Inter-strain chimeric mice to study the role of the placenta in the pathogenesis of neurodevelopmental disorders

Neurodevelopmental disorders (ND), such as autism and schizophrenia, are common psychiatric conditions that have their origins during fetal stages, when the fundaments of a functional brain are established and are more vulnerable to genetic or environmental perturbing factors. Little is known about the pathogenesis underlying ND, especially concerning the maternal-fetal networks regulating brain development. In this sense, the placenta has a crucial role in the control of fetal growth, and it represents an active signaling interface between the maternal environment and the fetus. In this project, we propose to establish a mouse model to investigate the influence of the placenta on neurodevelopment and behavior by examining the fetal brain and the behavior of chimeric mice possessing a placenta and a fetus belonging to two different strains, the BTBR T+Itpr3tf/J (BTBR) mouse model of autism and the "normo-behaving" strain C57Bl6J (B6). To this end, we will refine and validate an innovative RNA interference approach to manipulate early cell fates in BTBR or B6 embryos for the generation of inter-strain chimeras having discordant genotypes in the placental and fetal lineages. Subsequently, BTBR↔B6 chimeras will be generated systematically to investigate the role of the placenta in the pathogenesis of neurodevelopmental disorders. We hypothesize that chimeric B6 offspring developing with a BTBR placenta may display autistic-like behaviors, and that a B6 placenta may mitigate the autistic-like phenotype in BTBR offspring. Furthermore, brain and placental development of the chimeras will be examined at different fetal stages using histochemistry, in order to investigate early placental influences on neuronal differentiation and the development of specific brain areas. An important outcome of the project will be the establishment of a straightforward method for the construction of chimeras possessing discordant genotypes in the placenta and the fetus. As growing evidence demonstrate a pivotal role of the placenta in programming fetal development, our method may represent an important tool to investigate the placental contributions to the occurrence of diseases in the offspring, including cardiovascular and metabolic disorders. By using the proposed model, we expect to provide a consistent answer on whether the placenta has a role in mediating brain development and its postnatal functions in BTBR mice. Understanding early biological interactions between the fetus, its mother and the placenta, may help developing prophylactic strategies in pregnancy at risk of conceiving a child affected by neurodevelopmental disorders. Furthermore, the project may pave the scenario for the discovery of placental biomarkers, which inform about fetal life, thus pursuing early diagnosis and preventive therapies for neurodevelopmental disorders.