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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. Micrglia 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 ASLP 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 ASLP. 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 benefically treated by HSCT. The microglia replacement in CNS may be facilitated by HSCT; however, this issue warrants further investigations.