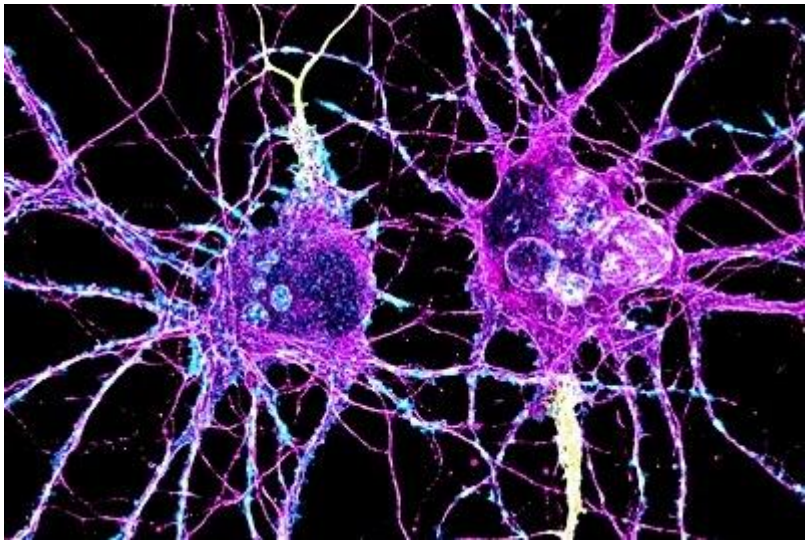
Multiple sclerosis (MS) is a chronic inflammatory disease leading to demyelination and neurodegeneration of the central nervous system (CNS). Several lines of research have demonstrated a link between aberrant expression of human endogenous retroviruses (HERVs) and autoimmune diseases, including MS. Pregnancy significantly improves the course of MS, and the beneficial effect of gestation on MS is highest in the third trimester. In this study, the researchers from Italy investigated HERV expression in the placentas and peripheral blood of pregnant women diagnosed with MS and healthy mothers, in the umbilical cord blood of their newborns, and in the blood of healthy non-pregnant women of childbearing age.

HERVs represent 8% of our genome. During evolution, the accumulation of mutations blocked the capacity to produce infectious virions. However, some viral sequences are transcribed, and a few encode proteins such as Syncytin 1 (SYN1) and Syncytin 2 (SYN2), which are involved in essential physiological functions, placental syncytiotrophoblast formation, and maternal-fetal immunotolerance.

Numerous experimental and clinical studies indicate that HERV overexpression is involved in initiating and maintaining MS. Two crucial elements are MS-associated retrovirus (MSRV) and SYN1.

MSRV was initially detected in 1997 in MS patients, as an endogenous retrovirus belonging to the HERV-W family. It was shown that MSRV expression in MS patients correlated with the inflammatory cytokines interleukin (IL)-6 and IL12p40. In 2006, Rolland et al. demonstrated that the surface subunit of the envelope (*env*) protein from MSRV interacted with toll-like receptor (TLR)4, and CD14. Ultimately, this *env*–TLR4–CD14 interaction stimulated the production of multiple proinflammatory cytokines, such as TNF-alpha, IL-12p40, IL-12p70, and IL6, and promoted the development of a Th1-type immune response. (Russ, E.; Iordanskiy, S. Endogenous retroviruses as modulators of innate immunity. Pathogens 2023, 12, 162.) https://doi.org/10.3390/pathogens12020162



About the study

The blood samples were collected from 20 pregnant women diagnosed with MS, 27 healthy pregnant women, 38 non-pregnant women of childbearing age, and another 20 non-pregnant women. The umbilical cord blood samples were collected from the 22 neonates (6 males, 27%) born to mothers with MS and 27 neonates (10 males, 37%) born to healthy mothers.

The placental tissue samples were collected at delivery from women diagnosed with MS and healthy pregnant women.

The median age of the MS group was 33.9 years (ranging from 31.4 to 37.7) and for healthy controls 39.1 years (ranging from 33.2 to 41.3). The rate of preterm delivery (gestation < 37 weeks) was similar in both groups, 25% in the MS group and 26% in the healthy controls.

The authors examined the transcription levels of the polymerase (*pol*) genes of the three HERV families, HERV-H, -K, and -W, as well as the envelope (*env*) genes of syncytin 1 (SYN1) and syncytin 2 (SYN2) and MS-associated retrovirus (MSRV). They also investigated the expression of tripartite motif 28 (TRIM28) and SET domain bifurcated histone lysine methyltransferase 1 (SETDB1), which are key players in the epigenetic mechanisms that modulate the cellular response to external stimuli. Epigenetic mechanisms, like those regulated by TRIM 28 and SETDB1, are implicated in the activation of HERVs in MS.

Results

Transcription levels of HERVs in the peripheral blood

In both groups of pregnant women, mothers with MS and healthy mothers, HERV mRNA levels were significantly lower than in non-pregnant women of childbearing age. Nonpregnant women also had higher median transcription levels of TRIM28 and SETDB1 than both groups of mothers.

Importantly, HERV-K-*pol*, SYN2-*env*, MSRV-*env, and* TRIM28/SETDB1 expression levels were significantly lower in pregnant women diagnosed with MS than in healthy pregnant women.

Transcription levels of HERVs in the placenta

In the decidua basalis and chorion from mothers with MS, transcription levels of the *pol* genes of HERV-H and HERV-K (but not for HERV-W), the *env* genes of SYN1, SYN2, MSRV, and TRIM28/ SETDB1 were significantly lower than in those from healthy mothers.

Transcription levels in umbilical cord blood of neonates

Neonates born to mothers with MS and those born to healthy mothers had comparable median transcriptional levels of every HERV tested, except HERV-W-*pol* which was significantly higher in the former. The median transcriptional levels of TRIM28 and SETDB1 were also comparable between the two groups of newborns.

Conclusion

This study showed significantly lower HERVs and TRIM28/SETDB1 expression in pregnant women than in nonpregnant women at delivery, suggesting that gestation is characterized by lower HERVs and TRIM28/SETDB1 expression levels. The impaired transactivation of HERVs was evident in the chorion and decidua basalis and the peripheral blood of mothers with and without MS.

The HERV expression was lower in pregnant women with MS than in healthy pregnant women. Importantly, reduced HERV activation in pregnant women seems to be a specific maternal feature, as it was absent from the umbilical cord blood of newborns.

The authors discussed the negative impact of estriol, progesterone, and corticosteroids on HERV expression. However, they noted that the different expression levels of HERVs and TRIM28/SETDB1 in the peripheral blood and placenta of mothers with MS compared to

healthy mothers are difficult to explain by any hormone or other circulating factor.

The authors concluded that these data require further investigation. Since pregnancy significantly improves the course of MS, the authors support the idea of innovative therapeutic interventions that should block HERV activation and control aberrant epigenetic pathways in patients with MS.

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