Endogenous Retroviruses Activity in Mouse

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Endogenous retroviruses (ERVs) are genetic elements resulting from relics of ancestral infection of germline cells, now recognized in human as cofactors in the etiology of several complex diseases as neurodevelopmental disorders. Autism spectrum disorders, attention deficit hyperactivity disorders, and schizophrenia are neurodevelopmental disorders, currently attributed to the interplay among genetic vulnerability, environmental risk factors, and maternal immune activation. The role of ERVs in human embryogenesis, their intrinsic responsiveness to external stimuli, and the interaction with the immune system support the involvement of ERVs in the derailed neurodevelopmental process. Although definitive proofs that ERVs are involved in neurobehavioral alterations are still lacking, both preclinical models and human studies indicate that the abnormal expression of ERVs could represent a neurodevelopmental disorders-associated biological trait.

endogenous retroviruses (ERVs) autism neurodevelopmental disorders ASD animal model.

1. Mouse Endogenous Retroviruses

The completion of the human genome project [1] has allowed the subsequent important discovery that more than half was composed of mobile genomic elements, named transposable elements [2],[3]. Among them, DNA transposons move by a cut-and-paste mechanism [4], while retrotransposons mobilize by a copy-and-paste mechanism via an RNA intermediate [5]. The retrotransposons comprise long terminal repeats (LTR)-elements, namely human endogenous retroviruses (HERVs) [6], and non-LTR elements, which include long and short interspersed nuclear elements (LINEs and SINEs, respectively) [7]. LINEs, moving autonomously, are widely spread within the genome [1] and also supply reverse transcriptase for the retro transposition of other endogenous retroelements [8]. HERVs are derived from their exogenous retroviral counterpart by a process of germline infection and proliferation within the host genome [9],[10], and their integration as proviruses led to the fixation and the vertical transmission, following Mendelian laws [11]. Endogenous retrovirus sequences are highly represented within the mammalian genomes, as they account for 5% to 10% of the genetic material [1],[12] in different species [13].

The mouse genome also harbors LINEs and SINEs that are sources of germline mutations via new insertions [14], [15] and contains numerous groups of retrotranspositionally active ERVs that cause the most reported insertional mutations [14]. ERVs constitute about 10% of the genome and are typically classified into three classes (class I, II, and III), according to the similarity to the exogenous viral counterpart [12],[14]. The majority of ERVs loci exist only as solitary LTRs, as the result of recombination events, and some of ERVs lost coding capability due to mutational degradation, occurred during evolution [14]. Nevertheless, some of them are retrotranspositionally active, leading

to germline mutations via new integration events [15]. Particularly, the intracisternal A-particle (IAP) is responsible for the most reported mutations due to new ERVs insertions, with a substantial contribution of the early transposon (ETn)/mouse endogenous proviruses (MusD) ERVs group [15]. IAP sequences belong to class II and are highly abundant in the mouse genome [14]. Although some IAP elements contain an env gene, most of them have lost *env* and adopt an intracellular retrotranspositional life cycle [16], resulting in the accumulation of high copy numbers in the genome [17]. Elevated IAP transcripts have been reported during embryogenesis (see Rowe and Trono, 2011, for a comprehensive review) [18] as well as in differentiated tissues, particularly in the thymus [19]. Of note, in lymphoid tissues, somatic insertions of IAP can lead to oncogene or cytokine gene activation [20],[21]. Moreover, it is known that IAP can influence the transcriptional profile of nearby genes, providing functional promoter elements and modulating local epigenetic landscape through changes in DNA methylation and histone modifications [22]. In addition to IAPs, the ETn/MusD group is responsible for the next highest number of germline mutations. ETns have no coding capacity, and their retrotransposition is mediated by the coding competent MusD elements [23]. As for IAPs, these elements also encode strictly intracellular virus-like particles since they lack the env gene [24]. During the embryogenesis, the expression analysis demonstrated that ETn and MusD are highly transcribed [18], and they are responsive to embryonic transcription factors [25]. Moreover, in mouse embryogenesis, several complex regulatory networks are responsible for the modulation of retroelements, and, in turn, the development is controlled by their temporal and spatial activity. Particularly, IAP elements are carried from the oocyte into early embryos, degraded and then peak again at the blastocyst stage, until the IAP sequences undergo DNA methylation. Conversely, MusD/ETn are highly transcribed in post-implantation embryos [18]. Moreover, two murine env genes, each present at a single copy and phylogenetically unrelated to human syncytins, are expressed in the placenta, where they exhibit a fusogenic activity contributing to the syncytiotrophoblast development [26]. The conservation of their coding status suggested that their function is most probably similar to that of the human syncytins since mice knockout for either of the two syncytin genes displayed impaired placental trophoblast fusion [27]. Furthermore, more recent data demonstrated the involvement of syncytins in the cell–cell fusion of myoblast in mice [28] and of ex vivo human osteoclasts [29] suggesting their crucial role in different host physiologic processes.

2. Animal Models of Autism

Animal models are crucial tools to deeply understand the human Autism spectrum disorders (ASD), as they allow the investigation of the pathways and the pathophysiological processes involved, to explore the brain district, mostly inaccessible in humans, and to evaluate the potential translational value of peripheral biomarkers. Several types of ASD animal models have been developed, including those obtained by genetic manipulations, by using behavioral screening of inbred strains of mice to find an ASD-like phenotype and by prenatal exposure to chemicals or infection/inflammation (see Ergaz et al., 2016 for a comprehensive review) [30]. Genetic models consist of mutagenesis or knockout of various isolated genes that are thought to be involved in the pathology of both syndromic and non-syndromic ASD, such as FMR1 (Fragile X syndrome), NF1 (Neurofibromatosis type 1), TSC1 (Tuberous sclerosis), DHCR7 (Smith–Lemli–Opitz syndrome), MeCP2 (Rett syndrome), and of genes known to be associated to high risk of ASD, such as SHANK2, CNTNAP2, eukaryotic translation initiation factor 4E

(eIF4E), transgenic mouse targeting Oxytocin, Vasopressin, Reelin, Dishevelled-1, Sert (serotonin transporter), MAOA (monoamine oxidase A), HOXA1, PTEN, and Neuroligins [30]. On the other side, unknown genetic changes able to induce ASD-like phenotype in animals, in turn, may bring into light similar changes in humans.

Using behavioral screening, the BTBR T+tf/J (BTBR) inbred mice were identified, as they showed several traits relevant to ASD, such as impairments in social and communication domains, reduced cognitive flexibility, and high levels of repetitive behaviors. For this idiopathic ASD model, the inbred C57BL6/J mice have usually been used as a standard control strain [31].

Based on epidemiological studies in humans concerning the association between prenatal infections with increased risk for ASD, other animal models were developed by the prenatal exposure to compounds that stimulate the maternal immune activation (MIA), such as the polyinosinic-polycytidylic acid [Poly(I:C)] or the lipopolysaccharide (LPS) to mimic viral and bacterial infection, respectively [32],[33]. In rodents, MIA leads to a dysregulation of the immune system in offspring and the acquisition of an autistic-like phenotype until adulthood, and, similar to what is observed in ASD children, interleukin (IL)-6 was supposed to be acting through inhibition of DNA methylation [34]. Notably, by a single poly(I:C) injection, the offspring of the first generation showed an autistic-like phenotype that persists via the paternal lineage, in the second and third generation, without any further intervention [35]. The type of changes that are transmitted through the generations (transgenerational inheritance) are not yet clarified. Nevertheless, a key role played by the immune system could be supposed. Accordingly, an apparent rescue of the behavioral abnormalities was obtained by the administration of neutralizing antibodies against IL-6 and IL-17 [34],[36]. Moreover, following MIA induction, several other cytokines, such as Tumor necrosis factor-alpha (TNF-α), Interferon-β (IFN-β), and IL-1β, were found overexpressed, but not the anti-inflammatory IL-10 [37].

Based on the clinical evidence, prenatal exposure to valproic acid (VPA) has been proposed as a drug-induced model of ASD in rodents [38] since in humans, the maternal intake of the anticonvulsant VPA has been associated with an increased risk of somatic anomalies, ASD, and other developmental disabilities in the offspring [39],[40]. Multiple mechanisms are called upon to explain the effects of VPA: direct interference with GABAergic neurotransmission, interaction with neural remodeling and neurogenesis, modulation of folate metabolism, free radicals' production, interference with cell proliferation/migration patterns and alterations of inflammatory and immunologic markers [41],[42],[43],[44],[45]. Animal studies demonstrated that VPA also acts on the regulation of gene expression via epigenetic mechanisms, since it is a non-selective inhibitor of histone deacetylase of class I and II (HDAC1 and HDAC2), resulting in the modulation of several genes and proteins implicated in neuronal excitation and inhibition and in brain and immune system development [42],[46],[47],[48]. The prenatal exposure to VPA in mice and rats leads to the acquisition of behavioral traits that resemble those observed in autistic patients (decreased social interactions, increased repetitive/stereotypic behaviors, lower sensitivity to pain, impaired sensorimotor gating or eye blink conditioning, increased anxiety, reduced exploratory behavior and abnormally high and longer-lasting fear memories), depending on dose and time of exposure [49]. Moreover, Choi and co-authors showed the transgenerational non-genetic inheritance of the ASD-like phenotype in mice prenatally exposed to VPA [50].

3. Evidence of Abnormal ERVs Activity in Mouse Models of Autism

Recently, our group investigated the transcriptional activity of different ERVs, including members of ETn and IAP families, in two models of ASD, the BTBR mice and the CD-1 outbred mice exposed to VPA in utero [51]. In both animal models, beginning from intrauterine life and up to adulthood, higher ERVs levels were found in BTBR and VPA-treated animals than in corresponding controls. Particularly, in BTBR mice, the transcriptional activity of ERVs was already altered in whole embryos samples and maintained in both blood and brain samples analyzed at different postnatal ages, suggesting that a long-lasting activation of ERVs could affect brain functions throughout the life span. In the VPA model, ERVs activity was modified immediately after drug administration both in pregnant dams (personal, unpublished data) and in embryos, suggesting a direct and rapid effect of VPA. Abnormal expression of ERV has also been found in the offspring (first generation, F_1) immediately after the birth, both in blood and brain, but high levels, stable until adulthood, were observed only in the brain from VPA-treated mice (Figure 1). In the VPA-induced ASD model, the differences in ERVs expression observed in the two tissues could be attributed to the different cell turnover. In fact, the rapid turnover of blood cells can dilute the VPA effect on the ERVs transcription in these cells, while, since the cellular turnover in the brain is slow/absent, the VPA can induce a permanent increase in ERVs expression, similarly to those found in BTBR mice. Moreover, in both models, the expression of some ERVs families was found to be positively correlated with expression levels of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) and Toll-Like Receptor3 (TLR3) and TLR4 in embryos and brain, supporting the hypothesis of the interplay between ERVs activity and immune response [51] (Figure 1).

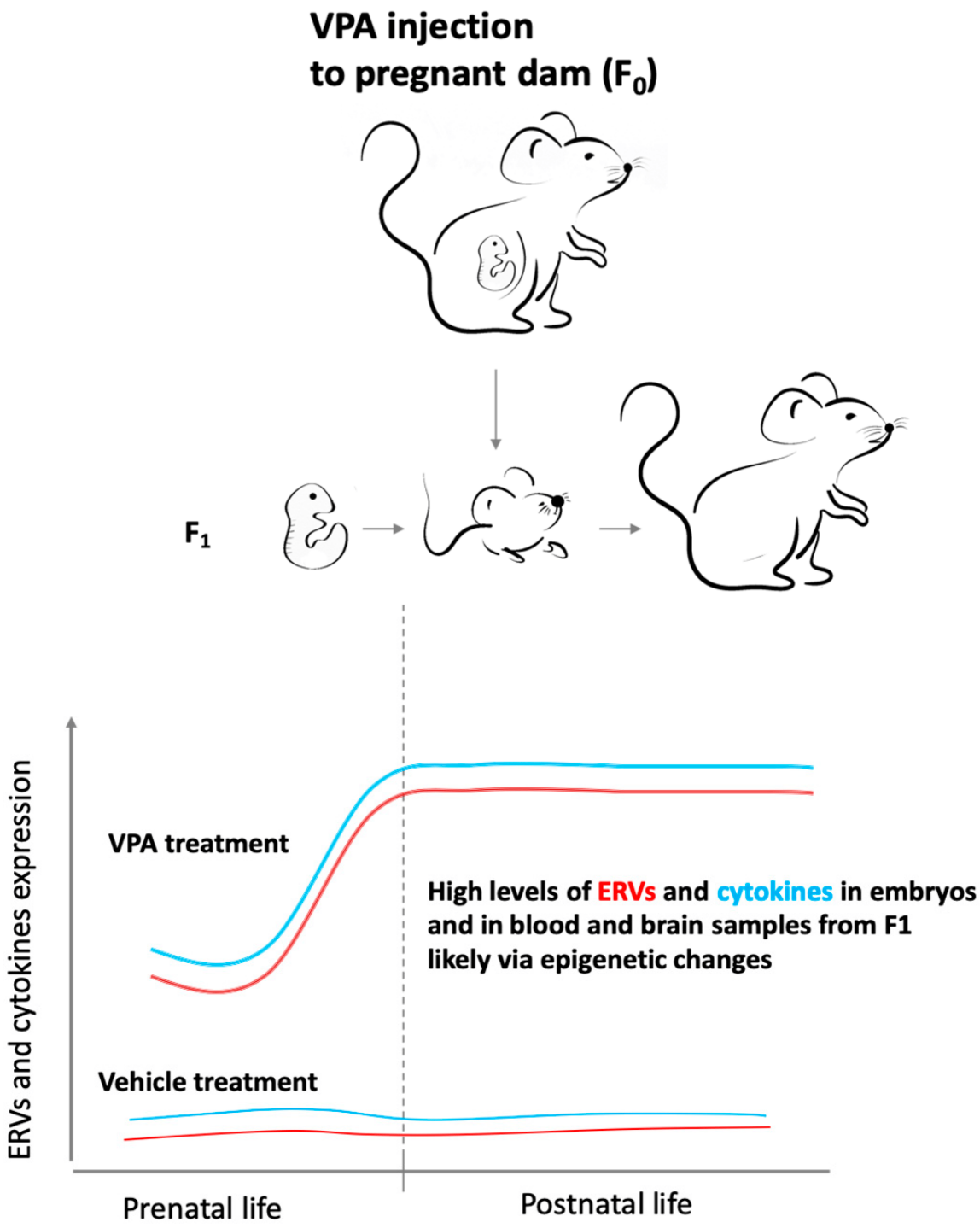

Figure 1. The abnormal endogenous retroviruses (ERVs) and cytokines expression from intrauterine life to adulthood in the first generation (F_1) prenatally exposed to valproic acid (VPA) could be due to the drug-induced epigenetic changes. ERVs activity (red lines) and cytokines expression (light blue lines) were represented both for VPA- and vehicle-treated mice.

4. Recent Findings on the Transgenerational Inheritance of the Abnormal ERVs Expression in a Mouse Model of Autism: the Conceivable Underpinning Mechanisms

Recently, the abnormal expression of ERVs observed in mice prenatally exposed to VPA has also been demonstrated across generations until the third one that lacks direct exposure to the drug, in parallel with the transmission of behavioral alterations [52]. Notably, larger VPA effects on ERVs expression was found in females within the first generation (F_1) and along maternal lineages in the second and third generation (F_2 and F_3, respectively) [232]. The vulnerability of the female sex could be due to the larger epigenetic effect of prenatal VPA exposure reported in female fetal brains, associated with sexually dimorphic methylation of H3K4 induced by VPA [53].

The transgenerational transmission of altered ERVs expression could be due to the activity of VPA as a direct HDAC inhibitor, inducing a histone hyperacetylation, but also to its ability to trigger other epigenetic changes, such as histone methylation and DNA demethylation [54]. The administration of the drug during pregnancy could modify the global epigenetic status of the first and also of the second generation (F_2), present in the embryos of the first generation as germline cells. The VPA-induced epigenetic changes would then be fixed in F_2 and transmitted to the next generation (F_3), the first that lacks a direct exposure to the drug [55]. Other mechanism by which ERVs deregulation could be trans generationally transmitted comprises the acquisition of a newly modified genotype by the increased copy number of ERVs (Figure 2). This hypothesis is in agreement with evidence in the literature, showing that ERVs in mice can cooperate with each other and with non-ERV elements (such as LINEs) by complementation in trans, increasing their intrinsic capability to retrotranspose [15],[56] and their proviral copy number. The reintegration of ERVs would lead to the emergence of polymorphisms, as shown in the human genome for HERV-H and HERV-K (HML2) [57],[58] without differences in the polymorphism rate between sexes for HERV-K [59]. Moreover, the copy number of Human endogenous retrovirus W/ Multiple Sclerosis-associated retrovirus was found to be increased in patients with multiple sclerosis and influenced by gender and disease severity as well as Copy Number Variation (CNV) of LINE-1 was found in schizophrenia (SCZ) patients [59],[60]. The reintegration of ERVs in the host genome could also contribute to genetic instability and the appearance of chromosome rearrangements, deletions, and duplications according to the detection of CNV and somatic mutation in ASD and SCZ [61],[62]. The increase in copy number of ERVs could also explain the more marked effect that prenatal exposure to VPA exerts on ERVs expression in females than males: oocytes persist long in life while spermatozoids life is short and their high turnover could dilute the effect of the drug.

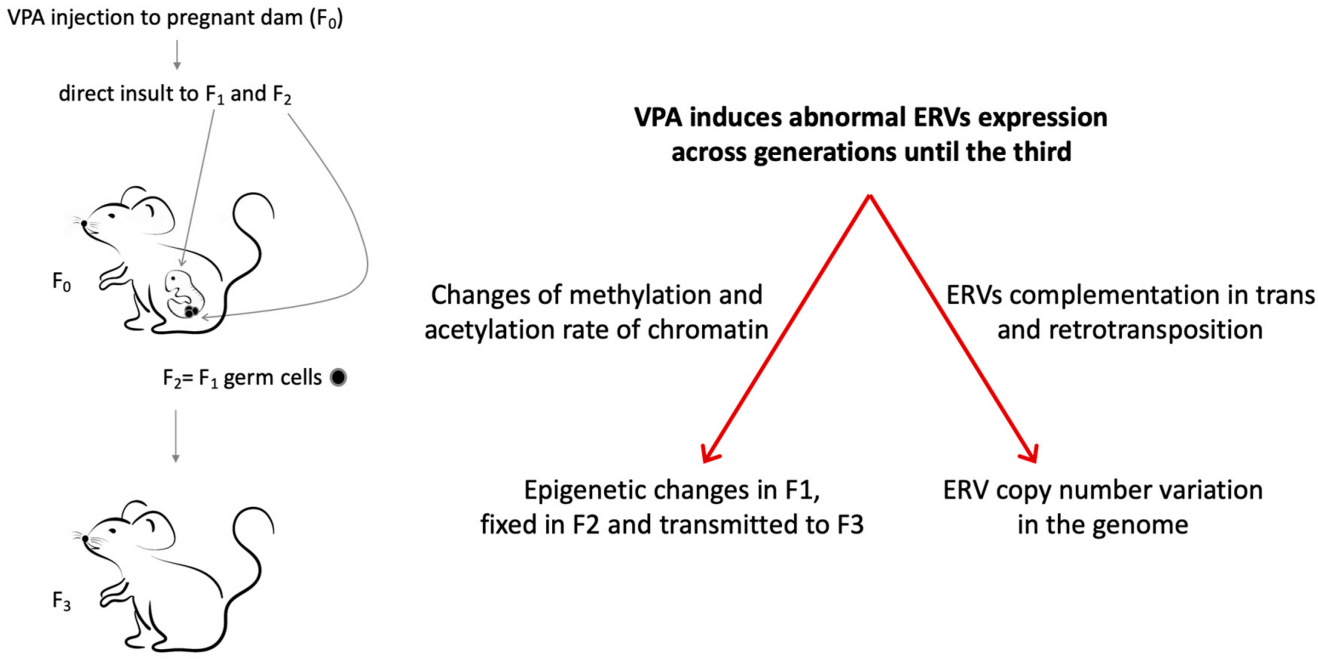

Figure 2. Transgenerational inheritance of altered ERVs activity in the VPA-induced mouse models of autism spectrum disorders (ASD), potentially involved mechanisms. VPA exposure of the pregnant dam (F_0) leads a direct insult to the fetus (F_1) and to germ cells that will generate the F_2 generation, while the F_3 is the first generation not directly exposed. Transgenerational transmission of abnormal ERVs expression induced by VPA could be due to changes in the epigenetic status or of the ERVs copy number variation in the genome.

Transgenerational studies on ASD in preclinical models provide new perspectives in ASD susceptibility, by which autistic traits seem to be inherited in subsequent generations after the first exposure to an insult, thus supporting the view that epigenetic inheritance could play a role in the development and heritability of ASD and more generally in neurodevelopmental disorders.

The publication can be found here: https://www.mdpi.com/1422-0067/20/23/6050/html

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