to stress and the dynamic genome: Steroids, epigenetics, and the transposome

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Retrotransposons constitute a majority of mammalian DNA, but their role in the cell is still poorly understood. Long thought to be useless, new evidence links retrotransposon expression to a variety of negative consequences. Furthermore, through interactions with steroid hormone receptors, retrotransposons are proposed to play a role in the pathology of psychological stress.

Keywords: retrotransposons, stress, brain, epigenetics

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In a recent paper, Hunter at al.[1] propose a functional role for retrotransposons in the brain and mammalian stress response. In contrast to the predominant paradigm of "junk" DNA or parasitic leftovers,[2] they hypothesize that these mobile genetic elements have been co-opted by cells to regulate the expression of protein-encoding genes in response to environmental insults. Retrotransposons were thought to be "controlling elements" of gene expression by their discoverer,[3] but this view was not widely shared until recently and remains controversial.[4] Due to the advent of next-generation sequencing, it is now possible to answer questions about their evolutionary role and effects on complex behaviors, such as psychological stress, that had been impossible to address even a few years ago.

The prevailing assumption is that retrotransposons are leftover from viral inserts, duplication errors, or runaway transposition—and functionally useless.[5] This negative hypothesis is difficult to demonstrate, and also hard to accept based on the principal of parsimony: biological systems do not waste energy needlessly, or are replaced by others that can do the same thing more efficiently. Because of the unbalanced ratio of retrotransposons to protein-encoding genes, if the "junk" hypothesis was correct, the trillions of cells present in a single organism would be spending 10 times the energy needed to replicate. The cost is even higher when the negative effects of errant retrotransposon transcription are taken into account. In the long evolution of eukaryotes, it is unlikely that this would not have been selected against. Thus, the simplest solution is that the vast regions of non-protein coding DNA, including retrotransposons, do *something* biologically relevant, even if the purpose is poorly understood at present.

Just as many genes were discovered through malfunctions leading to disease, several disorders show some level of transposon dysregulation. Retrotransposons have been implicated in schizophrenia, addiction, and post-traumatic stress disorder, among others.[6,7] Their unwanted overexpression can even lead to physical degeneration of the nervous system.[8] It is possible that loss of control of retrotransposon expression could be either a cause or a predictive biomarker of other psychological disorders.

The brain must be malleable in order to adapt to environmental stresses, including psychological stress.[9] Because a large number of brain cells are post-mitotic, and persist from birth until death, fine-tuned control of the genome is paramount if the organism is to survive. The dynamic nature of neuronal DNA has been the target of intense research into how neuronal structure and function are affected by varying the likelihood that certain genes will be expressed through changes in histone and DNA marks. The portion of the genome consisting of retrotransposons appears to be inversely correlated with the

availability for horizontal gene transfer from the environment. As most neurons are post-mitotic their need to adjust to new stimuli and deal with complex computations makes them likely to benefit from the genomic and transcriptional diversity that retrotransposons have the potential to provide. This has already been established to be the case in the mammalian immune system, where the retrotransposons derived V(D)J recombination system is vital to generating antibody diversity.[10]

A single stressor can induce immediate changes in gene expression in the brain. The effects are context and tissue dependent, with a high degree of individual variation. Furthermore, stress history also affects the response to both repeat and novel stressors.[11,12] These intracellular changes may even serve as a sort of "memory" of previous stressful conditions.[13] Changes induced by stressful events can have lifelong effects, and have even been shown to influence the stress reactivity of subsequent generations through epigenetic means[14] — a putative source of the "missing heredity" that has exacerbated the search for biological causes of many psychological disorders.[15] It is worth noting in this context that retrotransposons represent the single largest source of individual variation in the genome: it is estimated that each of us has at least one "private" or utterly unique retrotransposon variant in our genome.[16]

In addition to epigenetic control of protein-encoding genes, acute stress reduces the expression of retrotransposons in the hippocampus via stress induced increase in levels of the histone H3 Lysine 9 trimethyl mark, which is involved in silencing gene expression. This appears to represent a genomic stress response designed to control retrotransposon expression.[17,18] Structural changes accompany epigenetic changes on the brain, notably in the hippocampus. Hunter et al. posit that control of retrotransposon activity in the brain may be yet another mechanism of plasticity.

Evidence points to mammals having evolved a complex system of fine-tuned control over retrotransposons.[19] In contrast to the aforementioned H3K9me3-mediated short interspersed element (SINE) repression in rats, mice have been shown to upregulate SINE retrotransposons in response to heat shock stress.[17] The B2 SINEs inhibit transcription, which could be beneficial to an organism by reducing the amount of misfolded proteins due to the denaturing effects of hyperthermia. A reduction in the expression of transposons seen in the hippocampus[18] fits with this hypothesis, as making a memory of the stressful event—in order to avoid the same circumstances again—requires protein synthesis.

Steroid receptors have co-evolved in the presence of retrotransposons, and some are known to bind within special regions of ALUs—a subclass of SINEs—and affect transcription of genes far downstream.[20] SINEs are associated with glucocorticoid binding,[21] and long interspersed elements (LINEs) with androgen receptors.[22] Reciprocally, polypeptides translated from LINEs act as an androgen receptor coactivator.[23] Tissues producing high levels of steroids, like the brain, adrenals and placenta, also seem to be hot beds for the transcription of retrotransposons. This considerable interplay raises the possibility that fluctuating levels of steroid hormones during development and between males and females may affect the levels of retrotransposon expression, accounting for the pronounced age and sex differences in some psychological disorders.

Many simple questions still remain unanswered about the role of retrotransposons in mammalian behavior. While experimental data is currently scarce, what we do know suggests rapid-acting and important regulatory controls in response to stress, which may ultimately have an influence on physical and mental health.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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