Box S5 | A potential role for retroviruses in the pathogenesis of schizophrenia

Of the many classes of human endogenous retrovirus (HERV) known, HERV-W (about 40 copies in the genome), may be unusually resistant to methylation and piwi-repression1,4. By molecular cascades that remain unclear, it is re-activated and amplified in microglial and other immune-competent cells upon infection by, for example, herpes virus-2 and the protozoan, *Toxoplasmosis gondii*1,4,5. The most vulnerable period is during pregnancy, perhaps since methylation-silencing is relaxed during embryogenesis and zygote formation5,9. In adolescence/young adults, a further infection-related methylation-disrupting and/or “immune event” may recruit pre-activated copies of HERV-W. How and why this happens is uncertain, but it is possibly related to the risk factors of: 1) urbanicity and migration (exposure to new infections) and 2) stress and drug-abuse, both of which are immune-suppressant1,8.

The HERV-W envelope protein is a partial agonist at cytokine-activated Toll-like receptor 4 (TLR4). Accordingly, it possesses pro-inflammatory and neurotoxic properties and interferes with oligodendrocyte-coordinated myelin production and repair, disrupting neural plasticity and releasing pro-inflammatory cytokines like interleukin-6 from microglia5,19. Other potentially deleterious actions include dopamine D3 receptor recruitment10 and CREB-mediated transcription of Ca2+-gated K+ channels encoded by the gene *KCNN3*: this channel is genetically associated with schizophrenia and linked to cognitive dysfunction11.

Most studies of HERV-W have been undertaken in serum and evidence for increased HERV-W activity in brain as a causal factor for schizophrenia is limited1,12,13. Furthermore, infections have detrimental effects independent of HERV-W retroviral resuscitation. For example, *Toxoplasmosis gondii*-induced loss of grey matter in infected schizophrenic subjects may reflect excess cytokine and kynurenine formation, and/or auto-immune actions of immunoglobulin IgG antibodies against NMDA receptors6,14,16. Furthermore, there is no one-to-one relationship of HERV-W with schizophrenia since some infected individuals remain asymptomatic, while many schizophrenics are not infected1.

A causal, neuro-inflammatory role of the HERV-W family member, multiple sclerosis-associated retrovirus, in provoking white matter lesions in multiple sclerosis is compelling. Studies of this disorder suggest potential course-altering therapies, including passive vaccination with humanised antibodies against the pro-inflammatory retrovirus envelope17. Though antibodies against HERV-W retroviruses would not counter infection/inflammatory events independent of HERV-W, and require entrance into the brain for full activity, they avoid the immune-suppressive impact of TLR4 antagonists and side-step the risks of chronic treatment with non-steroidal anti-inflammatory agents.

Therapeutic trials of antibody neutralisation and antivirals in schizophrenia could most realistically be performed around the first episode of psychosis, consistent with the high HERV-W titres seen in recent-onset schizophrenia7,13,18,19. Intriguingly, valproate inhibits both HERV-W transcription20 and *Toxoplasmosis gondii* replication21, possibly by epigenetic mechanisms (see main text), but this remains to be clarified.

This interesting avenue to potential course-altering therapy for schizophrenia, at least in a sub-population of patients, warrants further study.