Novel therapeutic approach mediated by microglia for rare brain diseases

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Microglia are derived from primitive macrophages in the yolk sac and maintained by local precursors that colonize in brain independently from circulating mononuclear cells. Microglia are critical effectors and regulators of changes in CNS homeostasis during development and in healthy and pathological conditions. New evidence has emerged that primary microglial dysfunction substantially contribute to the pathogenesis of the rare neurological diseases. This condition is now recognized as primary microgliopathy. Adult-onset leukoencephalopathy with spheroids and pigmented glia (ALSP) is an example of human primary microgliopathy. The causative gene for ALSP is *colony stimulating factor-1 receptor* (*CSF1R*), which is predominantly expressed in microglia. We previously showed that ALSP is caused by haploinsufficiency of *CSF1R* or loss of *CSF1R*-mediated signaling. The neuropathological examination revealed that density and number of microglia decreased in autopsied brain of ALSP. Moreover, individual microglia in ALSP brain demonstrated their characteristic morphology with thin processes and many knot-like structures. These findings have suggested that microglia dysfunction associated with loss of *CSF1R* signaling play an essential role in the pathogenesis of ALSP. Recently, bi-allelic mutations in *CSF1R* cause childhood-onset leukoencephalopathy that can be associated with a skeletal dysplasia. Almost complete loss of microglia was observed in brain of the patients for bi-allelic *CSF1R* mutation. Recently, hematopoietic stem cell transplantation (HSCT) was performed in three patients with ALSP, which provided a stabilization of disease progression. These findings raise the possibility that diseases caused by genetic defects in the microglial pathway as well as the other types of leukodencephalopathies could be beneficially treated by HSCT. The microglia replacement in CNS may be facilitated by HSCT; however, this issue warrants further investigations.