Matrix Metalloproteinase-7-mediated Cleavage of Fas Ligand Protects Tumor Cells from Chemotherapeutic Drug Cytotoxicity

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ABSTRACT

Recent evidence suggests that one mechanism whereby cytotoxic drugs, such as doxorubicin, kill tumors is the induction or up-regulation of Fas ligand (FasL) expression on the tumor cell surface. The ensuing engagement of Fas by FasL on adjacent cells leads to apoptosis. However, despite cytotoxic drug-induced FasL expression, Fas-sensitive tumors frequently resist chemotherapy, suggesting that they may possess a mechanism that prevents or inactivates Fas-FasL interactions. In the present work, we addressed the involvement of the FasL/Fas signaling pathway in doxorubicin-induced apoptosis and the ability of matrix metalloproteinases (MMPs) to proteolytically cleave FasL in tumor cells. Doxorubicin-induced apoptosis was inhibited by expression of soluble Fas or incubation of the tumor cells with MMP-7 but not with MMP-2 or MMP-9. Resistance to doxorubicin was also induced by expression in the tumor cells of constitutively active MMP-7 but not of a catalytically inactive mutant. Conversely, inhibition of MMP-7 expression in tumor cells by transfection of MMP-7 cDNA in antisense orientation resulted in sensitization to doxorubicin. MMP-7 efficiently cleaved recombinant FasL in vitro and reduced cell surface FasL expression. Our observations provide evidence that one mechanism whereby MMP-7 may promote tumor survival and resistance to doxorubicin is by cleaving FasL and reducing its effectiveness in triggering Fas-mediated apoptosis.

INTRODUCTION

Despite the frequent success of surgical and chemotherapeutic measures in controlling primary tumor growth, metastatic disease is seldom amenable to surgery, displays resistance to chemotherapy, and is the major cause of terminal illness. Expression of the multidrug resistance gene, mdr-1 (1), provides an important mechanism for tumor resistance to chemotherapy, but there is also increasing evidence that the ability of cancer cells to evade or subvert signals that lead to programmed cell death, or apoptosis, plays a major role in tumor survival in the face of cytotoxic drug regimens (2). The anticancer action of drugs such as doxorubicin and cisplatin is in large part attributable to their ability to induce apoptosis of tumor cells (3) and is therefore dependent on the integrity of the cellular signaling pathways that lead to apoptotic cell death. Defects in some of these pathways are common in malignant tumor cells, especially of metastatic origin (2), and are therefore likely to underlie tumor resistance to chemotherapy.

Recent evidence has implicated the Fas pathway in the induction of tumor cell death (4–6). Engagement of Fas (CD95/Apo-1), a member of the tumor necrosis factor receptor superfamily (7), by its ligand (FasL) (8) initiates the recruitment of the adaptor molecule Fas-associated death domain (8) that provides a docking surface for and facilitates the autoprocessing and activation of Fas-associated death domain-like interleukin 1β converting enzyme or caspase-8 (6, 9). Activated Fas-associated death domain-like interleukin 1β converting enzyme triggers the processing and activation of several effector caspases that cleave vital components of the cell and lead to its demise. FasL is a type II integral membrane protein expressed in activated immune cells, immune-privileged tissues (testis, eye, brain, and placenta; Ref. 10), and a wide variety of tumors, many of which also express Fas (11, 12). FasL is observed to be proteolytically cleaved from the surface of some cell types, by an enzyme(s) the biochemical characteristics of which are consistent with those of members of the MMP family (12, 13). A recent report has identified MMP-7 as one member of the MMP family that is capable of cleaving FasL (14). The ability of the cleavage product, or sFasL, to induce apoptosis is significantly lower than that of its cell surface precursor (15, 16), suggesting that proteolytic cleavage of FasL may provide a mechanism for at least partial protection against Fas-mediated cell death.

MMPs are zinc-dependent enzymes that help regulate the turnover of ECM components. They are considered to play an important role in embryo development, morphogenesis, and tissue remodeling, as well as in tumor invasion and metastasis. Current opinion holds that MMPs promote tumor growth and metastasis by a variety of mechanisms that include ECM degradation, induction, and promotion of angiogenesis, and possibly, regulation of tumor cell growth itself (16). All MMPs are synthesized, and most are secreted as latent proenzymes that are activated by a variety of proteases (18). In steady-state conditions, MMP activity in tissues is nearly undetectable, partly because of low levels of constitutive expression and partly because of efficient homeostatic inhibitory mechanisms that include tissue inhibitors of metalloproteinases. Invading and metastatic tumor cells typically secrete MMPs and induce MMP production by surrounding stromal cells that may overwhelm the local tissue capacity to maintain their proteolytic activity in check. Synthetic MMPIs, including BB-94 (batimastat) and BB-2516 (marimastat), have been shown to prevent tumor cell-induced remodeling of extracellular matrix and angiogenesis and provide potentially useful reagents for the control of cancer spread (19, 20).

Interestingly, broad-spectrum MMPIs can block shedding of sFasL (12, 13), causing its accumulation on the cell surface (13) and induction of apoptosis in Fas-sensitive cells (21). We have also observed that inhibition of sFasL shedding augments doxorubicin-induced apoptosis in Fas-sensitive tumor cells (21), suggesting that FasL is involved in anticancer drug-induced cell death. However, the mechanism of FasL cleavage in tumor cells and its significance in cancer biology remain to be resolved. In the present work, we addressed the role of FasL and its shedding in doxorubicin-induced apoptosis in cancer cells. We show that the FasL/Fas pathway, which mediates doxorubicin-induced tumor cell death, is inhibited by exogenous or tumor cell-derived, proteolytically active MMP-7, which cleaves FasL from the tumor cell surface and reduces its efficacy in triggering Fas signals. Our results suggest that the proteolytic activity of MMP-7, which is broadly expressed in primary and especially metastatic human malignancies, may contribute to tumor resistance to cytotoxic

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2 The abbreviations used are: FasL, Fas ligand; sFasL, soluble FasL; MMP, matrix metalloproteinase; MMPI, MMP inhibitor; ECM, extracellular matrix; Rg, receptor globulin; MTI, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.
agents and thereby constitute a potential therapeutic target, inactivation of which may enhance the efficacy of conventional cancer chemotherapy.

MATERIALS AND METHODS

Cell Culture. The Ewing’s sarcoma cell lines SK-N-MC, TC-248, TC-71, TC-32, A4573, 5383, CHP100 (clone-S and clone-L), and TC-268, which have been described previously and shown to have the characteristic translocation and/or EWS/Fli-1 fusion gene product of the Ewing’s sarcoma (12), as well as the SW-480 colon carcinoma cell line (American Type Culture Collection, Manassas, VA) were grown in DMEM (Cellogro, Herndon, VA) with 100 units/ml penicillin, 100 μg/ml streptomycin, and 10% FCS (Cellogro).

Western Blotting. Cells were scraped, centrifuged briefly, and lysed for 30 min on ice in a lysis buffer [50 mM Tris-HCl (pH 8), containing 120 mM NaCl and 1% NP40], supplemented with the Complete-TM mixture of proteinase inhibitors (Boehringer Mannheim). The samples were cleared by centrifugation (14000 rpm for 30 min at 4°C) and assayed for protein concentration. Biotinylated proteins, representing the cell surface proteins, were immunoprecipitated with Streptavidin-agarose for 2 h at 4°C and separated by SDS-PAGE, and FasL levels were detected as described previously.

Cloning and Expression of Human MMP-7. The full-length human MMP-7 sequence was amplified by PCR using an HT29 colon carcinoma expression library cloned into the pCDM8 vector and appropriate synthetic oligonucleotide primers corresponding to sequences encoding the NH2- and COOH-terminal extremities of the precursor protein and cloned into the mammalian expression vector pcDNA3.1-TOPO-V5-His (Invitrogen, Carlsbad, CA). The correct orientation and sequence were verified by restriction analysis and dyeoxy sequencing, respectively. A construct expressing constitutively active, V5-tagged MMP-7 (pcDNA3.1-caMMP7) was created by removing nucleotides 64–282, corresponding to the inhibitory prodomain (amin residues 22–94), using the Excite site-directed mutagenesis kit (Stratagene, La Jolla, CA). The deletion was verified by sequencing. For verification of enzymatic activity, NIH3T3 cells were transfected with pcDNA3.1-caMMP7 or empty vector with Lipofectamine-Plus (Life Technologies, Inc., Gaithersburg, MD). Forty-eight h later, the cells were harvested, and zymographic analysis performed as described previously (23), revealed strong MMP activity, corresponding to MMP-7 in cells transfected with pcDNA3.1-caMMP7 but not the empty vector. For use as a negative control, pcDNA3.1-caMMP7 was mutated at the active center (Glu 215 to Ala; pcDNA3.1-MMP7mut215) using the QuikChange site-directed mutagenesis kit (Stratagene).

SK-N-MC cells were transfected with pcDNA3.1-caMMP7, pcDNA3.1-MMP7mut215, or empty vector using Superfect. Forty-eight h later, the cells were treated with or without doxorubicin (0.1 μg/ml) for additional 48 h. Cell death was evaluated with MTT as described previously.

Immunoprecipitation of MMP-7 and FasL. SK-N-MC cells were transfected with pcDNA3.1-MMP7mut215-V5 or empty vector using Superfect. Forty-eight h later, the cells were lysed and incubated with 1 μg/ml anti-V5 monoclonal antibody overnight. After precipitation with protein G-Sepharose and SDS-PAGE, immunoblotting analysis for FasL was performed.

Transfection with Antisense MMP-7. The full-length human MMP-7 sequence, amplified by PCR as described previously, was cloned in the antisense orientation into the mammalian expression vector pcDNA3.1-TOPO-V5-His (Invitrogen) and transiently transfected into the SK-N-MC cells using Superfect. Forty-eight h after the initiation of the transfection, the cells were treated with or without doxorubicin (0.1 μg/ml) for an additional 48 h. Cell death was evaluated with MTT as described previously. The inhibition of MMP7 expression was verified by Western blotting.

Immunohistochemistry. Ten formalin-fixed, paraffin-embedded specimens removed from lung metastases of Ewing’s sarcoma patients were obtained from the files of the Laboratory of Pathology at the National Cancer Institute and stained for MMP-7 expression with the monoclonal antibody Ab-1 (dilution: 1:100). The avidin-peroxidase method was used, as described previously (12).

Statistical Analysis. Quantitative comparisons were examined with the ANOVA method, followed by Duncan’s test.

RESULTS

A Functional FasL/Fas Pathway Is Necessary for Doxorubicin-induced Apoptosis of Ewing’s Sarcoma and Colon Carcinoma Cells. To address the role of FasL in doxorubicin-mediated apoptosis and to identify the MMP(s) responsible for FasL cleavage, we used...
the Ewing’s sarcoma SK-N-MC cell line, which is highly sensitive to Fas- and doxorubicin-induced apoptosis (21). After 48 h of culture in the presence of doxorubicin, ~50% of the cells undergo apoptosis, as determined by MTT and terminal deoxynucleotidyltransferase-mediated nick end labeling assays. We have shown previously that expression of both Fas and FasL is increased in SK-N-MC cells treated with cytotoxic agents (24). To provide evidence that FasL up-regulation and its subsequent interaction with Fas are required for anticancer drug-induced apoptosis, we transiently transfected the SK-N-MC cell line with an expression vector containing a cDNA encoding the extracellular domain of human Fas ligated to the constant region of the Fc fragment of human IgG1 (Fas-IgG). Expression of this construct leads to production of a soluble Fas-IgG chimeric molecule (FasRg; Ref. 22) that may act as a decoy inhibitor of Fas activation. A CD8-IgG construct (22) was used as a control. Transient expression of FasRg, but not CD8Rg, reduced doxorubicin-induced SK-N-MC cell death, supporting the notion that Fas/FasL plays a role in doxorubicin-associated cytotoxicity (Fig. 1A).

To determine whether the Fas/FasL pathway plays a role in doxorubicin-mediated cytotoxicity in other tumor types, we repeated these experiments using the histologically unrelated, Fas-sensitive colon carcinoma cell line SW-480. Doxorubicin was observed to augment FasL protein levels in SW-480 cells (Fig. 1B) and to induce SW-480 cell death, albeit more slowly (after 72–96 h of incubation). Similar to SK-N-MC cells, doxorubicin-induced apoptosis was inhibited by transient expression of FasRg but not CD8Rg (Fig. 1C), suggesting that Fas engagement by FasL is not a cell type-restricted event in cytotoxic drug-mediated tumor cell death. This notion is supported by reports of a similar role for a Fas/FasL interaction in chemotherapy-induced cell death in leukemic (25), hepatoma (26), and neuroblastoma cells (27) and brain tumors (28).

**Proteolytically Active MMP-7 Protects Ewing’s Sarcoma and Colon Carcinoma Cells from Doxorubicin-induced Apoptosis and Cleaves FasL.** Our observations that FasL is cleaved from the cell surface by an MMP-like enzyme and that FasL shedding protects tumor cells from undergoing apoptosis in culture, whereas inhibition of FasL shedding by a synthetic MMP1 sensitizes tumor cells to doxorubicin (12, 21), raised the possibility that MMP activity may augment cancer cell resistance to cytotoxic drugs. We therefore tested the effect of MMPs that are commonly expressed by tumor cells and that have been implicated in tumor progression, including MMP-2, MMP-7, and MMP-9, on the survival of doxorubicin-treated SK-N-MC and SW-480 cells. Exogenously added purified active human MMP-7, but not MMP-2 or MMP-9, inhibited doxorubicin-induced death of SK-N-MC (Fig. 2A) and SW-480 (Fig. 2B) cells.

To determine whether FasL is an MMP substrate, we incubated recombinant human FasL with purified active MMP-2, MMP-7, and MMP-9 in vitro. Only MMP-7 cleaved FasL efficiently, yielding a product of the expected size (Mr ~19,000), and cleavage was completely inhibited by the hydroxamic-acid based MMP inhibitor BB-3103 (Fig. 3A). Because we have shown previously that MMP inhibitors increase the levels of FasL on the surface of SK-N-MC cells (21), we assessed the effect of proteolytically active MMP7 on cell surface FasL expression. As expected, surface FasL levels were reduced in SK-N-MC cells incubated with active MMP7 (Fig. 3B).

To provide evidence that MMP-7-mediated protection against cytotoxic drug-induced apoptosis is attributable to its enzymatic activity, we compared the effect of proteolytically active MMP-7 to that of a loss of function mutant on doxorubicin-mediated tumor cell death. Human MMP-7 cDNA was inserted into the mammalian expression vector pcDNA3.1 and rendered constitutively active by removing sequences encoding amino acid residues 22–94 that correspond to the inhibitory prodomain (18). Enzymatic activity of the prodomain-deletion construct was confirmed by expression in NIH3T3 cells and zymogram analysis (data not shown). A loss of function mutant was obtained by a Glu215Ala substitution, located within the active site of the enzyme (18). Expression of constitutively active, but not inactive MMP-7, protected SK-N-MC cells from doxorubicin-induced apoptosis, providing direct evidence that the protective effect of MMP-7 is attributable to its proteolytic activity (Fig. 3C).

To demonstrate physical interaction between MMP-7 and FasL in vivo, we performed communoprecipitation experiments. Enzymatically inactive, V5-tagged MMP-7 was transiently expressed in SK-N-MC cells, and 48 h later, the cells were harvested and lysed, and MMP-7 was immunoprecipitated using an anti-V5 monoclonal antibody. Immunoprecipitates were subjected to SDS-PAGE, transferred onto blotting filters, and tested for the presence of FasL by Western blot analysis using anti-FasL antibody (Fig. 3D). FasL was observed to communoprecipitate with MMP-7, providing evidence that the two molecules interact in tumor cells.

**The Protective Effect of MMP-7 on Doxorubicin-induced Apoptosis Is FasL dependent.** The importance of MMP7 in conferring protection against anticancer drug-induced apoptosis was further underscored by observing the effect of specific inhibition of MMP7 expression on the survival of SK-N-MC cells after exposure to doxorubicin. The coding sequence of human MMP-7 was cloned in antisense orientation into the mammalian expression vector pcDNA3.1 and was transiently expressed in SK-N-MC cells. The resulting transfectants displayed reduced expression of MMP-7 protein and an increased sensitivity to doxorubicin compared with cells transfected with the expression vector alone (Fig. 4A). To further determine whether MMP-7-dependent reduction in doxorubicin-induced tumor cell death implicates FasL, antisense MMP-7 cDNA was transiently expressed in SK-N-MC cells that lack FasL, expression attributable to the stable expression of a plasmid carrying the human FasL sequence in antisense orientation. These cells were found to be resistant to
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Fig. 3. MMP-7 cleaves Fasl. A, immunoblot analysis of recombinant Fasl after incubation with MMP-7 in vitro. MMP-7 efficiently cleaved recombinant Fasl, and this effect was completely inhibited by the MMPI BB-3103. B, incubation of SK-N-MC with MMP-7 for 3 h at 37°C resulted in a reduction of cell surface Fasl levels. C, cell death, as estimated by MTT, of SK-N-MC cells treated with 0.1 µg/ml doxorubicin for 48 h after transfection of pcDNA3.1-camMMP7, pcDNA3.1-1-MMP7mut215, or empty vector. Constitutively active MMP-7, but not the enzymatically inactive mutant, had a protective effect (P < 0.001). Bars, SD. D, immunoblotting analysis with anti-Fasl, of anti-V5 monoclonal antibody immunoprecipitates from lysates of SK-N-MC cells transfected with V5-tagged MMP7mut215 in pcDNA3.1 or empty vector.

MMP-7 is Widely Expressed in Ewing’s Sarcomas. Having established the ability of MMP-7 to protect tumor cells from anticancer chemotherapy, we evaluated the expression of MMP-7 in Ewing’s sarcoma. Immunoblotting analysis of a panel of nine Ewing’s sarcoma cell lines revealed significant MMP-7 expression (Fig. 5A). Of 10 tumor specimens of the Ewing’s sarcoma family that were evaluated immunohistochemically, MMP-7 immunoreactivity was found in 9 (Fig. 5B).

DISCUSSION

Recent studies have suggested that the Fasl-Fas signaling pathway is involved in apoptosis induced by anticancer chemotherapeutic drugs (25, 27–29). We have shown here that Fasl-Fas interactions mediate, at least in part, doxorubicin-induced cell death in two distinct tumor cell types, based on the observations that expression of soluble Fasl-immunoglobulin fusion proteins in Ewing’s sarcoma and colon carcinoma cell lines inhibited doxorubicin-induced apoptosis. Furthermore, our observations provide evidence that doxorubicin cytotoxicity is attenuated by tumor cell expression of MMP-7, which proteolytically cleaves Fasl.

Shedding of Fasl from the cell surface has been observed in activated immune cells (13) and tumor cells (12) and may provide a mechanism for partial protection of Fasl-sensitive cells from apoptosis (21). Biochemical evidence has suggested that Fasl shedding is catalyzed by matrix metalloproteinase type enzymatic activity (12, 13, 21), and a recent report has shown that MMP-7 cleaves Fasl in vitro and colocalizes with Fasl on prostate epithelial cells (14). In our study, MMP-7 expressed in tumor cells was found to coimmunoprecipitate with Fasl and to reduce Fasl protein expression on the tumor cell surface. The observed reduction in cell surface Fasl expression was most likely attributable to proteolytic cleavage, because MMP-7 cleaved Fasl in vitro, consistent with findings by others (14). Because soluble Fasl displays reduced proapoptotic potency compared with its cell surface precursor (12, 13, 15, 16, 21), MMP-7-mediated Fasl cleavage could provide tumor cells with a mechanism to evade apoptosis induced by the concomitant expression (constitutive or cytotoxic drug-induced) of functional Fasl and Fasl, thereby facilitating tumor survival and progression. This notion is supported by the observations that exogenous, proteolytically active MMP-7, but not MMP-2 or MMP-9, inhibited doxorubicin-induced tumor cell death and that this inhibitory effect could be reproduced by overexpression of active MMP-7 but not of an enzymatically inactive mutant.

Recent work by others (14) suggests that MMP-7-mediated Fasl cleavage enhances prostate involution, and that the apoptotic index of involuting prostate epithelium in MMP-7-deficient mice is reduced. Taken at face value, these observations suggest that MMP-7 expression correlates with increased apoptosis, which would appear to contradict our present findings. However, in vivo behavior of tissues in MMP-7-null mice may be subject to the action of potential compensatory mechanisms for the loss of MMP-7. Moreover, normal epithelial cells and tumor cells may display different sensitivity to signals induced by soluble Fasl. It is therefore possible that by cleaving Fasl, MMP-7 may help promote involution of normal tissues while contributing to the survival of neoplastic cells. MMP-7 is widely expressed in human cancer, including colorectal (30), gastric

Fig. 4. Inhibition of MMP7 expression sensitizes cancer cells to doxorubicin. A, cell death, as estimated by MTT, of SK-N-MC cells treated with 0.1 µg/ml doxorubicin for 48 h after transfection of pcDNA3.1-antisenseMMP7 or empty vector. Transfection of pcDNA3.1-antisense MMP7 lowered MMP-7 protein levels (protein levels for actin are shown for comparison) and sensitized cells to doxorubicin (P < 0.001). Mean values from triplicate experiments are shown; bars, SD. B, the same experiment as in A was performed in SK-N-MC cells stably transfected with a vector carrying the chloramphenicol acetyltransferase (CAT) gene or the human Fasl sequence in the antisense orientation. The former cells were, once again, sensitized to doxorubicin by the inhibition of MMP-7 expression by pcDNA3.1-antisense MMP-7 (■) as compared with the empty vector (□; P < 0.001). In contrast, the latter cells, which lacked Fasl expression, were constitutively resistant to doxorubicin and were not sensitized by transfection of pcDNA3.1-antisense MMP-7. Mean values from triplicate experiments are shown; bars, SD.

Fig. 5. MMP-7 is widely expressed in Ewing’s sarcomas. Having established the ability of MMP-7 to protect tumor cells from anticancer chemotherapy, we evaluated the expression of MMP-7 in Ewing’s sarcoma. Immunoblotting analysis of a panel of nine Ewing’s sarcoma cell lines revealed significant MMP-7 expression (Fig. 5A). Of 10 tumor specimens of the Ewing’s sarcoma family that were evaluated immunohistochemically, MMP-7 immunoreactivity was found in 9 (Fig. 5B).

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(30), esophageal (31), and endometrial carcinomas as well as in Ewing’s sarcoma cell lines and metastatic tumor specimens, as we showed in this study. In support of our present findings, MMP-7 expression levels have been shown to correlate with the clinical aggressiveness of various tumor types (31), and overexpression of MMP-7 in colon carcinoma cells increased their tumorigenicity in vivo without altering their invasiveness in vitro (32). These observations support the notion that tumor progression associated with MMP-7 activity may not be attributable to proteolytic degradation of a structural component of the ECM but rather may relate to the regulation of tumor cell survival itself. Consistent with this possibility, we found that down-regulation of MMP-7 protein levels, by transfection of a plasmid carrying the human MMP-7 sequence in vitro, we found that down-regulation of MMP-7 protein levels, by transfection of a plasmid carrying the human MMP-7 sequence in vivo, sensitized tumor cells to doxorubicin, supporting our previous finding that inhibition of FasL shedding by a broad-spectrum synthetic MMP inhibitor sensitizes tumor cells to doxorubicin (21). Taken together, these observations suggest that specific inhibition of MMP7 may provide a potentially effective approach toward increasing the efficacy of chemotherapy in at least a subset of carcinomas.

Our observations do not exclude the possibility that other MMPs may play a similar role to that of MMP-7 uncovered here in other cell types in which cytotoxic drugs exert part or most of their effect through the Fas pathway. It is also possible that MMP-7 may cooperate with other MMPs in the catalysis of FasL shedding. Nevertheless, the regulation by a specific MMP of FasL cleavage and cytotoxic drug-induced apoptosis may not only shed new light onto the complex mechanisms by which MMP activity controls tumor invasion and metastasis but provide a potential target for the development of new therapeutic approaches that may significantly augment the efficacy of conventional chemotherapy.

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