

Letter to the Editor

Long interspersed retrotransposable elements and susceptibility to schizophrenia

In a recent paper, Bundo et al. described an increased number of long interspersed elements (LINEs or L1) within neurons in the prefrontal cortex of schizophrenic patients. Moreover, they reported that these inserted L1 elements were preferentially localised in regions containing synapse- and schizophrenia-related genes. In addition, they found that immune activation using poly-I:C led to increased L1 copy numbers in animal models (1).

Notably, densely clustered areas of retroelements, including short interspersed elements (SINEs) and LINEs, have also been identified in the major histocompatibility complex (MHC) region of chromosome 6. Genes within this MHC region encode proteins that function in the immune response, including members of the human leukocyte antigen class II family, which participate in antigen presentation (2).

Therefore, the insertion of L1 elements between synapse- and schizophrenia-related genes, as well as within the MHC region, may suggest that the immune system can modulate (e.g. poly-I:C) L1 retrotransposition activity. Thus, we hypothesise that alterations in both the frequency and location of retrotransposition within such genes might constitute an intracellular mechanism for brain-immune crosstalk. In this context, mutations in these retrotransposable elements might lead to increased susceptibility to schizophrenia, as suggested by Lozano et al. (3).

Indeed, it is known that L1 elements are frequently and independently mobilised in single cells during adult neurogenesis, resulting in newly transposed L1 elements in differentiated neurons (4,5). Taken together, one might generalise the immune-brain crosstalk hypothesis by assuming that the 'communication' occurs via insertions of common somatic retrotransposable elements (e.g. pseudogenes, SINEs and LINEs) in genetic regions that are involved in neuronal development. In this way, differential crosstalk models might be constructed based on the future functionality of the cell. Thus, immunological factors and/or neurotransmitter receptor types could modulate this crosstalk.

We would also like to highlight some potential areas of future research. Given the large number of

papers that indicate a relationship between immune regulation and schizophrenia, it would be interesting to investigate whether there are parallels that can be drawn between the DNA rearrangements (somatic recombination) that occur during B-cell activation (i.e. stimulation by a specific antigen leading to specific immunoglobulin production by mature B lymphocytes) and the events that occur in neurons. Indeed, it is possible that under certain pathological circumstances (e.g. mutations in retrotransposable elements), immune-associated stimuli acting over an extended period of time on a specific type of neuronal receptor could result in altered neuronal somatic mosaicism through the retrotranslocation of L1 elements. Furthermore, it might be interesting to examine whether some atypical antipsychotics can influence the activity of these mobile elements via neurotransmitter receptors.

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References

1. BUNDO M, TOYOSHIMA M, OKADA Y et al. Increased L1 retrotransposition in the neuronal genome in schizophrenia. *Neuron* 2014;**81**:306–313.
2. ANDERSSON G, SVENSSON AC, SETTERBLAD N, RASK L. Retroelements in the human MHC class II region. *Trends Genet* 1998;**14**:109–114.
3. LOZANO R, MARÍN R, FREIRE I, SANTACRUZ MJ, PASCUAL-GARCIA A. Analysis of the cumulative effect of

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- schizophrenia-related single nucleotide polymorphisms. *Neuropsychiatr Dis Treat* 2014;**10**:1079–1080.
4. COUFAL NG, GARCIA-PEREZ JL, PENG GE et al. L1 retrotransposition in human neural progenitor cells. *Nature* 2009;**460**:1127–1131.
 5. MUOTRI AR, CHU VT, MARCHETTO MC et al. Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. *Nature* 2005;**435**:903–910.