COMMENTARY - BRAIN BEHAVIOR IMMUNITY

Immune activation during gestation: developmental trajectories and the risk for psychopathology.

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There is now a general agreement that psychiatric disorders have their roots in early life. Preclinical studies, supported by large epidemiologic data, have clearly demonstrated that exposure to adverse life experiences in combination with a genetic background may predispose toward the development of mental illnesses, such as schizophrenia (Marin, 2016). As a consequence of these events, a derangement of the normal pattern of brain maturation may occur, with a sequela of modifications that will alter the correct function and responsiveness of brain circuits participating in the manifestation of disease symptomatology. Furthermore, most of these alterations become manifest at the transition between adolescence and adulthood when specific brain regions and neuronal circuits reach maturity (Marin, 2016). In a recent paper, published in *Brain, Behavior, and Immunity*, Nakamura et al. (2019) provide novel evidence for a close link between the Arx gene and PVB neurons in the context of the neurodevelopmental alterations brought about by exposure to environmental adversities during gestation. In particular, the authors used the well-established model of maternal immune activation (MIA) in mice, which is based upon administration of the viral mimetic poly(I:C), to investigate GABAergic dysfunction and the potential mechanisms that may contribute to such alterations. At behavioral and functional level, they confirmed that adult animals exposed to MIA show prepulse inhibition deficits, with a reduction of acoustic-evoked gamma and theta oscillation, which may be relevant for the schizophrenia-like phenotype. Interestingly, the authors, in agreement with previous studies (Richetto et al., 2014), show that exposure to MIA produces profound changes of the GABAergic system, with a significant reduction of somatostatin levels in the hippocampus and PVB levels in both prefrontal cortex and hippocampus. Interestingly, by performing transcriptional analyses on poly(I:C)-exposed rats, they found a consistent reduction, during fetal life as well as at adulthood, in the expression of Arx, a transcription factor that appears to be important for the maturation of PVB neurons (Dickel et al., 2018). Last, in order to strengthen the potential link between Arx and psychopathologies originating from the exposure to early-life adversities, the authors show the presence of a significant association between mutations in the Arx gene and psychiatric diseases (Nakamura et al., 2019).

This work is capturing several key issues relevant for the susceptibility to develop schizophrenia and, more broadly, for mental disorder. The first aspect is the link between environmental events and changes in the developmental trajectories of genes that may contribute to psychopathology. Indeed, the authors show the presence of significant alterations

already in the fetal brain with reduced expression not only of Arx, but also of other transcription factors relevant for the migration and maturation of GABAergic neurons (Kelsom and Lu, 2013). This may represent one mechanism contributing to the vulnerability of selected neuronal population, such as PVB positive interneurons, which are crucial for the development of oscillatory activity in prefrontal cortex and hippocampus and that play a key role in cognitive function. Indeed, a dysregulation of these neurons has been demonstrated in post-mortem brains from schizophrenic patients as well as in developmental models of schizophrenia (Lewis et al., 2012; Richetto et al., 2014). This brings us a second aspect of interest, which is the vulnerability of this specific cell subtypes during critical time window of development. Interestingly, different mechanisms may contribute to PVB neuron's vulnerability. For example, it has been demonstrated that they may be susceptible to oxidative stress during development in a time dependent manner, thus interfering with the maturation and functional connectivity of specific neural circuits contributing to psychopathology (Cabungcal et al., 2019). Furthermore, the potential role of the transcription factor Npas4 in PVB neurons during brain maturation has also been demonstrated. Accordingly, a reduction of Npas4 within PVB positive neurons leads to decreased PVB-dependent inhibitory transmission and to behavioral abnormalities resembling schizophrenia (Shepard et al., 2019).

The results by Nakamura et al. (2019), as well as the data from other developmental models of schizophrenia, provide support to the notion that a disruption of different mechanisms may interfere with the correct maturation of brain circuits, which will eventually determine the onset of a pathologic condition later in life. The specificity of these changes depends upon the 'timing' of occurrence and it is generally associated with a delay in the onset of the pathologic phenotype (Marin, 2016). With this respect, another important issue for linking 'gestational' adversities to psychopathology is to establish if a single 'disrupting' event is sufficient or if multiple hits are required for the development of a pathologic phenotype. MIA appears to act as a "primer", which enhances the susceptibility to the effects of the genetic background as well as to environmental adversities that will trigger pathological symptoms later in life. We have previously demonstrated that sub-threshold MIA requires the exposure to peripubertal stress in order to produce a constellation of behavioral abnormalities resembling schizophrenia (Giovanoli et al., 2013). A similar possibility must also be taken into account for the study by Nakamura et al. (Nakamura et al., 2019), since animals exposed to MIA were single housed from young adulthood, which may represent a stressful condition able to unmask the predisposed phenotype originating form MIA.

The identification and characterization of the sequelae of events and mechanisms that will lead to the pathologic phenotype as a consequence of adverse early life experiences is a relevant translational aspect of these studies. Indeed, some of these mechanisms could represent novel therapeutic targets to treat specific functional domains, such as cognitive deficits that, to date, are still poorly responsive to pharmacological approaches. With this regard, it will be important to identify markers of vulnerability associated with the exposure to the initial adverse experience in order to predict potential outcomes, but also to develop therapeutic strategies that may protect the individuals and prevent the full-blown manifestation of the pathologic condition. Indeed, therapeutic intervention might influence brain function differently depending on the stage of the disorder suggesting that at early stage such treatments may change the course of illness rather than counteracting the symptomatologic manifestation of the disease, as occurring at later stages (Marin, 2016; Millan et al., 2016).

All in all, while the etiology of schizophrenia is complex, only a better understanding of the causative mechanisms contributing to the development of specific pathologic domains may help us to build rational therapies aimed to improve the lives of affected individuals.

References

Cabungcal JH, Steullet P, Kraftsik R, Cuenod M, Do KQ., 2019. A developmental redox dysregulation leads to spatio-temporal deficit of parvalbumin neuron circuitry in a schizophrenia mouse model. Schizophr Res. pii: S0920-9964(19)30077-5.

Dickel DE, Ypsilanti AR, Pla R, Zhu Y, Barozzi I, Mannion BJ, Khin YS, Fukuda-Yuzawa Y, Plajzer-Frick I, Pickle CS, Lee EA, Harrington AN, Pham QT, Garvin TH, Kato M, Osterwalder M, Akiyama JA, Afzal V, Rubenstein JLR, Pennacchio LA, Visel A., 2018. Ultraconserved Enhancers Are Required for Normal Development. Cell. 172(3):491-499.

Giovanoli S, Engler H, Engler A, Richetto J, Voget M, Willi R, Winter C, Riva MA, Mortensen PB, Feldon J, Schedlowski M, Meyer U., 2013. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. Science. 339(6123):1095-9.

Kelsom C, Lu W., 2013. Development and specification of GABAergic cortical interneurons. Cell Biosci. 3(1):19.

Lewis DA, Curley AA, Glausier JR, Volk DW., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35(1):57-67.

Marìn O., 2016. Developmental timing and critical windows for the treatment of psychiatric disorders. Nat Med. 22(11):1229-1238.

Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, Gallinat J, Giedd J, Grayson DR, Heinrichs M, Kahn R, Krebs MO, Leboyer M, Lewis D, Marin O, Marin P, Meyer-Lindenberg A, McGorry P, McGuire P, Owen MJ, Patterson P, Sawa A, Spedding M, Uhlhaas P, Vaccarino F, Wahlestedt C, Weinberger D., 2016. Altering the course of schizophrenia: progress and perspectives. Nat Rev Drug Discov. 15(7):485-515.

Nakamura JP, Schroeder A, Hudson M, Jones N, Gillespie B, Du X, Notaras M, Swaminathan V, Reay WR, Atkins JR, Green MJ, Carr VJ, Cairns MJ, Sundram S, Hill RA., 2019. The maternal immune activation model uncovers a role for the Arx gene in GABAergic dysfunction in schizophrenia. Brain Behav Immun. 81:161-171.

Richetto J, Calabrese F, Riva MA, Meyer U., 2014. Prenatal immune activation induces maturation-dependent alterations in the prefrontal GABAergic transcriptome. Schizophr Bull. 40(2):351-61.

Shepard R, Heslin K, Hagerdorn P, Coutellier L., 2019. Downregulation of Npas4 in parvalbumin interneurons and cognitive deficits after neonatal NMDA receptor blockade: relevance for schizophrenia. Transl Psychiatry. 9(1):99.