Review Article

Selective Serotonin Reuptake Inhibitors May Improve the Efficacy of Hematopoietic Stem Cells Transplantation

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Abstract

Hematopoietic stem cell (HSC) transplantation is the most effective therapeutic modality for certain malignant and non-malignant diseases. Although umbilical cord blood can be a source of HSCs, the harvest from a single cord is insufficient for transplantation. Protocols have been developed to overcome this problem, but in vivo expansion of transplanted HSCs would be most desirable. Serotonin is a monoamine neurotransmitter that can increase the ex vivo expansion of both HSCs and bone marrow stromal cells (BMSCs). Selective serotonin reuptake inhibitors (SSRIs) increase the free serotonin concentration by binding to the serotonin transporter (SERT), thereby preventing reuptake by pre-synaptic cells. Studies have shown that SSRIs also have immunosuppressive effects. We hypothesized that the immunosuppressive effects of SSRIs may be due to the expansion of BMSCs, which can result in a decrease in the incidence of graft versus host disease (GVHD). Finally SSRIs may promote efficacy of transplantation by increasing the in vivo expansion of HSCs and decreasing GVHD incidence.

Introduction

Hematopoietic stem cells (HSCs) are stem cells that have the potential to develop into blood and immune cells. Especially, HSCs are defined by their ability to self-renew and produce cells able to differentiate into any blood cell type, although only small numbers are defined by their ability to self-renew and produce cells able to differentiate to a mature lineage. These properties differentiate into any blood cell type, although only small numbers are defined by their ability to self-renew and produce cells able to differentiate to a mature lineage. These properties render HSCs attractive for use in stem cell therapies. Transplantation of HSCs is the most effective modality for treating malignant and non-malignant diseases including leukemias and lymphomas, aplastic anemia, and hemoglobinopathies; genetic disorders such as lysosomal storage disease; and immunodeficiencies such as human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS).

The most common sources of HSCs for transplantation are bone marrow and mobilized peripheral blood. Major factors limiting the success of transplantation from these sources are graft-versus-host disease (GVHD) and engraftment failure. Since 1988, umbilical cord blood has increasingly become an alternative source of HSCs for transplantation, due to easy availability, lower risk of viral infection, and reduced GVHD. The number of HSCs in umbilical cord blood is low, but a population adequate for transplantation may be gained via ex vivo expansion. Most methods of ex vivo expansion, however, are not able to maintain stem cell properties and therefore are not appropriate for clinical application. Most desirable would be a new method that can induce the in vivo expansion of HSCs.

Small-molecule compounds (SMCs) are a relatively new tool for the expansion of HSCs, although these natural chemical products have been used in molecular biology and pharmacological treatments for many years. It has been shown that SMCs are able to modulate the signaling pathways of HSCs. One of these SMCs is serotonin (or 5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter that is often produced in Enterochromaffin (EC) cells of the gut and brain, and stored in platelets and mast cells.

Antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs) prevent the uptake of serotonin by SERT (serotonin reuptake transporter). This results in enhanced serotonin signaling. SSRIs are used to treat many diseases, including major depression and anxiety disorders (e.g., obsessive-compulsive disorder and panic disorder). Relative to other antidepressants, they cause fewer undesirable side effects. Paroxetine, citalopram, fluvoxamine, sertraline and fluoxetine are examples of SSRIs.

SSRI treatments have been associated with changes in the proliferation, cytokine secretion, and viability of peripheral blood lymphocytes. Generally, SSRIs appear to inhibit the proliferation of T lymphocytes, with the exception of fluoxetine, whose stimulatory or inhibitory effects are dependent on the concentration of mitogen (concavalin A) and degree of lymphocyte activation in vitro.

Serotonin has been identified as an important factor in the activation of T lymphocytes. Evidence-based conclusions are that serotonin receptors are not responsible for the mitogenic effects of serotonin on T lymphocytes, but rather SERT is responsible for these effects via the uptake of serotonin; internalization of serotonin; and activation of T lymphocytes. Taler et al. showed that, ex vivo, a higher concentration of the SSRIs paroxetine and sertraline

Keywords: Selective serotonin reuptake inhibitor; Hematopoietic stem cell transplantation; Serotonin; 5-hydroxytryptamine; Stem cell expansion.

Abbreviations: AIDS, acquired immune deficiency syndrome; BMSCs, bone marrow stromal cells; EC, enterochromaffin; GVHD, graft versus host disease; HIV, human immunodeficiency virus; HSC, hematopoietic stem cell; SERT, serotonin reuptake transporter; SMCs, small-molecule compounds; SSRIs, selective serotonin reuptake inhibitors; TNF, tumor necrosis factor.

Received: 25 June 2015; Revised: 23 August 2015; Accepted: 8 September 2015

DOI: 10.14218/JERP.2015.00001
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**Hypothesis**

By increasing the amounts of serotonin in bone marrow, SSRIs may improve the efficacy of HSC transplantation (Fig. 1). Most studies concerning SSRIs have focused on the effects of sertraline and fluoxetine. Because the effects of fluoxetine on lymphocytes are variable under different conditions, we suggest sertraline, as its effect is solely immunosuppressive. The routine starting dosage of sertraline as an antidepressant is 50 mg/day, and the maximum is 200 mg/day, but higher doses are probably required for immunosuppression. The normal concentration of serotonin in plasma is 0.62±0.11 µg/L. Future studies must focus on the dosage of sertraline that will generate the optimum concentration of plasma serotonin for in vivo expansion of HSCs.

**Evaluation of hypothesis**

In addition to bone and hematopoietic cells, nerve cells are also within the microenvironment of the bone marrow, and interactions among these cells regulate the fate of stem cells in vivo. The following evidence suggests that these complex interactions may be through the serotonin neurotransmitter. Firstly, serotonin can stimulate megakaryopoiesis via the 5-HT2 receptor. In the early stages of megakaryocytopoiesis, serotonin regulates proliferation and survival of megakaryoblasts through its anti-apoptotic effects. Sertraline that will generate the optimum concentration of plasma serotonin for in vivo expansion of HSCs.

**Discussion and conclusions**

There are several sources of serotonin in the body. Among them, infiltrating neurons in bone marrow and other tissues may secrete serotonin and other ligands that can affect the expansion of HSCs. We consider that human consumption of SSRIs after infusion of CD34+ HSCs may be beneficial from multiple aspects.
These drugs can increase the accessibility of serotonin to HSCs by several pathways; one of which is blockage of SERT in the nerve terminals of infiltrating neurons to the bone marrow microenvironment and megakaryoblast. Reuptake of serotonin is prevented by inhibition of SERT, and therefore serotonin concentrations increase in the microenvironment of the bone marrow.

There is also some evidence that megakaryoblasts are able to synthesize serotonin. Our hypothesis is that serotonin cannot enter megakaryoblasts because of SERT blockage. It seems likely that this results in elevated levels of serotonin in the bone marrow, by increasing serotonin synthesis via megakaryoblasts (compensating for serotonin deficiency). Finally, this will lead to the expansion of CD34+ HSCs and early progenitors, in vivo.

Serotonin also can increase expansion of BMSCs. These cells have immunoregulatory properties and can decrease GVHD symptoms. To take advantage of this property, co-infusion of mesenchymal stem cells with CD34+ HSCs was recently reported as a novel protocol in HSC transplantation.8-10 On the other hand, some studies have shown that SSRIs have immunosuppressive effects, and we hypothesized that this may be due to increased serotonin in the bone marrow microenvironment that leads to an increase in the expansion of BMSCs. Therefore, the observed immunosuppressive effects may be the result of expansion of BMSCs that lead to a decrease in GVHD symptoms. Hirato et al.17 demonstrated that serotonin (10 μM) was able induce rat BMSC differentiation into smooth muscle-like cells in vitro. Moreover, SSRIs (except citalopram) have been shown to have negative effects on human osteoclasts and osteoblasts.11 Thus the possible side effects of SSRIs should be considered.

Altogether we conclude that SSRIs may promote the efficacy of HSC transplantation by increasing the in vivo expansion of HSCs and decreasing the incidence of GVHD.

Acknowledgements

The present work is supported by Tarbiat Modares University, Tehran, Iran.

Conflict of interest

None.

Author contributions

Writing the manuscript (AA, MAR, AA, MS).

References


