Hematopoietic Gene Therapies for Metabolic and Neurologic Diseases

Alessandra Biffi, MD

KEYWORDS

• Hematopoietic stem cells • Gene therapy • Nervous system • Storage
• Degeneration

KEY POINTS

- Hematopoietic stem cells can generate upon transplantation a myeloid cell progeny in the brain that is endowed with the potential to release therapeutic molecules.
- Genetic engineering of the cells to be transplanted can instruct their progeny for alleviating neurometabolic and neurodegenerative disorders.
- A deep understanding of microglia origin and maintenance during adulthood will allow more extensive exploiting of these events.

INTRODUCTION

An increasing number of patients affected by metabolic diseases affecting the central nervous system (CNS), such as adrenoleukodystrophy or Hurler syndrome, and neuroinflammatory disorders, such as multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS), receive hematopoietic cell transplantation (HCT) from healthy compatible donors or in the context of an autologous procedure in the attempt to slow the course of their disease, delay the onset of new clinical symptoms or attenuate their manifestations, and improve some pathologic findings. New indications are also hypothesized that include classic neurodegenerative diseases, such as Alzheimer disease (AD). The rationale for the use of HCT to treat these disorders is complex and based on multiple mechanisms, most of which relate to the possible replacement of brain-resident myeloid cells by the transplanted cell progeny. Indeed, microglia and, to a minor extent, brain-associated macrophages play a central role in these pathologic conditions and their replacement by cells novel to the patients' pathologic brain environment may interrupt or mitigate disease-associated pathologic cascades by modulation of local inflammation, establishment of proper metabolism, and induction of

Gene Therapy Program, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Smith 1158, 450 Brookline Avenue, Boston, MA 02115, USA
E-mail address: Alessandra.Biffi@childrens.harvard.edu

Hematol Oncol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.hoc.2017.06.004 **hemonc.theclinics.com**

neuroprotective effects. Genetic engineering of the hematopoietic stem cells (HSCs) to be transplanted (HSC gene therapy) may endow the brain myeloid progeny of these cells with enhanced or novel functions contributing to these therapeutic effects. However, an intense debate questions the actual contribution of HCT to microgliosis.

MICROGLIA

The CNS is composed of 2 major cell types, nerve cells and glial cells. Glial cells consist of astrocytes, oligodendrocytes, and microglia. Microglia account for approximately 10% of the total glial cell population within the CNS and are commonly referred to as the brain-resident immune cells or tissue-resident macrophages.[1] Indeed, microglia belongs to the mononuclear phagocyte lineage, related to other organ-specific macrophage populations, such as Kupffer cells of the liver and bone osteoclasts. Microglia was first recognized as a distinct cell type by Nissl who named them Staebchenzellen (rod cells) for their rod-shaped nuclei and considered them as reactive neuroglia. According to the classic morphologic studies based on silver carbonate staining, microglia cells were originally divided into ameboid, ramified, and intermediate forms. Interestingly, depending on their localization in the CNS, microglia present major morphologic differences with regard to the size and orientation of their ramifications. In this way, the shape of the ramified microglia is well adapted to the architecture of the CNS region they populate. Similarly, the density of microglia cells seems to be determined by region-specific cues in both rodents and humans. Such heterogeneity of microglia density and morphology might be linked to a functional heterogeneity. In support of this view, among the most remarkable features of microglia is their high level of morphologic and functional plasticity in response to activating stimuli. They respond not only to changes in the brain parenchymal integrity but also to very small alterations in their microenvironment, such as imbalances in ion homeostasis that precede pathologic changes.[2] In this context, classification of microglia can also describe their activation status, distinguishing between resting, activated, and ameboid phagocytic microglia.[3,4] Importantly, under multiple pathologic conditions, activation of microglia is coupled with their proliferation, which leads to the focal accumulation of activated cells, a process termed microgliosis.[2,5] Moreover, the expression of biological and biochemical microglial markers may vary according to different parameters, including interspecies variations and maturation or activation state. For example, neonatal microglia, differently from adult microglia, share some phenotypic and functional features with neural stem or progenitor cells, such as the in vitro and in vivo expression of nestin, a neural stem cell marker,[6–8] and the ability to express oligodendrocyte or neuronal markers under appropriate in vitro conditions.[7,9] Such neural stem cell-like features, whose functional relevance remains uncertain, were not evidenced in other populations of tissue-resident macrophages.

Microglia in Neurodegenerative Diseases

Microglia activation is present in diverse neurodegenerative diseases and is closely associated with pathologic condition, being crucial to the cause and the progressive nature of most of these disorders. For this reason, in a large variety of diseases, microglia is thought to be a promising target for therapeutic intervention.

Microglia and metabolic storage disorders

Metabolic storage disorders (SDs) are a group of inherited disorders caused by defects in the genes, which determine accumulation of undegraded material within