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Follicular Dendritic Cells Protect Malignant B Cells from Apoptosis Induced by Anti-Fas and Antineoplastic Agents

Ying X. Schwarz,* Ming-yan Yang,* Dahui Qin,* Jiuhua Wu,* W. David Jarvis,† Steven Grant,* Gregory F. Burton,* Andras K. Szakal,‡ and John G. Tew2*§

The observation that follicular dendritic cells (FDC) reduce apoptosis in B cells prompted the hypothesis that FDC might enhance tumor cell survival by protecting malignant B cells from apoptotic death. To test this notion, apoptosis was induced in B cell lymphomas by anti-Fas or various antineoplastic agents in the presence and absence of FDC. Apoptosis was detected and quantified by TUNEL analysis. Induction of apoptosis with anti-Fas, etoposide, cyclophosphamide, and busulfan was markedly antagonized by FDC at FDC to B cell ratios of ≥1:16. For example, treatment with 10 ng/ml anti-Fas caused 60–90% of A20 cells to undergo apoptosis in 6 h, whereas addition of FDC reduced apoptosis to background levels (3–15%). Similarly, treatment with busulfan induced apoptosis in 55–80% of A20 cells, whereas addition of FDC reduced B cell death to ≤15%; moreover, depletion of FDC abrogated the protective actions. In contrast, the apoptosis-inducing effect of Adriamycin was not reversed by FDC. The ability to block apoptosis induced by anti-Fas or busulfan was not limited to A20 but was observed in four other malignant pre-B cell or B cell lines. The mechanism by which FDC spare malignant B cells from apoptosis did not involve alterations in levels of Bel-2, Bel-XL, or Bax. Collectively, these data raise the possibility that FDC may enhance tumor cell survival by protecting malignant B cells against apoptosis induced by anti-Fas and some but not all chemotherapeutic agents. The Journal of Immunology, 1999, 163: 6442–6447.

In the absence of a positive survival signal, germinal center B lymphocytes are programmed to undergo an apoptotic form of cell death (1–3). The nature of the positive signal is currently unknown, but evidence indicates that follicular dendritic cells (FDC) may be important in its delivery. FDC intimately interact with B cells in germinal center light zones. Their numerous dendrites, which retain Ags in the form of immune complexes, surround B cells and deliver signals for B cell differentiation and proliferation (3–7). In germinal center dark zones, B cells undergo somatic hypermutation to generate high affinity Ag receptors (8–10). B cells that express B cell receptors of the highest affinity preferentially bind Ag-bearing FDC dendrites, receive survival signals, and persist (1, 11). B cells that fail to bind FDC proceed along the apoptotic pathway (1, 11), and death is believed to occur as a consequence of ligation of Fas/CD95/Apo-1 on the B cell surface (12, 13). Thus, FDC are able to rescue germinal center B cells from apoptotic death (1), prompting the hypothesis that FDC may rescue germinal center B cells by blocking the Fas pathway, and recent studies support this model (14).

Currently, little information is available concerning the potential role of FDC in regulating Fas/Apo-associated or other apoptosis-related pathways in malignant lymphoid cells. However, if FDC protect malignant B cells from apoptosis, as they do in the case of their normal counterparts, it is conceivable that they might thereby promote tumor cell survival. One objective of the present study was to establish a system in which neoplastic murine B cells undergo apoptosis triggered by Fas ligation and to determine whether FDC might rescue them from apoptotic death. In this system, high levels of Fas are expressed as a result of neoplastic transformation, rather than as a consequence of Ag engagement. A second objective was to determine whether FDC may protect malignant B cells from apoptosis induced by chemotherapeutic agents. Accruing evidence indicates that many if not all antineoplastic agents, including those used in the treatment of hematological malignancies, exert their lethal effects in vitro and in vivo via an apoptotic mechanism (15–17). Recent studies suggest a link between drug-mediated apoptosis and activation of the Fas/Apo pathway (18). If such a link does in fact exist, it is plausible to propose that interference with Fas-induced apoptosis might also reduce the susceptibility of cells to cytotoxic drug-mediated cell death. Currently, no information is available concerning the possible influence of FDC on the response of neoplastic B cells to chemotherapeutic agents. Herein we report a novel finding that FDC can protect tumor cells from apoptosis induced by Fas ligation as well as by several chemotherapeutic agents. Thus, FDC may act to promote survival of malignant cells exposed to otherwise lethal stimuli.

Materials and Methods

Animals

Female BALB/c mice 6 to 8 wk of age were purchased from The Jackson Laboratory (Bar Harbor, ME). The mice were housed in standard plastic shoe-box cages with filter tops. Food and water were supplied ad libitum, and the mice were used between 8 to 20 wk of age.

FDC isolation

FDC were isolated from popliteal, brachial, axillary, inguinal, periaortic, and mesenteric lymph nodes by procedures described previously (19) except that the mice were injected i.p. with cyclophosphamide monohydride ISOPAC (300 mg/kg) rather than using exposure to ionizing irradiation to
eliminate lymphocytes. FDC are highly resistant, whereas B cells are very sensitive to cyclophosphamide (19), rendering this drug effective in eliminating B cells in the lymph nodes used to isolate FDC. Three days after cyclophosphamide treatment, the lymph nodes were removed and minced into small pieces with 26.5-gauge sterile needles to facilitate enzyme digestion. The dissociated lymph nodes were incubated with 1 ml of 8 mg/ml collagenase D (lot FA148; Boehringer Mannheim, Indianapolis, IN) and 0.5 ml of 10 mg/ml DNase I (lot 32H545; Sigma, St. Louis, MO) in 1 ml of DMEM at 37°C for 35 min. Then cells were dislodged from the stroma by gentle pipetting. The media containing free cells were collected, and the digestion was repeated to achieve optimal release of cells from the remaining tissue. The collected free cells were then layered directly onto a continuous Percoll gradient (50%) and centrifuged for 20 min at 700 × g. The low density (1.050–1.060 g/ml) FDC-enriched fraction was removed and washed twice. Finally, the adherent cells including macrophages were removed by incubating the cells at 37°C for 1 h. The nonadherent cell suspension typically contained ~20–40% FDC, and this type of FDC preparation is generally referred to simply as FDC in the figures and text. The majority of the contaminating cells were medium to large lymphocytes. FDC isolated by cyclophosphamide treatment contain ~10% B cells as detected by flow cytometry with PE-conjugated anti-B220 Ab.

**FDC depletion**

FDC were depleted from the enriched FDC preparations by using a biotin-labeled FDC-specific mAb FDC-M1 (20, 21). FDC preparations were incubated with rat serum at 4°C for 30 min to block nonspecific Fc binding of rat mAb. Biotinylated FDC-M1 was then added, and cells were incubated for 30 min at 4°C. Cells were then washed three times before streptavidin-coupled magnetic Dynabeads (m-280, Dynal AS, Great Neck, NY) were added at concentration of 15 beads/cell in a final volume of 2.5 ml for another 30 min at room temperature. FDC bound to Dynabeads were separated by a magnetic particle concentrator (Dynal). The remaining cells represent the FDC-depleted fraction.

**B cell lines and cell culture**

The BALB/c-derived B lymphoma cell line A20 was cultured in RPMI 1640 supplemented with 1.0% sodium pyruvate, nonessential amino acids, l-glutamine, gentamicin (all from Life Technologies, Grand Island, NY), and 10% heat-inactivated FCS (HyClone, Logan, UT); all cultures were maintained under a fully humidified atmosphere in 95% room air, 5% CO2 at 37°C. Murine B lymphoma cell lines WEHI 279 and M12 were provided by Dr. Daniel Conrad (Department of Microbiology, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, VA); pre-B cell lines Bcl-1 and 1-8 were obtained from Dr. Deborah Lebman (Cancer Center of Medical College of Virginia Campus, Virginia Commonwealth University). These cell lines were cultured in RPMI 1640 supplemented with 10% heat-inactivated FCS, 2 mM glutamine, 1.0% sodium pyruvate, 10 U/ml penicillin, 10 μg/ml streptomycin, 10 mM HEPES, and 50 μM 2-mercaptoethanol (2-ME). The B cells were cultured at a density of 5 × 10^6 cells/ml in 25-cm² flasks or in six-well culture plates. Anti-Fas was used for 15 h to induce apoptosis of WEHI 279 cells (100 ng/ml); Anti-Fas was used for 6 h to induce apoptosis of Bcl-1 cells (100 ng/ml) and A20 cells (anti-Fas, 10 ng/ml); Anti-Fas was used for 15 h to induce apoptosis of WEHI 279 cells (100 ng/ml). All cell lines were cultured with 20% heat-inactivated FCS, 2 mM glutamine, 10 mM HEPES, and 50 μM 2-mercaptoethanol (2-ME). The amount of protein added to the samples was determined using a protein assay reagent (Pierce, Rockford, IL). The amount of protein added to each sample was calculated as the percentage of the PE-conjugated anti-Fas Ab detected by flow cytometry with PE-conjugated anti-B220 Ab.

**Induction of apoptosis**

A20 cells were cultured at a density of 2–4 × 10^5 cells/ml in a 100–15-mm diSPO petri dish (Scientific Products, McGaw Park, IL), and cultures were typically set up in triplicate. When FDC were added, the final cell number was adjusted to the same as the cultures without FDC so that each cell was exposed to the same amount of anti-Fas. (For all the experiments, cell number was held constant so that each cell was exposed to the same amount of anti-Fas.) B, Relationship between dose of cells in the FDC preparation and protection against anti-Fas-induced apoptosis. A20 cells were treated with 10 ng/ml anti-Fas for 6 h with FDC added at various FDC to B cell ratios.

**TUNEL assay using FACScan analysis (23)**

To detect apoptotic DNA damage induced by various agents, cultured B cells were labeled with PE-conjugated anti-mouse B220 Ab for 30 min at 4°C. Cells were then washed, fixed with 4% formaldehyde for 10 min at room temperature, and then washed twice before treatment with 0.1% Triton X-100 in 0.1% sodium citrate for 2 min on ice to permeabilize cell membranes. Cells were then incubated with TdT and FITC-conjugated dUTP (Boehringer Mannheim, Indianapolis, IN) for 1 h at 37°C. The negative control was prepared with staining with the FITC-dUTP labeling solution in the absence of TdT. The positive control was treated with DNase I (10 μg/ml, 10 min at room temperature) after permeabilization to induce DNA strand breaks and then labeled (24). Washed cells were subjected to FACScan analysis essentially as described by Piqueras et al. (24). Apoptotic cells were FITC⁺ manifested by increased FITC intensity, and the percentage of apoptotic B cells was determined by analyzing the PE⁺ population, thus ensuring that non-B cells were excluded. Consequently, the extent of apoptosis was calculated as the percentage of the PE⁺ “FITC⁺” population vs the PE⁺ “FITC⁻” population.

**Western blot analysis**

Cells (~10⁶) were collected by centrifugation and washed twice with ice-cold PBS, cell pellets were suspended in 200 μl PBS, and the cells were lysed by adding 200 μl 2% loading buffer containing 4% SDS, 5.76 mM 2-ME, 20% glycerol, 0.1% bromphenol blue in 60 mM Tris base (pH 8.6), and sonicated. All cell lysates were boiled for 5 min and centrifuged at 14,000 × g for 5 min. Protein content was determined using Coomassie protein assay reagent (Pierce, Rockford, IL). The amount of protein added to represent each experimental group was standardized, and the individual proteins were separated by SDS-PAGE gel (5% stacking, 12% separating).
These proteins were then transferred from the gels to nitrocellulose membranes (Bio-Rad, Hercules, CA), and the membranes were blocked with 5% milk/PBS-Tween for 1 h before addition of primary Abs (rabbit polyclonal Ab to mouse Bcl-2 (1:1000), rabbit polyclonal Ab to mouse Bcl-XL /s (1:1000), and rabbit polyclonal Ab to mouse Bax (1:500)) and incubated at 4°C overnight. The Abs were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). After a thorough washing with PBS-Tween, an HRP-conjugated secondary goat anti-rabbit Ab (Kirkegaard and Perry Laboratories, Gaithersburg, MD) at a dilution of 1:2000 was added and incubated for 1 h at 22°C. After three washings in PBS-T, blots were developed with a Chemiluminescence Kit (NEN Life Science Products, Boston, MA).

**Statistical methods**

Data in the figures represent the mean ± SEM, and Student’s t test was used to establish whether differences were statistically significant.

**Results**

**FDC-mediated protection against Fas-induced apoptosis**

We first sought to determine whether, and to what extent, FDC could protect neoplastic B cells from anti-Fas-mediated apoptosis. A20 cells treated with anti-Fas underwent apoptosis in a dose-dependent manner, and 10 ng/ml anti-Fas was able to kill the majority of
cells within a 5-h period (data not shown). To test the effect of FDC, A20 cells were treated with 10 ng/ml anti-Fas in the presence and absence of FDC. In the absence of FDC, the majority of A20 cells (e.g., 60–90%) underwent apoptosis after treatment with anti-Fas. In contrast, the level of apoptosis induced by anti-Fas was markedly reduced in the presence of FDC (Fig. 1A). In dose-response studies, an FDC to B cell ratio of 1:10 fully reversed the anti-Fas-mediated effect, but FDC to B cell ratios 1:50 were without detectable effect (Fig. 1B).

**FDC-mediated protection against apoptosis induced by chemotherapeutic agents**

A variety of chemotherapeutic agents were studied to assess their ability to induce apoptosis in A20 cells. At appropriate doses, busulfan, etoposide, Adriamycin, and cyclophosphamide all induced apoptosis of 20–80% of the cells (data not shown). Each of these agents was then studied to determine whether FDC might modify lethality. Busulfan was a potent inducer of apoptosis in A20 cells, and a majority (e.g., 55–90%) of the B cells underwent apoptosis at a dose of 200 μg/ml (Fig. 2A). Significantly, addition of FDC dramatically reduced apoptotic death in busulfan-treated A20 cells (Fig. 2A). Optimal protection was achieved at a FDC to B ratio of 1:8; although significant reductions in apoptosis were obtained at a ratio of 1:16 (Fig. 2B). FDC also exerted significant protection against apoptosis induced by other agents, (e.g., p < 0.05 when compared with cells treated with agent alone) including etoposide (Fig. 2C) and cyclophosphamide (Fig. 2D). In contrast, FDC did not exert discernable protective effects toward cells exposed to cytotoxic concentrations of Adriamycin even at FDC to B cell ratios as low as 1:4 (Fig. 2E).

**Effect of FDC on Bcl-2, Bcl-XL, and Bax levels in A20 cells**

The B cells that survive and emerge from germinal centers express Bcl-2 (2). Furthermore, cell death decisions may depend on the relative abundance of anti-apoptotic (e.g Bcl-2, Bcl-XL) vs pro-apoptotic proteins (e.g., Bax) (25, 26). These considerations a prompted us to determine whether the protective actions of FDC could be attributed to induction of Bcl-2, Bcl-XL or a decrease in Bax expression. As illustrated by the Western blot analysis shown in Fig. 3, A20 cells expressed all of these molecules, and contact with FDC did not substantially modify levels of Bcl-2, Bcl-XL, or Bax proteins.

**Effect of FDC depletion on apoptosis**

The FDC populations used in these studies were enriched but not pure; consequently, it remained possible that protection might be mediated by cells other than FDC. To exclude this possibility, FDC were removed from FDC preparations by using biotinylated FDC-M1 Ab and streptavidin-conjugated Dynabeads to generate a FDC-depleted fraction. The FDC-depleted fraction was added to cultures in the same ratios as the FDC-enriched population. Under these conditions, busulfan-mediated and anti-Fas-mediated apoptoses were not abrogated, supporting the concept that FDC are directly responsible for antagonizing drug and anti-Fas related apoptosis in this malignant B cell line. Fig. 4 illustrates results obtained with busulfan, and the anti-Fas data revealed a similar pattern (data not shown).

**FDC-mediated protection against apoptotic death in a variety of malignant B cells and pre-B cells**

To determine whether the ability of FDC to block apoptosis represented a more general phenomenon, and not restricted solely to A20 cells, we examined four additional malignant B cell or pre-B cell lines. Two of the lines were not susceptible to anti-Fas-mediated killing, but all four were susceptible to busulfan-induced lethality. In all cases in which anti-Fas or busulfan induced apoptosis, the presence of FDC markedly reduced the killing effect (Table I).

**Discussion**

The results described herein demonstrate that ligation of Fas on murine B lymphoma cell lines triggers apoptosis and indicate for the first time that FDC can protect malignant cells from Fas-induced cell death. The importance of FDC in this phenomenon was supported by the observation that FDC-enriched preparations depleted of FDC did not protect against lethality, suggesting a specific cytotoxic effect (Fig. 4). FDC are believed to play an important role in regulating germinal center B cell apoptosis (1–3),...
and the nature of FDC-mediated antiapoptotic activity is of great interest. Fas expression on B cells increases after somatic hyper-mutation in germinal center dark zones, and interactions with germinal center T cells bearing Fas ligand then trigger cell death unless the B cell Ag receptor has high affinity. High affinity B cell receptor efficiently competes for Ag trapped on FDC, and this leads to B cell-FDC interactions and FDC-mediated reversal of Fas-induced programmed B cell death. To date, studies of the ability of FDC to inhibit apoptosis have been restricted to normal B cells (1, 3, 27–29). The present findings extend these data and indicate that a similar phenomenon occurs in malignant B cells where apoptosis may be induced simply by interactions with anti-Fas. In this neoplastic B cell model, engagement of specific Ag on the FDC by the B cell does not appear to be necessary to reverse the apoptotic signal.

It has generally been assumed that different classes of agents induce apoptosis through distinct signaling pathways. For example, Fas ligand and TNF-α initiate apoptosis through ligation of cell surface receptors, leading to a cascade of events culminating in activation of the protease cascade. In contrast, chemotherapeutic drugs are believed to trigger the cell death process through interaction with nuclear components such as DNA (i.e., in the case of alkylating agents, topoisomerase inhibitors, and antimetabolites) or microtubules (i.e., in the case of Vinca alkaloids or taxol). The specific sensors that detect damage to these cellular constituents and initiate apoptotic events remain largely unknown. However, attention has recently been focused on possible connections between chemotherapeutic drug-induced cell death and the Fas/Apo pathway. Friesen et al. (18, 30) provided evidence suggesting that a deficiency in activation of the CD95 pathway could serve as the basis for drug resistance in human leukemic cells (18). Although it is unclear how genomic damage (i.e., by cytotoxic drugs) involves a cell surface receptor-based system to trigger cell death, it may be pertinent that apoptosis induced by the nuclear transcription factor c-myc has recently been shown to be antagonized by defects in the Fas/Apo pathway (31). It may also be relevant that certain chemotherapeutic agents have been shown to up-regulate Fas expression in leukemic cells (18), raising the possibility that the Fas pathway may be involved in drug-related events. A20 cell apoptosis induced by two alkylating agents (cyclophosphamide and busulfan) and a topoisomerase II inhibitor (etoposide) was substantially reversed by FDC in a manner similar to that observed in the case of anti-Fas-induced cell death. This finding is consistent with the concept that certain chemotherapeutic agents induce apoptosis through engagement of at least part of the Fas pathway and further suggests that FDC may block the cascade of drug-induced cell death distal to its convergence with the Fas pathway.

In contrast to busulfan, etoposide, and cyclophosphamide, FDC failed to block apoptosis induced by the topoisomerase II inhibitor Adriamycin. Friesen et al. (18) have shown that high concentrations of Adriamycin do not induce Fas system expression in leukemic cells. Consequently, Adriamycin, particularly when administered at high concentrations, may utilize a pathway other than Fas/Apo to induce cell death. For example, the lethal action of Adriamycin may stem from the generations of free radicals and resulting membrane damage (32), events that may not directly involve Fas/Apo activation. In any case, this observation indicates that FDC-mediated protection against drug-induced apoptosis is very likely pathway specific.

The mechanism(s) by which FDC protect malignant B cells from apoptosis has (have) not been established. It is known that B cells selected to emerge from normal germinal centers express Bcl-2, and Bcl-2 is found in follicular lymphomas which are characterized by the presence of FDC (33, 34). Also, cell death decisions may depend on the relative abundance of antiapoptotic (e.g., Bcl-2, Bcl-X<sub>L</sub>) vs proapoptotic proteins (e.g., Bax) (26). These considerations prompted us to determine whether contact with FDC resulted in induction of Bcl-2, Bcl-X<sub>L</sub>, or a decrease in Bax expression. The data revealed that all of these molecules were present in A20 cells, but contact with FDC did not substantially modify levels of Bcl-2, Bcl-X<sub>L</sub>, or Bax protein. Thus, it appears unlikely that the cytoprotective activity of FDC stems from altering the relative abundance of pro- and antiapoptotic proteins. We cannot, however, presently rule out the possibility that FDC act by modifying interactions between these proteins, i.e., by reducing levels of the free Bax (35). In preliminary studies, we sought to explore the possibility that FDC might block apoptosis induced through the mitochondrial pathway. Staurosporine is known to induce apoptosis through this pathway (25), and FDC antagonizes the ability of staurosporine to induce apoptosis (Tew et al., unpublished observations). Furthermore, the level of active caspase 9 (caspase 9 p10) was reduced when FDC were added to staurosporine-treated cells. Thus, these data suggest that FDC can interfere with apoptosis induced through a pathway linked to mitochondrial function, a possibility that is currently under investigation. It also appears that cell membrane-associated molecules are important in the mechanism used by FDC to rescue B cells from an apoptotic death. Experiments were done using transwell culture chambers with 0.3-μM pore size Nucleopore membranes that allows rapid diffusion of medium between upper and lower chambers while keeping cells separated. The addition of anti-Fas to these cultures caused apoptosis in the tumor cells, but an FDC effect was not detectable when FDC were confined to the upper chamber and A20 cells were confined to the lower chamber (e.g., 72 ± 3% apoptosis with A20 cells alone vs 71 ± 7% apoptosis in the A20 cells when FDC were present in the upper chamber). These data suggest that FDC-B cell contact and membrane-associated molecules are an important part of the mechanism used by FDC to rescue B cells

<table>
<thead>
<tr>
<th>Apoptotic Tumor Cells (%)</th>
<th>After anti-Fas treatment</th>
<th>After busulfan treatment</th>
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<tbody>
<tr>
<td></td>
<td>Without FDC</td>
<td>With FDC</td>
</tr>
<tr>
<td>Bcl-1 (pre-B cell line)</td>
<td>66</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>M12 (B cell line)</td>
<td>NS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>1-8 (pre-B cell line)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>WEHI 279 (B cell line)</td>
<td>57</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significantly lower (p ≤ 0.05) than without FDC.
<sup>b</sup> NS, not susceptible; —, apoptosis was not induced by the addition of anti-Fas to cultures of these cells.
from apoptotic death. In a recent study, we found that CD21L on the FDC engaged CD21 on the B cell, leading to optimal Ab production and that these membrane molecules may be important in delivering the survival signal (7). This possibility is supported by recent data indicating that B cells lacking CD21 do not survive well in germinal centers (36).

The results reported here raise an issue that has potential clinical significance. For example, FDC are abundant in non-Hodgkin’s lymphomas derived from the follicular center or the mantle zone, where they interact with and support the survival of these malignant B cells (37). Furthermore, chemotherapeutic drugs kill many cells in secondary lymphoid tissues, including some germinal center B cells, and this may allow tumor cells to enter normal lymphoid follicles and interact with FDC. Based on the present findings, FDC-associated malignant B cells could theoretically escape apoptosis triggered by certain chemotherapeutic agents and cytotoxic T cells that utilize Fas ligand for killing. Thus, a possible implication of these findings is that FDC could provide a mechanism by which malignant lymphoid cells escape the lethal effects of some chemotherapeutic agents and cytotoxic T cells. In vivo studies designed to test this hypothesis are currently in progress.

References