Stem Cell Homing

Subjects: Infectious Diseases

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Stem cells are essential to the regenerative processes with a primary function to replace damaged cells in the body. Their ability to differentiate into functional cells is an outcome of their response to micro-environmental changes, i.e., stem cells' interaction with signals released by the affected tissue. Cell homing is a stem cell's ability to find a point of destination, be it a tissue in distress or a niche. Cell homing is a diverse term. Many cell types, including stem cells, progenitors, and mature, specialized T cells, are homing to their respective niches—environments that promote their self-renewable state.

Keywords: stem cells ; intrathecal administration ; neurodegenerative diseases

1. Introduction

Stem cells are essential to the regenerative processes with a primary function to replace damaged cells in the body. Their ability to differentiate into functional cells is an outcome of their response to micro-environmental changes, i.e., stem cells' interaction with signals released by the affected tissue. Stem cells reside in many tissues and organs, including fat, bone marrow, liver, brain, or umbilical cord—blood and lining. Medical use of stem cells requires their isolation with an end goal to culture sufficient quantities of stem cells for therapeutic effect. A stem cell application refers to the transplantation of stem cells with the ultimate intention to reach the targeted area. There are two fundamental issues to consider before each stem cell application. The first issue refers to methods that will enable the stem cell transformation to targeted cells or successful engrafting. The second issue is how to direct the migration of most of the transferred cells to the desired location. There are many proposed solutions to the first issue. The second issue is the subject of cell homing. It is logical to conclude that the higher the number of administered cells or administration closer to the targeted site, the higher is the homing likelihood success of transplanted cells. Currently, it is known that the greater the number of administered stem cells, the better the treatment outcomes. However, the number of delivered cells has a saturation plateau, after which no additional treatment enhancement is noted [1]. Understanding the intrinsic mechanisms of cell homing may be essential to increase the success of the stem cell-based treatment and accomplish more with a reduced number of the administered cells.

For a spectrum of neurodegenerative diseases, such as, but not limited to, Alzheimer's disease, autism, stroke, Parkinson's disease and Huntington's disease, or multiple sclerosis, the targeted area is in the brain. The literature is abundant with evidence of positive results for non-invasive methods of stem cell transplant [2][3][4]; however, parenteral routes of administration typically result in dissipation of stem cells to other organs rather than the brain. Intrathecal space is also known as subarachnoid space. It is a space between the membranous layers of the arachnoid matter and pia matter and surrounds the brain and the spinal cord, filled with cerebrospinal fluid (CSF). Intrathecal administration is a preferred method of drug delivery when the blood–brain barrier (BBB) restricts the delivery to the brain [5][6], for example, via oral or parenteral administration.

2. Cell Homing

2.1. A Definition

Cell homing is a stem cell's ability to find a point of destination, be it a tissue in distress or a niche. Cell homing is a diverse term. Many cell types, including stem cells, progenitors, and mature, specialized T cells, are homing to their respective niches—environments that promote their self-renewable state. Note that the focus is on stem cell transplantation with the ultimate goal of the remission of neurodegenerative diseases. The purpose frames the context for a definition. Thus, the researchers may adopt that cellular homing implicates a mechanism by which a location of damage releases signaling molecules that start recruitment, proliferation, migration, and the differentiation of stem and progenitor cells. It is an endogenous mechanism that drives stem cells from their niches to a site of injury or inflammation to respond to signals coming from damaged areas. Transplanted stem cell homing is a directed migration from the application site to the targeted location. This definition illustrates that for stem cell-based therapies, it is imperative to understand the

mechanisms that increase the possibility of the controlled directing of the stem cells to the targeted tissues [7]. The question at hand—“How to improve cell homing?, comes down to methods that can improve the “attractiveness” of the targeted location to administrated cells and prevent their dissipation to unintended sites. For better clarity of research results of homing mechanisms, it is crucial to establish a common ground between results of different research groups or standardize protocol aspects. Yusuf et al. outlined a classic protocol on homing of hematopoietic stem cells (HSC) to the bone marrow (BM), with procedures that adapt to a design and a goal of an experiment [8]. Protocols tailor different points of interest, such as cytokine release or study of the homing outcome with no induced injuries.

2.2. Homing Evidence Following Intrathecal Application

The result’s assessment of in vivo clinical trials of stem cell intrathecal applications targets the side effects, feasibility, safety, and visible and measurable health improvements after the application [9][10][11]. The assumption is that in the case of intrathecal application in humans, (most of) the injected cells will migrate to the central nervous system (CNS) lesion or affected area in the brain. Compared to other application methods, guided neurosurgical delivery is superior in the function of the absolute cell count reaching the brain. However, it comes at the risk of focal bleeding, with the intrathecal application as a good, if not a primary, alternative [12].

Several clinical studies demonstrated that serious adverse events of intrathecal applications are rare; instead, they have mild and temporary side effects. The health improvements are present in different degrees, many with confirmed values of monitored parameters within limits of other studies and with an overall focus on the procedure’s success, feasibility, and safety [13], even on five-year follow-up [14]. Reported complications are headache [15], potential risk of hydrocephalus, and lumbosacral radiculopathies [16][17]. Phase I/II study on the tolerability of MSCs intrathecal transplantation in patients with early multiple system atrophy showed that intrathecal is as safe as intravascular administration, with mild side effects at higher doses. The efficacy was slightly lower compared to historical groups. They also registered neurotrophic factors in CSF, indirectly demonstrating the occurrence of homing [18].

An initial number of molecules of substances delivered via intrathecal administration may decrease due to CSF’s role in facilitating waste products [19]. The intrathecal administration shortens the path to the target location in the brain and thus lowers the unwanted dissipation of transferred stem cells. Hence, intrathecal administration may be a preferred choice in terms of efficiency for cell migration to the desired location. However, Kim et al. reported that only 2.4% of the intrathecally injected Wharton’s Jelly-derived MSCs (WJ-MSCs) reached the rat’s brain. Their study was the first to measure the ratio of homing cells at the target location. A tenfold dosage increase resulted in increased homing efficiency by 2.6. They also concluded that the migration time is between 6 and 12 h, indicating that the human’s homing time is probably longer because of the anatomical differences. They argue that most stem cells never left the lumbar area since they did not migrate to other organs and that the increased homing rate at higher dosage is due to a higher clumping tendency on higher concentrations, which made them robust to CSF clearing [20].

Although Kim et al. reported no migration to other organs 12 h after injection, Quesada et al. detected dissipation to mice heart 24 h later, and brain and heart four months later, thus providing evidence that homing exceeds the intended location given sufficient time [21].

Barberini et al. tracked the technetium radiolabeled MSCs and reported better distribution of MSCs within the subarachnoid space [22]. They also observed no trace of MSCs at the damaged tissue within a week after injection. Vaquero et al. reported arrest and improvement of Alzheimer’s type dementia symptoms and indirect homing evidence in the form of increased cerebral glucose metabolism. They measured cerebral glucose metabolism via 18F-fluorodeoxyglucose positron emission tomography after the administration [11].

One study demonstrated that the ratio of MSCs at the injured site vs. intact spinal cord was significantly high to conclude that MSCs primarily migrate to the injured area [23]. The same research paper also noted that some cells migrated to perivascular spaces of damaged tissue. Oh et al. administrated repeated intrathecal injections one month apart in two trials. They noted no acceleration in amyotrophic lateral sclerosis functional rating scale-revised in the first study and change from baseline to four at six months follow-up in the second study [24]. A. Sahrain et al. injected a booster dose after a year, with no adverse effects reported and a notable improvement in health progression [25]. Kuang et al. administered four intrathecal injections, a week apart each, with no adverse effects and with observable improvements in health [13]. None of these studies compared the improvements to the case of a single dose, partially because it was not feasible due to the studies’ designs. However, they all indirectly confirmed the homing effect in relative health improvement and verified the treatments’ feasibility and safety.

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