Enhancing of homing and/or engraftment of cord blood mononuclear cells in the central nervous system

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Value Proposition

Leukodystrophies are inherited disorders resulting in decreased motor function, muscle rigidity, degeneration of sight and hearing, and are ultimately fatal. There is a great lack of treatment, although cord blood mononuclear (CBM) and hematopoietic stem cell (HSCT) transplantation sometimes help in certain types. New research has demonstrated that certain types of leukodstrophy are caused by dysregulation of microglia, which are brain-resident immune cells that maintain CNS homeostasis. HSCT/CBM is used as a therapy with the hope that enzyme-replete donor cells will replace enzyme-deficient host microglia. However, HSCT/CBM as a therapy for leukodystrophy is incomplete, possibly because microglia are long-lived, so donor cells do not engraft well. Depletion of endogenous microglia may facilitate engraftment of host cells. A means of effectively depleting endogenous microglia to provide a “niche” for blood-derived monocytes to enter and differentiate into microglia would facilitate microglial replacement therapies.

Technology

Using the small molecule CSF1R inhibitors PLX3397 or PLX5622 to deplete resident microglia can improve the efficacy of HSCT/CBM donor myeloid cell engraftment in the CNS. This was demonstrated in murine models of genetic deficiency of microglia (CX3CR1-cre-er x CSF1R-flox) and when mice were administered pharmacologic CSF1R inhibitors prior to HSCT transplantation. Donor monocytes engrafted the brain of these microglia-deficient mice, and were long-lived up to 12 weeks after transfer. These engrafted macrophages retained a distinct molecular signature compared to endogenous microglia, yet differentiated into microglial-like replacements.

Other applications

Many neurological and psychiatric disorders are driven in part by microglial dysfunction. Strategies to improve the homing and engraftment of donor myeloid cells to the CNS may improve treatment options for several debilitating disorders including:

Rett Syndrome, caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2), which results in deficient resident microglia.

Amyotrophic Lateral Sclerosis (ALS), in which microglia over-expressing the mutation SOD1 produce free radicals and induce

neuronal cell death.

Alzheimer’s disease, in which bone-marrow derived progenitors are more effective than resident microglia in removing Aβ plaques.

Advantages

- No current effective treatment options exist for many of these rare diseases.
- Current standard of care therapy is mainly symptomatic relief.
- The small molecule CSF1R inhibitors are less toxic than myeloablative therapies (chemotherapies such as busulfan and lethal irradiation) currently used to deplete endogenous microglia.
- PLX3397 is in many advanced-phase clinical trials for other indications