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Is prolonged stem cell mobilization detrimental for hematopoiesis?

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Abstract

Multiple hematological side effects have been reported to result from treatment with psychoactive phenothiazines. These reported toxicities include leucopenia, granulocytopenia, thrombocytopenia, agranulocytosis, and bone marrow aplasia. The physiological mechanism causing these potentially life-threatening blood dyscrasias is unknown. Recently, we discovered that phenothiazines exhibit antagonistic properties towards the VLA-4 integrin, an adhesion molecule that is responsible for homing and retention of hematological stem/progenitor cells (HSPCs) in the bone marrow. After administration of thioridazine we detected rapid mobilization of HSPCs into the peripheral blood. We propose that in patients receiving phenothiazines over a prolonged time period, continuous mobilization of stem cells out of the stem cell niche, results in a disorder of hematopoiesis. Furthermore, we also postulate that such cytopenias are caused by a loss of the niche environment, which is known to be essential for stem cell maintenance.

Introduction

Understanding mechanisms of drug-induced adverse effects provides valuable information, and potentially leads to the development of safer alternatives. The idea that off-target drug action can be responsible for adverse secondary effects is not new [1]. Here we present a hypothesis linking well-documented blood disorders that result from the treatment with psychoactive phenothiazines [2], and a new finding that phenothiazines and several other structurally related drugs exhibit properties of allosteric integrin antagonists. Moreover, phenothiazines mobilize hematopoietic progenitors into the peripheral blood [3]. (See also PubChem, AID: 2674, HTS for Identification of VLA-4 Allosteric Modulators from Validation Compound Set, active compounds).

Drug-induced blood dyscrasia

Serious drug-induced adverse hematological side effects have been reported in patients treated with psychoactive drugs. Phenothiazines were one of the first drugs that were

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documented to cause bone marrow hypoplasia or suppression. The effects of phenothiazines range from minor anaemia, to life-threatening granulocytopenia, thrombocytopenia, agranulocytosis, and trilineage bone marrow aplasia [2,4,5]. The mechanism of phenothiazine-induced bone marrow suppression is unknown. In several cases immune-mediated mechanisms, which include drug-dependent anti-blood cell antibodies, resulting in peripheral cell destruction, had been suggested. The suppression of hematopoietic precursors by prolonged administration of the drug without an immune component was also proposed [2,4]. In general, it is likely that multiple mechanisms may contribute to the etiology of drug-induced blood dyscrasias [5]. It is possible that a previously unrecognized mechanism also plays a role in the pathology of bone marrow suppression.

Schizophrenia, phenothiazines, and atypical lymphocytes

The etiology of schizophrenia is a longstanding mystery. Atypical lymphocytes, resembling early hematological progenitors, and therefore referenced as “blast-type atypical lymphocytes” have been reported in the peripheral blood of patients with schizophrenia [6,7]. These data led to the notion that an immune component contributes to the risk of the disease and resulted in a large number of studies implying a potential role of immune pathology in the etiology of schizophrenia [8,9]. Other studies suggested that the appearance of atypical cells coincides with the use of phenothiazine drugs, regardless of the disease status [10]. Nonetheless, the fact that cells resembling early hematopoietic progenitors are present in the peripheral blood of schizophrenic patients, often treated with phenothiazines, is well established.

VLA-4 integrin, phenothiazines as VLA-4 antagonists, and stem cell mobilization

CD49d/CD29, the $\alpha_4\beta_1$ -integrin known as Very Late Antigen-4 (VLA-4), plays a unique role in the retention, homing, and engraftment of HSPCs [11-13]. It is expressed on murine HSPCs, and human CD34+ early hematological progenitor cells [14-16]. Blocking the interaction between VLA-4 and its ligands expressed on bone marrow stroma using specific antibodies or small molecule inhibitors induces rapid mobilization of HSPCs in humans [17,18], primates [19,20], and mice [21]. Furthermore, VLA-4 blockade alone, without additional cytokine treatment, is sufficient to induce HSPC mobilization (see [20] and references therein). Thus, the effect of VLA-4 inhibitors on HSPC is very VLA-4-specific, since all VLA-4 antagonists studied to date do, in fact, induce HSPC mobilization.

Recently, we found that phenothiazines act as allosteric antagonists for the $\alpha_4\beta_1$ -integrin [3]. A number of phenothiazines blocked the binding of VLA-4 specific ligands to the integrin, and disrupted VLA-4 specific cellular aggregates [3]. To study whether this class of drugs also induces HSPC mobilization, mice were treated with thioridazine or plerixafor (AMD3100, a well known progenitor mobilizing agent, CXCR4 receptor antagonist [22]). Intraperitoneal administration of thioridazine significantly increased the number of colony-forming units in mice, and quantitatively, the effect of thioridazine was comparable to plerixafor [3]. Thus, in our experiments, phenothiazines induced mobilization of early progenitors in mice. Therefore, we propose that the VLA-4 antagonistic properties of phenothiazines may account for the phenomenon of “blast-type atypical lymphocytes” detected in patients treated with phenothiazines (see above).

Stem cell niche environment is essential for stem cell maintenance

The bone marrow environment is a complex association of multiple cell types including osteolineage cells, sinusoidal, endothelial, and mesenchymal cells that coexist in close

proximity to each other, and regulate and maintain the life cycle of HSPCs. These cells produce cytokines, chemokines, and other factors, both soluble and immobilized on surfaces, and together with the extracellular matrix provide a unique microenvironment where HSPCs reside [13,23,24]. Every year new cellular and molecular components of the HSPC niche are identified. The role of adhesive interactions and soluble factors acting at a short distance in the juxtacrine regulation of HSPCs is under intensive investigation [24]. However, the idea that multiple complex interactions contribute to the maintenance of stem cells is largely accepted and several components of the niche are indispensable. Thus, the mobilization of cells from the niche environment will result in a loss of cellular and molecular components that provide regulatory guidance to progenitor cells. Unless mobilized HSPCs can find a proper homing environment, these cells will not further participate in normal hematopoiesis

Our hypothesis

Thus, we postulate that in patients treated with psychoactive phenothiazines, and because of their antagonistic properties towards VLA-4 integrins, early hematopoietic progenitor cells are mobilized into the peripheral blood. Since these drugs are present in the blood for a prolonged time period (in the context of the typical treatment regimen), they prevent proper cell homing, and potentially stimulate the long-term sustained release of these cells into the circulation.

While mobilized from the bone marrow, progenitor cells will be deficient in the specific factors of the stem cell niche environment. This may affect cell proliferation and/or cell survival, and as a result this can lead to the suppression of hematopoiesis. Because of the differences in the type of drug, dose, patient's age, genetics, and other factors, different degrees of bone marrow suppression can be expected. Thus, it appears likely that prolonged stem cell release into the circulation would be detrimental to hematopoiesis.

This hypothesis raises a number of questions. Could short-term phenothiazine administration be used as a surrogate for stem-cell therapy in non-psychiatric disorders, where stem cell mobilization and subsequent homing, for example to the site of injury, is thought to be beneficial [25,26]? And moreover, can phenothiazines become a cheaper alternative for use in HSPC mobilization protocols for autologous stem cell transplantation? These questions can be rapidly examined since all compounds described in the paper [3] are FDA approved off-patent drugs.

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