Correction of the Abnormal Trafficking of Primary Myelofibrosis CD34+ Cells by Treatment with Chromatin-Modifying Agents

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Abstract
The abnormal trafficking of CD34+ cells is a unique characteristic of primary myelofibrosis (PMF). We have further studied the behavior of PMF CD34+ cells by examining their homing to the marrow and the spleens of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice. Following the infusion of PMF and normal granulocyte colony-stimulating factor–mobilized peripheral blood (mPB) CD34+ cells into NOD/SCID mice, reduced numbers of PMF CD34+ cells and granulocyte-macrophage colony-forming unit (CFU-GM) compared with mPB were detected in the marrow of these mice, whereas similar numbers of PMF and mPB CD34+ cells and CFU-GM homed to their spleens. The abnormal homing of PMF CD34+ cells was associated with reduced expression of CXCR4, but was not related to the presence of JAK2V617F. The sequential treatment of PMF CD34+ cells with the chromatin-modifying agents 5-aza-2′-deoxycytidine (5azaD) and trichostatin A (TSA), but not treatment with small molecule inhibitors of JAK2, resulted in the generation of increased numbers of CD34+CXCR4+ cells, which was accompanied by enhanced homing of PMF CD34+ cells to the marrow but not the spleens of NOD/SCID mice. Following 5azaD/TSA treatment, JAK2V617F-negative PMF hematopoietic progenitor cells preferentially homed to the marrow but not the spleens of recipient mice. Our data suggest that PMF CD34+ cells are characterized by a reduced ability to home to the marrow but not the spleens of NOD/SCID mice and that this homing defect can be corrected by sequential treatment with chromatin-modifying agents. [Cancer Res 2009;69(19):7612–8]

Introduction
In normal individuals, only a small fraction of hematopoietic stem cells (HSC) and hematopoietic progenitor cells (HPC) regularly exit the bone marrow (BM) and circulate in the peripheral blood (PB; ref. 1). The fine balance between mobilization, homing, and retention of HSCs/HPCs within the marrow microenvironment is a characteristic of normal adult hematopoiesis. Stem cell trafficking is largely dependent on the interaction between a number of integrins and chemokine receptors expressed by HSCs/HPCs and a variety of matrix proteins present within the marrow microenvironment and chemokines elaborated by marrow fibroblasts, osteoblasts, or endothelial cells (2). The administration of hematopoietic growth factors (granulocyte colony-stimulating factor, G-CSF) leads to transient increments in the number of circulating HSCs/HPCs (3). The interactions between CXC chemokine stromal-derived factor-1 (SDF-1) and its receptor CXCR4 play a pivotal role in determining the migration, homing, retention, proliferation, and differentiation of human HSCs/HPCs (2–4).

By contrast, the myeloproliferative neoplasm, primary myelofibrosis (PMF), is characterized by abnormal CD34+ cell trafficking, resulting in constitutive mobilization of CD34+ cells (5–8). We have reported that PMF PB CD34+ cells contain not only HPCs but also BM-repopulating cells belonging to the malignant clone (8). Whether this constitutive mobilization is a direct result of qualitative abnormalities of HSCs/HPCs, or a change in the interaction between PMF HSCs/HPCs and the BM stem cell niche, has been the subject of considerable investigation (9–14).

Homing is thought to be a coordinated, multistep process, which involves SDF-1/CXCR4 interactions, activation of lymphocyte function–associated antigen-1 (LFA-1), α4β1 integrin (VLA-4), and α5β1 integrin (VLA-5), and rearrangement of the cytoskeleton of HSCs/HPCs (15, 16). The homing of PMF CD34+ cells and the role of the SDF-1/CXCR4 axis and VLA-4 in this process have not been previously explored. Since reduced expression of CXCR4 by PMF CD34+ cells has been previously documented (12, 14), we hypothesized that PMF CD34+ cells might exhibit a compromised ability to home to the marrow.

A gain of function mutation in the JH2 domain of the Janus kinase 2 (JAK2V617F) has been identified in the Philadelphia-negative myeloproliferative neoplasms; the JAK2V617F mutation is present in ~50% of patients with PMF (17, 18). In ~10% of JAK2V617F-negative PMF, another somatic mutation at codon 515 of the transmembrane-juxtamembrane junction of the thrombopoietin receptor gene, MPL, has also been identified (19). The presence of these two mutations is associated with constitutive activation of JAK/STAT proteins, which results in HPC hypersensitivity to growth factors (17–19). The JAK/STAT pathway has also been reported to be involved in the activation of genes responsible for cancer cell growth, survival, invasion, and migration (20, 21), suggesting that abnormal PMF CD34+ cell trafficking might be a consequence of JAK2V617F.

The malignant phenotype in PMF likely results from a combination of genetic abnormalities and epigenetic modifications leading to the dysregulation of critical genes that contribute to cell proliferation, differentiation, and cell death (17–19, 22–24). Methylation of cytosine residues in the promoter region as well as transcriptional inhibitory complexes including histone deacetylases (HDAC) play a role in the transcriptional silencing of genes in a variety of human cancers (25–27). For instance, the reduced
expression of CXCR4 by PMF CD34+ cells has been attributed to hypermethylation of its promoter (14). Several reports have indicated that re-expression of silenced genes can be achieved by sequential treatment with a DNA methyltransferase inhibitor (28, 29). We have previously indicated that re-expression of silenced genes can be achieved by hypermethylation of its promoter (14). Several reports have resulted in up-regulation of CXCR4 expression by PMF CD34+ cells and restoration of their migratory response to SDF-1 (30). The homing of PMF CD34+ cells to the marrow and spleens of sublethally irradiated mice was studied and its correction by treatment with chromatin-modifying agents was assessed.

Materials and Methods

**Patient specimens and CD34+ cell isolation.** G-CSF–mobilized PB (mPB) CD34+ cells from 10 donors were purchased from StemCell Technologies. PB was collected from 33 patients who fulfilled the WHO diagnostic criteria for PMF (31). All patients had signed an informed consent approved by the Institutional Review Board of the Mount Sinai School of Medicine.

Granulocytes were isolated by previously described techniques (10, 17, 18). CD34+ cells were selected from PB low-density mononuclear cells using a CD34+ cell selection kit (StemCell Technologies) according to the manufacturer's instructions. The purity of the CD34+ cell population was analyzed using a FACScanto flow cytometer (Becton Dickinson). CD34+ cell populations with a purity of ≥90% was used in all experiments.

**JAK2V617F and MplW515L mutational analysis.** JAK2V617F and MplW515L were detected by analyzing the PB granulocytes of patients with PMF as described previously (32, 33). Among the 33 PMF patients used in this study, 19 patients were JAK2V617F positive, whereas none were MplW515L positive.

**Treatment of PMF CD34+ cells with 5azaD and TSA.** PMF CD34+ cells (1 x 10^7/mL) were cultured in Iscove's modified Dulbecco's medium (IMDM; Bio Whittaker) containing 30% fetal bovine serum (FBS; HyClone Laboratories) supplemented with 100 ng/ml stem cell factor, 100 ng/mL FLT-3 ligand, 100 ng/ml thrombopoietin, and 54 ng/mL interleukin-3 (IL-3; Amgen) and incubated in a humidified incubator maintained at 37°C with 5% CO2. After an initial 16 h of incubation, cells were exposed to 5azaD (Pharmachemie B.V.) at a concentration of 1 µmol/L. After 48 h, cells were washed and then distributed to new culture plates containing stem cell factor, FLT-3 ligand, and thrombopoietin with TSA (Sigma), which was added once at the beginning of the following 7-day culture at a concentration of 16.5 nmol/L. In addition, parallel cultures to which 5azaD/TSA were not added were performed. The CD34+ cells were reisolated as described above after 9 d of culture.

**Treatment of PMF CD34+ cells with small molecule inhibitors of JAK2.** PMF CD34+ cells (1 x 10^7/mL) were cultured in IMDM containing FBS and cytokines as described above. After an initial 16 h of incubation, cells were cultured in the presence or absence of JAK inhibitor 1 (Calbiochem) or AZ1480 (gift of AstraZeneca) at a concentration of 100 nmol/L. After 72 h, the cells were washed and analyzed for CD34 and CXCR4 expression.

**Flow cytometric analysis of CD34+ cells.** Primary PMF CD34+ cells, mPB, and PMF CD34+ cells after 3 or 9 d of culture were stained with anti-human CD34 monoclonal antibody (mAb) conjugated to allophycocyanin and CXCR4 (clone# 12G5) or VLA-4 conjugated to phycoerythrin. All mAb were purchased from Becton Dickinson Pharmingen. Each analysis was paired with a corresponding matched isotype control. Immediately before flow cytometric analysis, 1 µg/ml propidium iodide (Sigma) was added to exclude nonviable cells. Cells were analyzed flow cytometrically and at least 10,000 viable cells were acquired from each sample (Cell-Quest software, Becton Dickinson). To avoid underestimating CXCR4 expression, initially, we stained primary PMF CD34+ cells and mPB CD34+ cells using anti-human CXCR4 mAb purchased from R&D Systems. The mAb, 44717, which recognizes the second external loop of the CXCR4 receptor (34), has been reported to be capable of recognizing a greater degree of CXCR4 expression by primary and transformed T cells as well as primary B cells (35). By contrast 12G5, the mAb most commonly used to study CXCR4 expression recognizes extracellular loops 1 and 2 of the receptor (34) but identifies a smaller fraction of primary cells expressing CXCR4 (35).

**Homing assay.** NOD/LSz-Pkdce<sup>−/−</sup> (NOD/SCID) mice were purchased from the Jackson Laboratory. All experiments were approved by the Animal Care Committee of the Mount Sinai School of Medicine. The mPB CD34+ cells, primary PMF CD34+ cells, or PMF CD34+ cells reisolated after 90% was used in all experiments.

Figure 1. Homing of mPB and PMF CD34+ cells to the BM and spleens of NOD/SCID mice. A, a representative flow cytometric diagram demonstrating the percentage of human CD34+ cells per 10<sup>6</sup> cells present in the BM and spleens of recipient mice. Reduced numbers of PMF CD34+ cells and human CFU-GM (B) were detected in the marrow of these mice compared with mPB CD34+ cells. Similar numbers of PMF and mPB CD34+ cells and human CFU-GM (C), however, were detected in the spleens of these mice. **, P < 0.01; ***, P < 0.001.
were two-sided.

To assay for human HPCs, murine marrow and spleen cells from mice transplanted with human cells were cultured in semisolid medium as previously described (36). Mononuclear cells (5 or 10 × 10^6/mL) were suspended in methylcellulose [Methocult (H4230); Stem Cell Technologies] with 20% IMDM supplemented with 50 ng/mL human granulocyte macrophage colony-stimulating factor, 50 ng/mL human stem cell factor, and 50 ng/mL human IL-3, conditions previously reported to promote human colony formation. Using these conditions, no colony growth was observed when BM from saline-injected animals was assayed (36). We confirmed the human origin of these individual colonies by plucking and analyzing cells for the human GAPDH gene by reverse transcription-PCR. The presence of human CD34+ cells in BM and spleen cells was determined from the BM of two femurs, one tibia, and the spleens of the recipient mice. The homing of PMF and mPBCD34+ cells to the marrow is not solely a consequence of JAK2V617F.

Reduced expression of CXCR4 by PMF CD34+ cells. Several groups have suggested that the constitutive mobilization of PMF CD34+ cells might be related to the down-regulation of CXCR4.

Results

Reduced homing of PMF CD34+ cells to the marrow of NOD/SCID mice. The homing of PMF and mPB CD34+ cells to the marrow and spleens of sublethally irradiated NOD/SCID mice was evaluated. Figure 1A shows the presence of human CD34+ cells in the marrow and spleens of recipient mice. As shown in Fig. 1B, following the infusion of either PMF (n = 14) or mPB (n = 6) CD34+ cells, reduced numbers of marrow PMF CD34+ cells and human CFU-GM were detected [130 ± 35 PMF CD34+ cells/10^6 BM cells (BMC) versus 295 ± 28 mPB CD34+ cells/10^6 BMCs, P < 0.01; 0.62 ± 0.19% of input PMF CFU-GM versus 6.95 ± 2.13% of input mPB CFU-GM, P < 0.001]. By contrast, similar numbers of PMF and mPB CD34+ cells and human CFU-GM were detected in the spleens of these animals [463 ± 66 PMF CD34+ cells/10^6 spleen cells versus 526 ± 42 mPB CD34+ cells/10^6 spleen cells, P = 0.58; 0.41 ± 0.12% of input PMF CFU-GM versus 0.34 ± 0.20% of input mPB CFU-GM, P = 0.76; Fig. 1C).

The defective homing of PMF CD34+ cells to the marrow is independent of JAK2V617F. As shown in Fig. 2A and B, the numbers of human CD34+ cells and CFU-GM were equally reduced in the marrow of mice infused with either JAK2V617F-positive (107 ± 46 PMF CD34+ cells/10^6 BMCs, P < 0.01; 0.83 ± 0.34% of input PMF CFU-GM, P < 0.01) or JAK2V617F-negative PMF CD34+ cells (139 ± 41 PMF CD34+ cells/10^6 BMCs, P < 0.05; 0.36 ± 0.07% of input PMF CFU-GM, P < 0.01) compared with mPB CD34+ cells (295 ± 28 mPB CD34+ cells/10^6 BMCs and 6.95 ± 2.13% of input mPB CFU-GM). Similar numbers of CD34+ cells and human CFU-GM were detected in the spleens of mice infused with JAK2V617F-positive (434 ± 37 PMF CD34+ cells/10^6 spleen cells; 0.30 ± 0.17% of input PMF CFU-GM) or JAK2V617F-negative PMF CD34+ cells (484 ± 79 PMF CD34+ cells/10^6 spleen cells; 0.52 ± 0.18% of input PMF CFU-GM; Fig. 2C and D). These findings suggest that the impaired PMF CD34+ cell homing to the marrow is not solely a consequence of JAK2V617F.

Statistical analysis. The results are reported as the mean ± SD of data obtained from four to six individual experiments. Statistical significance was determined using Student’s t tests or paired samples t test. All P values were two-sided.

Figure 2. Homing of CD34+ cells from PMF patients with or without JAKV617F. The numbers of CD34+ cells (A) and human CFU-GM (B) detected in the marrow of mice infused with JAK2V617F-positive (n = 6) or JAK2V617F-negative PMF CD34+ cells (n = 8) were reduced compared with the behavior of mPB CD34+ cells (n = 6). There was no difference in the behavior of mice infused with JAK2V617F-positive or JAK2V617F-negative PMF CD34+ cells (P > 0.05). Similar numbers of CD34+ cells (C) and human CFU-GM (D) were detected in the spleens of mice infused with JAK2V617F-positive and JAK2V617F-negative PMF CD34+ cells compared with mPB CD34+ cells. *, P < 0.05; **, P < 0.01.
expression (12, 14). We therefore examined CXCR4 expression by PMF CD34+ cells. As shown in Fig. 3A, the percentage of PMF CD34+ cells that expressed CXCR4 was significantly lower (4.8 ± 2%; P < 0.05) than mPB CD34+ cells (15.3 ± 4.3%). The reduced expression of CXCR4 by PMF CD34+ cells, as indicated by the percentage of positive cells and the mean fluorescence intensity, was similar using mAb 12G5 or 44717 (Supplementary Fig. S1).

Vascular cell adhesion molecule-1/VLA-4 interactions also plays a role in HSC trafficking (39, 40). We therefore determined if differences in the expression of VLA-4 by PB CD34+ cells might also contribute to the abnormal trafficking of PMF CD34+ cells. The percentage of mPB and PMF CD34+ cells that expressed VLA-4 was however, similar (data not shown).

JAK2V617F was not associated with reduced expression of CXCR4 by PMF CD34+ cells. As shown in Fig. 3A, JAK2V617F-positive and JAK2V617F-negative PMF CD34+ cells exhibited a similar degree of reduced expression. We further examined if CXCR4 expression by JAK2V617F-positive PMF CD34+ cells could be altered by treatment with two JAK2 inhibitors, JAK inhibitor 1 or AZ1480. Treatment of PMF CD34+ cells with cytokines and either JAK inhibitors resulted in a 25% or 22% reduction, respectively, in the absolute number of CD34+ cells compared with cells exposed to cytokines alone. As shown in Fig. 3B and C, a greater number of CD34+ cells expressing CXCR4 were detected following the culture of JAK2V617F-positive PMF CD34+ cells with cytokines alone. However, the percentage and the number of JAK2V617F-positive PMF CD34+ cells that expressed CXCR4 was not further enhanced by treatment with JAK inhibitors *, P < 0.05; **, P < 0.01 versus primary PMF CD34+ cells.

5azaD/TSA treatment increased the numbers of PMF CD34+CXCR4+ cells. PMF CD34+ cells (1 × 10^5) generated greater numbers of cells when cultured in the presence of cytokines alone (19.94 ± 4.06 × 10^5) than in the presence of cytokines plus 5azaD/TSA (12.97 ± 1.66 × 10^5). The proportion of CD34+ cells expressing CXCR4 was significantly increased in the cultures containing cytokines plus 5azaD/TSA (B). *, P < 0.05; **, P < 0.01.
population. The percentage of CD34+ cells that was CXCR4 positive within the 5azaD/TSA-treated PMF CD34+ cell cultures, however, was significantly greater (27.86 ± 5.88%) than in cells exposed to cytokines alone (8.05 ± 1.43%; *P < 0.01) or primary PMF CD34+ cells (1.81 ± 0.52%; *P < 0.01; Fig. 4A). In addition, treatment of PMF CD34+ cells in vitro with cytokines plus 5azaD/TSA led to a 3- to 4-fold increase in the absolute numbers of CD34+CXCR4+ cells compared with CD34+ cells exposed to cytokines alone (P < 0.05) and a 24- to 72-fold increase of the number of CD34+CXCR4+ cells when compared with input PMF CD34+ cells (P < 0.05; Fig. 4B).

**Correction of the abnormal homing of PMF CD34+ cells by treatment with 5azaD/TSA.** We next determined if the up-regulation of CXCR4 by PMF CD34+ cells following the treatment with chromatin-modifying agents was associated with correction of the impaired homing of primary PMF CD34+ cells. After culture, CD34+ cells were reisolated and transplanted into NOD/SCID mice. As can be seen in Fig. 5A, treatment of PMF CD34+ cells with cytokines alone resulted in 3- to 6-fold greater number of CD34+ cells homing to NOD/SCID marrow than that observed with primary PMF CD34+ cells (P < 0.01). By contrast, 10- to 14-fold greater numbers of CD34+ cells treated with 5azaD/TSA homed to mouse marrow than primary PMF CD34+ cells (P < 0.001), whereas 2.5- to 3-fold greater numbers of 5azaD/TSA treated CD34+ cells homed to mouse marrow than PMF CD34+ cells treated with cytokines alone (P < 0.001). The proportion of assayable human CFU-GM that homed to the marrow of mice transplanted with PMF CD34+ cells from cultures treated with cytokines plus 5azaD/TSA was significantly greater (8.71 ± 2.28%) than the proportion of transplanted human CFU-GM from primary PMF CD34+ cells (1.81 ± 0.45%; *P < 0.05) or primary PMF CD34+ cells (0.52 ± 0.24%; *P < 0.05; Fig. 5B). The proportion of transplanted human CFU-GM from each type of graft that homed to the spleens of NOD/SCID mice was similar (Fig. 5C and D).

5azaD/TSA treatment reduces the percentage of JAK2V617F-positive CFU-GM that home to the marrow. A total of 6 of the 12 patients were JAK2V617F positive. In five of six patients, the JAK2V617F allelic burden ranged from 40% to 86%. We then analyzed the JAK2V617F allelic status of CFU-GM assayed from the BM and spleens of mice transplanted with human cells. As shown in Fig. 6A, the percentage of JAK2V617F-negative CFU-GM that homed to the BM of mice transplanted with CD34+ cells from cultures treated with cytokines plus 5azaD/TSA was significantly greater (68.91 ± 16.83%) than CD34+ cells exposed to cytokines alone (17.19 ± 8.23%; *P < 0.05) or primary PMF CD34+ cells (23.39 ± 9.29%; *P < 0.05). By contrast, the percentage of JAK2V617F-negative CFU-GM in the spleens of mice transplanted with 5azaD/TSA-treated PMF CD34+ cells was similar (23.49 ± 10.02%) to that transplanted with either PMF CD34+ cells exposed to cytokines alone (12.84 ± 6.67%) or primary PMF CD34+ cells (15.89 ± 8.30%; Fig. 6B). These findings suggest that the homing of PMF CD34+ cells to the marrow but not the spleen can be corrected by treatment with 5azaD/TSA. JAK2V617F-negative myeloproliferative neoplasm HPCs that persist following 5azaD/TSA treatment seem to preferentially home to the marrow but not the spleens of recipient mice.

**Discussion**

Abnormal CD34+ cell trafficking is an integral part of the pathobiology of PMF (5). We have shown that the homing of PMF CD34+ cells to the marrow but not the spleens of NOD/SCID mice is defective and is associated with down-regulation of CXCR4. Other groups have also showed that SDF-1/CXCR4 interactions play a crucial role in the homing of both normal HSCs/HPCS (41) and human leukemic HSCs to the BM of NOD/SCID mice (42). By contrast, the expression of the integrin VLA-4 that is also involved in stem cell trafficking does not seem to be aberrantly expressed by PMF CD34+ cells and therefore is not responsible for the abnormal cell trafficking in PMF.

Because PMF CD34+ cells still retain the ability to home to the spleen, this might play a role in their localization to extramedullary sites and the establishment of hematopoiesis. Such studies suggest
that the microenvironment within the marrow and spleen differs. Such distinct characteristics of the hematopoietic microenvironment at various locales may be important in disease progression in PMF. It has also been reported that elevated numbers of endothelial progenitor cells and mesenchymal stem cells, which exist within the CD34+ cell subpopulation in PMF, are present in the blood and spleens of patients with PMF (43, 44). Therefore, the mobilization of CD34+ cells from the BM and homing to the spleen might contribute to the creation of both vascular and stromal microenvironments that facilitate the development of the MPD clones at these sites.

Several studies have indicated that JAKs are key signaling elements affecting chemokine receptor signaling (45, 46). However, other investigators have not confirmed such relationships (47). Our data suggest that the impaired homing of PMF CD34+ cells is not related to the presence of the JAK2V617F because the expression of CXCR4 by PMF CD34+ cells was independent of the presence of the mutation and was not affected by treatment with JAK2 inhibitors. Recently, Bogani and colleagues (14) have reported similar results.

In the present study, we showed that the treatment of PMF CD34+ cells with 5azaD/TSA resulted in up-regulation of CXCR4 and correction of the impaired homing of PMF CD34+ cell to the marrow of NOD/SCID mice. Treatment of PMF CD34+ cells with 5azaD/TSA resulted in not only an increase of the number of CD34+ cells expressing CXCR4 but also an increased density of CXCR4 (data not shown). The up-regulation of CXCR4 by chromatin-modifying agents has been previously shown to be due to the reversal of abnormal methylation of the CXCR4 promoter and the subsequent enhanced transcription of CXCR4 mRNA (14). Moreover, the treatment of PMF CD34+ cell with 5azaD/TSA promoted JAK2V617F-negative CD34+ cells that persisted following 5azaD/TSA treatment to home to the marrow but not the spleens of NOD/SCID mice. The sequential treatment of PMF CD34+ cells with 5azaD/TSA has been reported to result in a reduction of the number of JAK2V617F-positive progenitor cells (30), whereas the treatment of normal BM and cord blood stem cells in vitro with these same agents leads to their symmetrical cell division and stem cell expansion (48). The correction of PMF CD34+ cell trafficking following the treatment of chromatin-modifying agents could, therefore, be due either to the increased expression of CXCR4 by malignant and normal CD34+ cells or an increased number of normal HSC/HPC relative to the number of malignant HSC/HPC. It also remains possible that the expression of other as yet unidentified integrins or chemokine receptors involved in stem cell trafficking might be also responsible for correction of HSCs/HPCs homing by chromatin-modifying agents.

In conclusion, our data indicate that PMF CD34+ cells are characterized by defective homing to the marrow but not the spleen and that this homing defect can be corrected by sequential treatment with chromatin-modifying agents. Chromatin-modifying agents represent a possible means of correcting the abnormal cellular trafficking characteristic of PMF, a therapeutic strategy that is currently being evaluated in the clinic. Furthermore, the use of such agents in combination with small molecule inhibitors of JAK2 in future therapeutic trials might represent an opportunity to target several abnormalities of PMF CD34+ cell behavior.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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