Adipocytes Impair Leukemia Treatment in Mice


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Abstract

Obesity is associated with increased cancer incidence and mortality. We have previously found that obesity in children is associated with a 50% increased recurrence of acute lymphoblastic leukemia (ALL) in high-risk patients. We have therefore developed novel in vivo and in vitro preclinical models to study the mechanism(s) of this association. Obesity increased relapse after monotherapy with vincristine (P = 0.03) in obese mice injected with syngeneic ALL cells. This occurred although the drug was dosed proportionally to body weight, equalizing blood and tissue drug levels. In coculture, 3T3-L1 adipocytes significantly impaired the antileukemia efficacy of vincristine, as well as three other chemotherapies (P < 0.05). Interestingly, this protection was independent of cell-cell contact, and it extended to human leukemia cell lines as well. Adipocytes prevented chemotherapy-induced apoptosis, and this was associated with increased expression of the two prosurvival signals Bcl-2 and Pim-2. These findings highlight the role of the adipocyte in fostering leukemia chemotherapy resistance, and may help explain the increased leukemia relapse rate in obese children and adults. Given the growing prevalence of obesity worldwide, these effects are likely to have increasing importance to cancer treatment.[Cancer Res 2009;69(19):7867–74]

Introduction

Obesity is associated with an increased risk of numerous types of cancer in adults (1–7). In addition, obese cancer patients have poorer outcomes than their leaner counterparts (7–9). Calle and colleagues (1) estimated that given the high prevalence of obesity in the United States and the strength of its association with cancer, 14% of all cancer deaths in men and 20% in women are attributable to obesity.

Leukemia is the most common childhood cancer, affecting ~2,000 children per year in the United States (10). We have previously shown that obese adults diagnosed with acute lymphoblastic leukemia (ALL) have a 50% higher likelihood of relapse than lean adults (11). Three recent studies have examined the relationships between obesity and ALL relapse in children. Two of these reported that obesity tended to increase (12) or had no detectable effect on relapse risk (13). However, these relatively small studies each had fewer than 25 obese subjects ages over 10 years. In a large cohort of 5,420 children, including 262 obese subjects ages ≥10 years, we found that obesity at the time of ALL diagnosis independently increased relapse rates by ~50% in children ≥10 years of age (14).

The mechanisms underlying the association between obesity and ALL relapse are likely multifactorial. Adipocytes could alter chemotherapy pharmacokinetics and/or induce drug resistance by secretion of adipokines. Other growth factors secreted in the context of obesity could enhance leukemia cell survival. Adipose tissue stromal cells promote solid tumor growth, and thus might affect leukemia cells as well (15). To investigate the roles of obesity in ALL relapse, we have established new in vivo and in vitro models. We focused our studies on vincristine, as it is used nearly universally as a first-line agent in the treatment of childhood leukemia, and vincristine resistance in vitro (16) and in mouse xenografts (17) is strongly prognostic of relapse. Here, we report how adipocytes impair the leukemia response to vincristine in vivo and of several drugs in vitro.

Materials and Methods

Diet-induced obesity model. Male C57BL/6 mice (The Jackson Laboratory) were weaned onto a high-fat diet (60% of calories from fat; Research Diets D12492) or a control diet (10% of calories from fat, D12450) until transplantations at ~20 wk of age. All experiments were approved by the Children’s Hospital Los Angeles Institutional Animal Care and Use Committee and performed in accordance with the USPHS Policy on Humane Care and Use of Laboratory Animals.

Cell lines. Murine pre-B-cell ALL was previously isolated from a BCR/ABL transgenic mouse (“8093 cells”; refs. 18, 19). A subset of these was transduced on retroenectin-coated plates with a retroviral vector containing pMIG-GFP (provided by M. Mueschen of Children’s Hospital Los Angeles, Los Angeles, CA). Human leukemia cell lines included RCH-ACV (pre-B ALL with an E2A-PBX1 fusion protein; ref. 20), BV173 (PreB Ph+ ALL; ref. 21), SD-1 (pre-B Ph+ ALL, DSMZ), and RS4-11 (pre-B t(4;11) ALL, American Type Culture Collection (ATCC)).

Murine fibroblasts and adipocytes were derived from 3T3-L1 cells (ATCC). 3T3-L1 cells were differentiated into adipocytes based on optimization of a method previously described (22). Briefly, cells were grown to confluence in DMEM (Invitrogen) with 10% fetal bovine serum (FBS), Glutamax, sodium pyruvate, and antibiotics in poly-l-lysine coated wells (day ~2). On day 0, the media were changed to DMEM with supplements plus 15% FBS, 20 mmol/L HEPES, 150 nmol/L insulin, 250 nmol/L dexamethasone, and 0.5 mmol/L isobutylmethylxanthine (Sigma). On day +2, dexamethasone and isobutylmethylxanthine were removed from the media, and on day +4, insulin was removed. Media changes were performed every 2 d until use. Adipocytes were used for coculture experiments between days +7 and +14. Undifferentiated 3T3-L1 fibroblasts were irradiated and then plated at confluence. Control experiments were also performed with nonirradiated 3T3-L1 cells at confluence. In different experiments, we used adipocytes differentiated from OP-9 murine bone marrow mesenchymal cells (ATCC) as described above (23), and undifferentiated (nonirradiated) OP-9 cells as control.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/). Requests for reprints: Steven D. Mittelman, Childrens Hospital Los Angeles, 4650 Sunset Boulevard, MS #93, Los Angeles, CA 90027. Phone: 323-361-7653; Fax: 323-906-8013; E-mail: smittelman@chla.usc.edu.

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In vivo leukemia model. To test whether obesity would impact proliferation of leukemia in vivo, we injected 5,000 8093 cells into mice via a retro-orbital route. Animals were euthanized upon development of progressive leukemia (weight loss of >10%, paralysis, hunched posture, or visible masses of >1 cm). Leukemia was verified by necropsy and/or by DNA qPCR for BCR/ABL in peripheral blood, using DNeasy kits (Qiagen) and Power SYBR Green master mix on an ABI Prism 7722 Sequence Detector (Applied Biosystems).

To examine the effects of diet-induced obesity (DIO) on leukemia treatment, we injected 10,000 8093 cells into 12 DIO, 12 control, and 7 vehicle mice as above. Eight days after the injection, mice were treated with vincristine in proportion to body weight (0.5 mg/kg/wk via i.p. injection ×4 wk, Vincasar, Teva Pharmaceuticals; ref. 24).

Five additional DIO mice were transplanted with GFP+ 8093 cells and treated for 3 to 4 wk with vincristine after an 8- to 10-d engraftment period. Mice were perfused with paraformaldehyde (PFA; n = 2) or PBS (n = 3) at time of leukemia relapse and sacrifice. Fat pads from the PFA-perfused mice were removed, cut into small (1-1 mm) pieces, and examined en bloc for the presence of GFP+ leukemia cells. Fat pads from the PBS-perfused mice were fixed in PFA, frozen in optimum cutting temperature (Sakura Tek), and sliced to 10-μm thickness (at ~20°C). Additional fat pads were digested with Liberase TM (Roche) at 2 U/mL for 30 min, spun at 350 g × 5 min, and pelleted cells were cultured for 3 to 5 d to test for viability and vincristine sensitivity.

Coculture experiments. Leukemia cells were seeded into 24-well plates with fibroblasts, adipocytes, or no feeder layer. In experiments of drug resistance, 25 nmol/L vincristine, 20 nmol/L nilotinib, 35 nmol/L daunorubicin, or 25 nmol/L dexamethasone was added (all at the IC50 in our culture system without feeder layers). After 72 h, the wells were triturated forcefully to remove cells within and below the feeder layers, and counted by a system without feeder layers. After 72 h, the well were trituated forcefully to remove cells within and below the feeder layers, and counted by a blinded observer by trypan blue exclusion.

The importance of cell-cell contact was assessed with 8093 leukemia cells in the upper chambers of polycarbonate 0.4-μm pore size TransWells (Corning, Inc.,). TransWells experiments were repeated with BV-173, SD1, RS4;11, and RCHACV human leukemia cell lines. To assess the importance of adipocyte viability, feeder layers were fixed with PFA before being used in TransWells. Mice were exposed to 4% PFA for 1 to 12 h, and then rinsed thrice with PBS followed by RPMI overnight. All experiments were done in triplicate and at least thrice unless otherwise noted.

Cell cycle and RNA expression studies. 8093 cells cultured in TransWells as above were analyzed for cell cycle and apoptosis by hemocytometric analysis (BrdUrd) incorporation (BrdU flow kit, BD Bioscience), and cells were analyzed on a FACScan (BD Biosciences, CellQuest software). Lymphocytes were defined based on forward and side scatter, and the percentage of this gated population in each cell cycle phase was determined. To assess gene expression, cells from a single TransWell were trypsinized, and cellswereanalyzedonaFACScan(BDBiosciences,CellQuestsoftware).

To address whether obesity impaired leukemia treatment via an interaction between adipocytes and leukemia cells, we next investigated whether adipose tissue could act as a "sanctuary" for leukemia cells during or after chemotherapy. Five obese mice were injected with GFP+ ALL cells and then treated with vincristine. Animals were sacrificed when signs of leukemia developed, which occurred during the vincristine treatment period in three of the five mice. Numerous GFP+ leukemia cells were visible in fat pads from all mice (Fig. 1C). These cells remained viable and proliferated in culture, and after 3 to 5 d, <10% were apoptotic, as measured by

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Annexin V and 7-AAD (n = 3; Supplementary Fig. S1). These cells also retained their sensitivity to 5 nmol/L vincristine (n = 3; data not shown). These findings support the concept that adipose tissue can be a sanctuary site for leukemia during vincristine treatment.

**Blood and tissue vincristine concentration.** To exclude the possibility that altered vincristine pharmacokinetics in obese mice confounded our survival results, we measured blood and tissue concentrations of vincristine after a 0.5 mg/kg vincristine injection in groups of DIO and control mice (see Supplementary Materials and Methods). As discussed, vincristine was given at doses proportional to body weight, so obese mice on average received ~28% more vincristine in total than control mice (19.7 ± 2.2 versus 14.7 ± 0.8 μg/mouse). However, vincristine profiles in blood and tissues were very similar between groups (Supplementary Fig. S2). Thus, poorer survival in obese mice was not likely due to altered exposure to the drug after dosage adjustment using body weight.

**Adipocytes protect leukemia cells against drug treatment.** To further characterize the possible effects of adipocytes on vincristine-induced cytotoxicity of leukemia cells, we developed an *in vitro* coculture system. Murine embryonic fibroblasts have been shown to provide significant protection to leukemia cells against some drugs (26, 27). 3T3-L1 fibroblasts were differentiated into adipocytes by exposure to a mixture of insulin, dexamethasone, and isobutylmethylxanthine (see Materials and Methods), and cultured together with 8093 leukemia cells. Irradiated, undifferentiated 3T3-L1 cells, which have a fibroblast phenotype, were used as controls.

The differentiated 3T3-L1 cells accumulated large lipid droplets as has been previously described (22). Leukemia cells rapidly (within 72 hours) migrated into and beneath the adipocyte layer (Fig. 1D), similar to what we had previously observed with murine embryonic fibroblasts. The proliferation of 8093 cells in coculture tended to be less with either 3T3-L1 fibroblasts (P = 0.27) or adipocytes (P = 0.09) after 3 days than without feeder layer, perhaps due to depletion of nutrients from the media (data not shown). However, coculture with adipocytes significantly decreased vincristine cytotoxicity toward leukemia. After 72 hours of vincristine exposure, the mean number of viable ALL cells was higher in cultures with adipocytes (52.8 ± 16.0 × 10³) than with fibroblasts (21.4 ± 7.0 × 10³; P = 0.048) or no feeder (8.5 ± 1.5 × 10³; P = 0.054; Fig. 2A, top). Similar coculture experiments were performed with three other antileukemia agents, each with different modes of antitumor activity (dexamethasone, daunorubicin, or nilotinib; Fig. 2A, top and bottom). For each drug, there were more surviving leukemia cells in coculture with adipocytes than with fibroblasts or no feeder.

**Protection of leukemia cells does not depend on cell-cell contact, but requires living adipocytes.** Because the leukemia cells established a close physical interaction with the feeder layers in coculture, we next investigated whether direct contact between adipocytes and leukemia cells is necessary for protection.

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**Figure 1.** DIO impairs vincristine treatment. A, obese (solid line) and nonobese (dashed line) mice transplanted with 5,000 syngeneic 8093 leukemia cells and left untreated (P = 0.22). B, mice transplanted with 10,000 8093 cells and treated with 0.5 mg/kg/wk vincristine (gray bar). Solid line, obese mice (n = 12); dashed black line, control mice (n = 12); gray dotted line, vehicle-treated controls (n = 7). C, GFP⁺ 8093 ALL cells in the perirenal fat pad of a transplanted obese mouse that developed progressive leukemia during vincristine treatment. Lipid is stained with Nile Red, and the image is counterstained with 4',6-diamidino-2-phenylindole. Image was taken on a Leica DM RXA2 with a ×20 objective with ×1.6 Optovar magnification (×32 final). Image is representative of fat pads obtained from the other four mice after vincristine treatment. D, GFP⁺ 8093 leukemia cells (green) and adipocyte feeder layer (lipid stained with Nile Red) after 48 h in coculture. Images obtained with a Zeiss LSM-510 laser scanning confocal/multiphoton microscope with a ×40 objective lens (Carl Zeiss, Inc.). Image represents Z-stack transformation (“side view”) of the adipocyte monolayer and leukemia cells (Velocity 4.3, Improvisation, Inc.).
Leukemia cells were cocultured in TransWells over the feeder layers, so that the two cell types were separated by a porous membrane that prevents physical contact. The feeder layers did not influence the leukemia proliferation rate in TransWells (Fig. 2B; *P = not significant for all comparisons). However, adipocytes in the lower chamber provided significant protection against vincristine (Fig. 2C). In fact, 5 nmol/L vincristine suppressed viable leukemia cells over adipocytes by only 11 ± 9% from the initial plated value, whereas those over fibroblasts or no feeder were much more significantly suppressed (by 55 ± 3%, and 85 ± 2%, *P = 0.009 and *P = 0.001 versus adipocytes, respectively).

To confirm that these coculture results are relevant to human leukemia, and not particular to the culture models used, we performed several additional experiments. To ensure that irradiation of the fibroblast feeder layers was not responsible for the lack of protection compared with adipocytes, we performed TransWell experiments with nonirradiated, senescent 3T3-L1 fibroblasts. These fibroblasts offered similar protection to leukemia cells in TransWell coculture did not alter leukemia proliferation rates (Fig. 3C). However, neither fixed fibroblasts nor fixed adipocytes protected 8093 leukemia cells against vincristine treatment (Fig. 3D).

**Mechanisms of adipocyte-induced vincristine resistance.** We considered the possibility that adipocytes might protect leukemia by sequestering the lipophilic vincristine, decreasing its availability. To examine this, vincristine levels were measured in fibroblasts and adipocytes after 48 hours of drug exposure (see Supplementary Materials and Methods). We found that adipocytes in TransWells did accumulate significantly more vincristine than fibroblasts (1.28 ± 0.28 versus 0.49 ± 0.12 nmol/L, *P = 0.002; Supplementary Fig. S3A). The accumulation of drug into these monolayers of cells, however, was not reflected by a detectible decrease in the concentration of vincristine in the media (Supplementary Fig. S3B) or leukemia cells (data not shown).

To further explore how adipocytes protect leukemia cells, we assessed the leukemia cell cycle and apoptotic status in our coculture system. 8093 cells were exposed to bromodeoxyuridine while in TransWells over the various feeder layers, and their cell cycle state was assessed using fluorescence-activated cell sorting analysis. Neither feeder layer altered the cell cycle kinetics under baseline conditions (Table 1). Addition of vincristine decreased the proportion of cells in S phase and increased the proportion of cells undergoing apoptosis. Compared with leukemia cells over no feeder (Fig. 4A) or fibroblasts (Fig. 4B), adipocytes partially reversed the effects of vincristine, by decreasing apoptosis and increasing the proportion of cells in G0-G1 and S phase during vincristine exposure (Table 1; Fig. 4C).
We next investigated the leukemia cell expression of apoptosis-related genes that might be altered by the presence of adipocytes. Adipocytes up-regulated Bcl-2 and Pim-2 expression, both with and without vincristine, and these results were verified by rTPCR (Fig. 5A). Overall Pim-2 protein level was up-regulated by adipocytes, particularly in the presence of vincristine (Supplementary Fig. S4; Fig. 5B). Because Pim-2 prevents apoptosis via inactivation of Bad, we assessed Bad phosphorylation, and found that adipocytes increased the level of phosphorylated Bad in 8093 leukemia cells. Thus, adipocyte protection of leukemia cells from vincristine was associated with up-regulation of Bcl-2 and Pim-2, and an increased phosphorylation of Bad.

Discussion

Elucidating the mechanism(s) linking obesity and leukemia relapse is complicated by the large number of effects of obesity, and the long list of potential factors that could lead to relapse. Therefore, we have developed cell culture and animal models of obesity and leukemia to explore this relationship. In our mouse model, we have recapitulated the increased ALL relapse observed in obese patients—obese mice injected with highly malignant pre-B lymphoblastic leukemia cells had a worse treatment outcome. Interestingly, we found leukemia cells associated with fat pads in vincristine-treated mice, suggesting that adipose tissue may be partly responsible for the effect of obesity to increase leukemia relapse. Although the fat depots were examined only once the mice developed progressive leukemia, three of the five mice developed progressive disease during the vincristine treatment period, showing that fat depots can harbor leukemia cells during chemotherapy. Interestingly, s.c. lymphoma cells have been noted to form a "rim" around adipocytes, implying a cell-cell interaction also between these two cell types (28).

Table 1. Cell cycle and apoptosis in 8093 cells over various feeder layers, with and without vincristine

<table>
<thead>
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<th>Condition</th>
<th>Feeder layer</th>
<th>G0/G1</th>
<th>S</th>
<th>G2+M</th>
<th>Apoptotic</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>None</td>
<td>39 ± 2</td>
<td>58 ± 2</td>
<td>3 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td></td>
<td>Fibroblasts</td>
<td>48 ± 1</td>
<td>48 ± 1</td>
<td>3 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td></td>
<td>Adipocytes</td>
<td>39 ± 11</td>
<td>53 ± 3</td>
<td>3 ± 0</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>None</td>
<td>19 ± 4</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>76 ± 6</td>
</tr>
<tr>
<td></td>
<td>Fibroblasts</td>
<td>38 ± 4</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>53 ± 4</td>
</tr>
<tr>
<td></td>
<td>Adipocytes</td>
<td>58 ± 4*</td>
<td>25 ± 10</td>
<td>10 ± 5</td>
<td>9 ± 1*</td>
</tr>
</tbody>
</table>

*P < 0.005 vs Fibroblasts.

NOTE: Numbers indicate percentage of cells in different states.
Thus, we developed in vitro models that showed that the adipocyte microenvironment may be a protective niche for leukemia cells during chemotherapy. First, we show that adipocytes are as competent as fibroblasts in supporting leukemia cell steady-state growth. This complements recent studies that seem to suggest that adipocytes impair the proliferation of normal hematopoietic cells (29), while they support the growth of malignant cells such as multiple myeloma cells (30). Second, we show that adipocytes confer a significant protection to leukemia cells against vincristine, daunorubicin, dexamethasone, and nilotinib. Thus, adipocytes may actively contribute to leukemia cell survival in the face of multiagent chemotherapy. Adipocytes also protected some, although not all established human pre-B ALL cell lines from vincristine. Interestingly, the one cell line tested that was not protected by adipocytes, RCH-ACV, harbors the (1;19) translocation, which is associated with increased sensitivity to many chemotherapies including vincristine (31). Thus, the inability of these cells to resist vincristine in the presence of adipocytes may reflect an overall inability of cells with this translocation to resist chemotherapy.

We next found that the presence of adipocytes decreases leukemia apoptosis and increases cell cycling in the face of vincristine. Adipocytes increased expression of prosurvival signals, which may shift the apoptotic balance of leukemia cells toward survival; this effect was maintained in the presence of vincristine. The main targets of this adipocyte-mediated effect are possibly the survival genes Bcl-2 and Pim-2. Overexpression of Bcl-2 causes leukemia cell resistance to several drugs, including vincristine (32), and high expression of Bcl-2 is strongly predictive of poor outcome in adults with acute myelogenous leukemia (33). Pim-2 is an oncogene that promotes growth of hematopoietic cells (34), as well as leukemia cell survival via multiple mechanisms (35), including phosphorylation of Bad (36). Indeed, Bad phosphorylation was increased by adipocytes both with and without vincristine, and this may be one of the mechanisms by which adipocytes protect leukemia cells from vincristine. Overall, our finding that adipocytes alter the balance of apoptotic signals toward survival is consistent with our finding that they protect leukemia cells from a variety of chemotherapeutics with different mechanisms of action.
It is unknown which specific adipose depots are relevant to leukemia escape from chemotherapy. Studies on the bone marrow tumor microenvironment generally ignore the role of adipocytes, the most abundant stromal cell in adult bone marrow (37). We showed in vitro that bone marrow-derived adipocytes (OP9 cells) can protect leukemia cells against vincristine. Since bone marrow adiposity does not increase substantially with obesity (38), marrow adipocytes may contribute to leukemia treatment resistance in both lean and obese patients, but are not likely responsible for the increased relapse in obese patients.

We also considered that vincristine accumulation in adipose tissue could be partly responsible for the association between obesity and leukemia relapse. Our measurements confirmed that vincristine accumulates in adipocytes more than in other cells such as fibroblasts, although this did not affect drug levels in the medium or leukemia cells. This was not unexpected, as in this uncomplicated system a single monolayer of adipocytes was exposed to a comparably large volume of media. In vivo, vincristine concentrations in blood and tissue were well-matched between obese and nonobese mice after a single iv. injection. However, this injection was dosed proportional to body weight. In clinical practice, chemotherapies such as vincristine are dosed in proportion to body surface area, which leads to lower doses per kilogram body weight in older and more overweight children—patients at higher risk of relapse. This underdosing may be compounded by the fact that chemotherapy doses are often “capped” to prevent dose-dependent toxicities. If obesity does lead to lower vincristine exposure in children, then this could be a significant factor in clinical outcome, particularly given the increasing prevalence of obesity worldwide. Pharmacokinetic experiments in obese patients will be needed to rigorously address this issue (39–41).

In summary, our findings show that obesity can directly impair the antileukemia efficacy of the first-line chemotherapy, vincristine. This effect is likely due in part to adipocytes interacting with leukemia cells, as their presence in coculture leads to impaired leukemia killing by this and other drugs. The protective effects of adipocytes may also contribute to poorer prognosis of obese patients with other malignancies, as adipose tissue has been suggested to play a protective role in the microenvironment of breast (42) and colon (43) cancer. However, further studies are necessary to elucidate the effects of adipocytes to alter chemotherapy pharmacokinetics, secrete cancer survival factors, or both.

Given that 32% of children are overweight and 16% are obese (44), therapy pharmacokinetics, secrete cancer survival factors, or both. Treatment of childhood acute lymphoblastic leukemia killing by this and other drugs. The protective effects of adipocytes may also contribute to poorer prognosis of obese patients with other malignancies, as adipose tissue has been suggested to play a protective role in the microenvironment of breast (42) and colon (43) cancer. However, further studies are necessary to elucidate the effects of adipocytes to alter chemotherapy pharmacokinetics, secrete cancer survival factors, or both.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

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