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Integration and tissue specific differentiation of fetal cells into maternal organs in a murine pregnancy model suggests multilineage differentiation potential

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Cell trafficking between fetus and mother during pregnancy resulting in a situation of maternal microchimerism is a widespread phenomenon in mammals including humans. We have investigated the trafficking of pregnancy associated progenitor cells (PAPC) to mother's brain in a murine pregnancy model. PAPCs can be detected first in mother's at delivery (P0) and up to 5 month post-partum, the longest time point examined, indicating long-term engraftment potential. Cells are found in different brain areas such as the cortex, striatum, olfactory bulb and hippocampus. We find cells predominantly in the CA1 area and at lower frequencies in the CA2/3 area and the dentate gyrus of the hippocampus. Strikingly, the frequency of PAPCs increases and the cell distribution is changed in Hippocampi of animals with experimental Parkinsonism demonstrating that PAPCs respond to changing homing cues.

In the brain, PAPCs coexpress mature neuronal specific markers indicating neuronal differentiation potential. In contrast glial cell markers are not coexpressed. Some PAPCs

were found to express stem/progenitor or immature neuronal markers such as nestin, doublecortin, and PS-NCAM. Further evidence for neuronal maturation comes from an increasing axonal/dendritic complexity over time. PAPC integration into the hippocampus is organotypical with neurons developing axonal/dendritic polarity which is indistinguishable from endogenous hippocampal neurons. In summary, PAPCs migrate to the maternal brain where they integrate and differentiate predominantly towards the neuronal lineage. PAPCs undergo a process of maturation and express stem/progenitor or immature neuronal cell specific markers when they are phenotypically immature. Mature neuronal markers are coexpressed when cells are phenotypically more mature. This might indicate that integration and maturation of PAPCs into the brain follows mechanisms similar to that observed during natural adult neurogenesis.

Furthermore, we find PAPC in maternal organs such as pancreas, small intestine as well as kidney where, like in the brain, cells

integrate organotypically. In the pancreas we found evidence for the coexpression of exocrine lineage markers which suggests pancreatic differentiation of PACs into acinar cells. We conclude that PACs as a population demonstrate multipotent lineage differentiation potential, a feature typical for stem cells. The fetal cell transfer model mimics an autologous transplantation paradigm and as such is an invaluable tool to study the integration, survival, differentiation, maturation and functionality of stem cells and their derivatives in different host tissues.

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