Utilization of Bone Marrow-Derived Endothelial Cell Precursors in Spontaneous Prostate Tumors Varies with Tumor Grade

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ABSTRACT

Id1 and Id3 genes are required for vascularization, growth, and metas-
tasis of xenograft tumors. In Id-deficient mice, tumor transplantation and proangiogenic factors fail to mobilize and recruit circulating endothelial precursor cells (CEPs) and hematopoietic cells, leading to defective tumor angiogenesis in various models. To investigate the requirement of Id genes and bone marrow incorporation in spontaneous prostate tumors, we crossed Id mutant mice with the transgenic adenocarcinoma of the mouse prostate (TRAMP) mice. Id1+/− Id3+−/− TRAMP mice display delayed tumor growth at 24 weeks compared with wild-type TRAMP mice. Id1 and Id3 were strongly expressed in the endothelial cells of poorly differentiated prostate adenocarcinoma but not in the vasculature of well-differentiated tumors, a finding that is corroborated in human prostate tumor samples. In Id-deficient TRAMP mice, the poorly differenti-
tated tumors show extensive hemorrhage, whereas well-differentiated tu-
ors exhibit none. Transplantation with Id wild-type bone marrow significantly reduced the hemorrhage in poorly differentiated prostate adenocarcinomas with bone marrow-derived endothelial cells contrib-
uting to 14% of the tumor blood vessels. However, in well-differentiated prostate adenocarcinomas, there was little evidence of bone marrow-
derived endothelial cell incorporation. These differences in the expression of Id genes, the effects of Id loss, and the recruitment of bone marrow-derived endothelial precursor cells in tumor vasculature between well-
differentiated and poorly differentiated prostate adenocarcinoma suggest that tumor angiogenesis varies depending on the tumor grade.

INTRODUCTION

The Id genes are a family of helix-loop-helix proteins lacking a basic DNA binding region. They bind to and antagonize the activities of several classes of transcriptional regulators and play an important role in cell differentiation and cell fate determination in many cell lineages (1). There are four Id genes in mammals, Id1 through Id4. Id1+/− Id3−/− mice exhibit hemorrhage in the forebrain and die sub-
sequently at embryonic day 13.5 with failed proliferation and branching of endothelial cells into the neuroectoderm (2), indicating that Id1 and/or Id3 are important in developmental angiogenesis. Id1 and Id3 also are essential for tumor angiogenesis. Xenograft tumors in Id1- and Id3-deficient mice either fail to grow completely or show slower growth with extensive hemorrhage and necrosis (2). Transplantation with wild-type bone marrow rescues the angiogenic defect, and tumor growth is restored (3). Virtually all of the vessels in tumor xenografts were shown to be bone marrow derived. Analysis of Id-deficient bone marrow shows impaired vascular endothelial growth factor (VEGF)-driven mobilization of VEGFR-2+ circulating endothelial precursor cells (CEPs) and expansion of VEGFR-1+ hematopoietic cells (3). The involvement of CEPs in tumor vascularization and the role of the Id genes were further investigated in several spontaneous tumor mouse models. The results from intercrosses between Id-deficient mice and Pten+/− or HER-2/neu tumor-prone animals have shown a tumor-type dependence on Id gene expression in the endothelium and the utilization of bone marrow-derived precursor cells in the tumor vasculature (4, 5).

Here, we report the role of Id genes and bone marrow-derived precursor cells in prostate tumor angiogenesis in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model. In this model, the prostate-specific rat probasin promoter drives expression of the SV40 Tag, and transgenic mice develop spontaneous prostate adenocarcinoma (6). TRAMP mice display low- and high-grade prostatic intraepithelial neoplasia and well-, moderate-, and poorly differenti-
ted prostate adenocarcinomas (7). Because there is such a dramatic variation in tumor grade in this model, this analysis allows us to determine whether tumor grade has any affect on angiogenic require-
ment for Id gene expression and/or bone marrow-derived precursor cells.

We show here that Id1+/− Id3+−/− TRAMP mice display delayed tumor growth at 24 weeks compared with wild-type TRAMP mice. Id1 and Id3 were strongly expressed in the endothelial cells in poorly differentiated prostate adenocarcinoma but not in the endothelium in well-differentiated prostate adenocarcinoma, showing for the first time that there is a variation in the endothelium of prostate tumors depending on tumor grade. As anticipated from the expression analysis, in Id-deficient TRAMP mice, the poorly differentiated tumors showed extensive hemorrhage, whereas well-differentiated tumors exhibited none. Transplantation with Id wild-type bone marrow sig-
ificantly reduced the hemorrhage in poorly differentiated prostate adenocarcinomas with bone marrow-derived endothelial cells contributing to 14% of its tumor blood vessels. However, in well-differentiated prostate adenocarcinomas, there was little evidence of bone marrow incorporation. These differences in the expression of Id genes in tumor endothelium, the effects of Id loss on tumor vasculature, and the recruitment of bone marrow-derived precursor cells in tumor blood vessels between well-differentiated and poorly differentiated prostate adenocarcinoma suggest that Id gene expression and the contribution of bone marrow-derived precursor cells into neovascularize vary depending on the tumor grade. This variation may provide a partial explanation for the neovascular heterogeneity between tumor stages.

MATERIALS AND METHODS

Generation of Id Mutant TRAMP Mice. TRAMP mice in a pure C57Bl6 background were obtained from Dr. Norman M. Greenberg (Baylor Medical College, Houston, TX) and maintained at the Sloan-Kettering Institute. TRAMP mice were crossed with Id1+−/− Id3+−−/− mice in a mixed C57Bl6/129Sv background to generate TRAMP Id1+/− Id3+−/− mice. These mice then were crossed with Id1/− Id3+−/− mice to generate TRAMP+−/− mice with intact Id copies or TRAMP+−/− mice lacking Id copies in different combina-
tions. All of the mice were genotyped by PCR according to previously published protocols (2) and maintained in compliance with Institutional Ani-
mal Care and Use Committee guidelines.

Histologic Analysis, Immunohistochemistry, and In situ Hybridization. Tumors were fixed in paraformaldehyde, and 8-μm paraffin sections were stained for H&E, mouse CD31 (rat antimouse CD31 monoclonal, 2.5 μg/mL;
Id1 and Id3 genes facilitate tumorigenesis or angiogenesis in this spontaneous prostate model, we crossed Id1<sup>-/-</sup> Id3<sup>+/+</sup> mice with TRAMP mice.

TRAMP mice were sacrificed at 12, 18, or 24 weeks. At 24 weeks, there was a significant delay in prostate tumor growth in Id1<sup>-/-</sup> Id3<sup>+/+</sup> TRAMP mice (Fig. 1A). Fifty-five percent of Id1/Id3 wild-type TRAMP mice (n = 20) developed large prostate tumors, grossly visible during dissection. Only 20% of Id1<sup>-/-</sup> Id3<sup>+/+</sup> TRAMP mice (n = 15) had grossly visible tumors at this time point, a statistically significant difference compared with wild-type TRAMP mice. A total of 84.2% of Id wild-type TRAMP mice (n = 19) and 72.7% of Id1<sup>-/-</sup> Id3<sup>+/+</sup> TRAMP mice (n = 11) developed either grossly visible or microscopic prostate tumors at this time (Fig. 1B), a measure of total tumor initiation. The difference was not statistically significant. Id1<sup>-/-</sup> Id3<sup>+/+</sup> TRAMP mice (n = 10) and Id1<sup>-/-</sup> Id3<sup>-/-</sup> TRAMP mice (n = 15) also developed fewer grossly visible tumors, although no statistically significant difference from Id1/Id3 wild-type TRAMP mice was observed (data not shown). These results suggest that tumor progression but not tumor initiation is affected by Id loss, and this effect depends on Id gene dosage. Additional TRAMP mice were not sacrificed at any fixed time point but studied for their overall survival time. Survival curve comparison between TRAMP animals in an Id wild-type or knockout background showed no significant difference (Fig. 1C), indicating that the prostate tumorigenesis in the TRAMP mice is only temporarily delayed by Id deficiency.

Id1 and Id3 are expressed in the endothelial cells of poorly differentiated but not of well-differentiated prostate adenocarcinomas. To investigate how Id deficiency delayed tumor growth, we studied where the Id genes were expressed in TRAMP prostate tumors. For these studies, we used a polyclonal antibody shown to be specific for Id1 using Id1<sup>-/-</sup> control sections (5). In adult TRAMP mice, Id1 was not expressed in normal prostate glands, prostatic intraepithelial neoplasia, or surrounding stroma cells (data not shown). Analysis of well-differentiated prostate adenocarcinomas (n = 6) showed that Id1 was weakly expressed in the tumor cells but not in the endothelial cells or other stroma cells (Fig. 2B). In contrast, in poorly differentiated adenocarcinomas (n = 10), the nuclei of endothelial cells were strongly stained with the Id1 antibody (Fig. 2A). Tumor cells were weakly stained in most tumors. In situ hybridization analysis with an antisense Id1 probe confirmed the results of the immunohistochemistry (data not shown). In situ hybridization with an Id3 probe showed a similar expression pattern as Id1 in the endothelial cells (data not shown), and Id3 was not expressed in tumor cells. The expression pattern of the Id1 and Id3 genes suggests that in TRAMP mice, Id genes may play an important role in prostate tumor angiogenesis rather than contribute to tumorigenesis directly.

**RESULTS**

**Id1<sup>-/-</sup> Id3<sup>+/+</sup> TRAMP Mice Showed Delayed Tumor Progression.** Prostate cancer progression in TRAMP mice has been investigated extensively (6, 7). By 24 weeks, large prostate tumors develop, and a full spectrum of pathology is observed. To examine whether Id1 and Id3 genes facilitate tumorigenesis or angiogenesis in this spontaneous prostate tumor model, we crossed Id1<sup>-/-</sup> Id3<sup>+/+</sup> mice with TRAMP mice.

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In Id1⁻/⁻ Id3⁺⁻ TRAMP mice, grossly visible poorly differentiated but not well-differentiated prostate adenocarcinomas show extensive hemorrhage. When prostate tumors were dissected, we noticed a difference in gross appearance of poorly differentiated tumors between Id wild-type and Id1⁻/⁻ Id3⁺⁻ TRAMP mice. In Id wild-type TRAMP mice, most tumors were white with enlarged blood vessels and small areas of local hemorrhage (Fig. 3A). In contrast, in Id1⁻/⁻ Id3⁺⁻ TRAMP mice, many tumors showed extensive hemorrhage throughout the tumors (Fig. 3B).

Computer automated scanning of the percentage of tumor area covered by RBCs was used as a quantitative indicator for tumor hemorrhage. In poorly differentiated prostate adenocarcinomas, 14.2% of the endothelium of these tumors. During dissection, some grossly visible tumors in Id1⁻/⁻ Id3⁺⁻ TRAMP mice were mostly white. Histologic analysis showed they were well-differentiated prostate adenocarcinomas. These tumors had relatively normal blood vessels and little hemorrhage, with no significant differences compared with the well-differentiated tumors in Id wild-type mice (Fig. 3C–E). The well-differentiated lesions in the Id1⁻/⁻ Id3⁺⁻ background had an average 0.6% area of hemorrhage, which is significantly less than that of poorly differentiated prostate tumors (P < 0.01). This result further indicated that angiogenesis in well-differentiated and poorly differentiated prostate tumors has inherent differences. The lack of effect of Id loss in well-differentiated tumors is consistent with the lack of Id1 expression observed in the endothelium of these tumors.

Bone marrow cells contribute to the blood vessel formation in poorly differentiated prostate adenocarcinomas but not in well-differentiated tumors. In xenograft models, transplantation with wild-type bone marrow rescued the angiogenic deficiency in Id1⁻/⁻ Id3⁺⁻ mice (3). To investigate whether bone marrow-derived precursor cells contribute to spontaneous prostate tumor vasculature, we transplanted Rosa-26 mouse bone marrow cells into TRAMP mice at 12 weeks and analyzed their prostates at 24 or 30 weeks.

In Id1⁻/⁻ Id3⁺⁻ TRAMP mice that received a wild-type bone marrow transplant, poorly differentiated tumors showed significantly decreased hemorrhage (mean, 1.6%), compared with those without bone marrow transplant (mean, 9.2%) or those that received a bone marrow transplant from an Id1⁻/⁻ Id3⁺⁻ donor (mean, 14.2%; Fig. 4A, B, and D). This indicates that Id wild-type bone marrow-derived cells were able to rescue the angiogenic defect in Id1⁻/⁻ Id3⁺⁻ TRAMP mice. Furthermore, hemorrhage increased in prostate tumors in Id wild-type mice transplanted with mutant bone marrow (mean, 7.4%; Fig. 4C and D), implying Id-positive bone marrow-derived cells are necessary to maintain neovasculature in poorly differentiated tumors.

In poorly differentiated prostate adenocarcinomas, 14.2% of the endothelial cells were stained blue, indicating bone marrow-derived cells contributed to their blood vessel formation (Fig. 5A and C). Staining with CD31 antibody confirmed the endothelial cell identity. However, X-gal staining in well-differentiated prostate tumors detected only 2.6% blue endothelial cells (Fig. 5B and C), suggesting the lack of significant bone marrow incorporation in well-differentiated tumors.
Multiple bone marrow-derived blood vessels were observed in clusters in poorly differentiated prostate adenocarcinomas, usually surrounded by bone marrow-derived hematopoietic cells (Fig. 5D), consistent with comobilization and recruitment of CEPs and hematopoietic cells to tumor vasculature in the more advanced tumor stage. However, no cluster of bone marrow-derived hematopoietic cells were ever observed in well-differentiated prostate adenocarcinomas (Fig. 5E), showing an additional difference in bone marrow utilization between these two tumor stages.

In Human Prostate Adenocarcinoma, Id1 Expression Is Stronger in the Endothelium of Tumors with Higher Gleason Score. To determine whether the aforementioned results are likely to apply to human prostate tumors, we assayed human samples with the Id antibody, which cross-reacts with human Id1.4 In human prostate adenocarcinoma samples with a low Gleason sum (2 to 4) indicative of a more well-differentiated tumor, Id1 immunohistochemistry showed no or weak staining in the neovasculature (Fig. 6A and D). In samples with higher Gleason sum (5 to 9; i.e., poorly differentiated tumors), Id1 expression was strong in the nucleus of tumor endothelium (Fig. 6B and D). There is a statistically significant trend that Id1 staining in neovasculature is stronger in tumors with higher Gleason sum (P < 0.01), indicating Id1 expression in the vasculature correlates with tumor grade. The similarity of the Id1 expression pattern in the endothelium of human prostate adenocarcinoma and in that of the TRAMP model suggests that Id gene involvement and bone marrow incorporation in neovasculature also may vary because of tumor grade in human prostate tumors.

Most prostate cells in human tumor samples are negative for Id expression; however, smooth muscle cells in some prostate samples stained positive (Fig. 6A and B). A similar result was observed in murine samples, but this staining was determined to be nonspecific as shown by similar staining in Id1−/− control sections (data not shown). However, in samples from patients treated with neoadjuvant androgen ablation therapy, there was Id1 expression in the nuclei of basal layer tumors. In all of the mice that received a Rosa-26 bone marrow transplant, RBCs were lacZ positive, indicating the success of the bone marrow transplant and staining procedures.

Vessels, and in recent years, increasing evidence indicates that tumor angiogenesis is a dynamic process during which the level of angiogenic factors such as VEGF and PIGF is elevated; metalloproteinases, especially matrix metalloproteinase-9, are activated; and bone marrow stromal cells subsequently release active cytokines like sKitL, which promote the proliferation and motility of CEPs and hematopoietic cells and increase their circulation in peripheral blood (13–16).

Id-deficient mice have a tumor angiogenesis defect caused by failed incorporation of bone marrow-derived precursor cells into tumor vasculature. This defect completely inhibits B6RV2 lymphoma growth after s.c. implantation, in which bone marrow-derived cells contribute to 95% of the blood vessels, showing bone marrow incor-

**DISCUSSION**

Tumor development is a multistage process. Angiogenesis often is activated during the early, preneoplastic phase of tumor growth in transgenic mouse models and human cancers (9), and the blood vessels in neoplasia are distinct from those of normal tissues (10, 11).

There are established processes that contribute to tumor blood vessel formation: the sprouting and co-option of adjacent pre-existing vessels, and in recent years, increasing evidence indicates that tumor angiogenesis also is supported by bone marrow-derived precursor cells, including CEPs and hematopoietic stem cells (12). Comobilization and recruitment of VEGFR-2+ CEPs and VEGFR-1+ hematopoietic cells facilitate the incorporation of CEPs into developing blood vessels. Bone marrow incorporation into tumor vasculature is a dynamic process during which the level of angiogenic factors such as VEGF and PIGF is elevated; metalloproteinases, especially matrix metalloproteinase-9, are activated; and bone marrow stromal cells subsequently release active cytokines like sKitL, which promote the proliferation and motility of CEPs and hematopoietic cells and increase their circulation in peripheral blood (13–16).

Id-deficient mice have a tumor angiogenesis defect caused by failed incorporation of bone marrow-derived precursor cells into tumor vasculature. This defect completely inhibits B6RV2 lymphoma growth after s.c. implantation, in which bone marrow-derived cells contribute to 95% of the blood vessels, showing bone marrow incor-
poration in neovasculature is essential in this xenograft tumor model (3). In the Pten−/−/H11001/−/H11002 tumor model, bone marrow-derived cells only contribute to 16% of vessels in spontaneous uterine carcinomas, but these vessels are essential to maintain the integrity of the vascular network (4). This number may be an underestimate of the number of vessels that use these cells because their incorporation into the vessel is a dynamic process (3), and only one time point was examined (4). Unlike uterine carcinomas, however, bone marrow-derived cells do not contribute to the neovascularization in lymph hyperplasia in Pten−/−/− animals, showing tumor type-dependent bone marrow contribution to tumor endothelium (4). Although Pten−/− Id1−/−/Id3+/− mice exhibit an angiogenic defect in all of the tumor types that express Id1 in the endothelium, the effect on tumor growth varies with tumor type. This probably is caused by escape from angiogenic stress in some tumors, reminiscent of what has been observed in other tumor models (5, 17).

Fig. 5. Bone marrow-derived blood vessels observed in poorly differentiated (PD) but not in well-differentiated (WD) prostate adenocarcinomas. A, Some blood vessels in poorly differentiated prostate tumors were derived from bone marrow, stained blue with X-gal (black arrowhead). B, Neovasculature in well-differentiated prostate tumors was not derived from bone marrow. The blue stain of RBCs indicated the bone marrow transplant procedure was successful (white arrowheads). C, The difference in the percentage of bone marrow-derived tumor vasculature between poorly differentiated and well-differentiated prostate tumors is significant (P < 0.005). D, Multiple bone marrow-derived blood vessels were seen in a cluster, surrounded by bone marrow-derived hematopoietic cells. CD31 staining is shown in inset. E, Blood vessel clusters derived from bone marrow were observed in poorly differentiated prostate tumors. No clusters were observed in well-differentiated prostate tumors. The difference of bone marrow-derived blood vessel clusters between poorly differentiated and well-differentiated is significant (P < 0.05); bar, 25 μm.

Fig. 6. Id1 immunohistochemistry showed stronger Id1 expression in neovasculature in human prostate adenocarcinoma with higher Gleason sum. A, The blood vessels (black arrowheads) were not stained with Id1 antibody in a prostate adenocarcinoma with Gleason sum 2. Antibody cross-reacted nonspecifically with smooth muscles. B, The endothelial cells (black arrows) were positive for Id1 staining in a prostate adenocarcinoma with Gleason sum 9. C, The basal layer cells of prostate glands (black arrows) were stained with Id1 antibody in the samples after neoadjuvant androgen ablation treatment. D, Id1 antibody staining in neovasculature is stronger in human prostate adenocarcinoma with higher Gleason sum. The staining intensity of Id1 antibody was scored as −, none; +/−, very mild; +, mild; ++, moderate; and ++++, heavy staining. E, Id1 mRNA expression from the microarray analysis of untreated, neoadjuvant androgen ablation-treated, and androgen-resistant prostate adenocarcinoma samples as indicated. Untreated and treated non-neoplastic prostate samples also were analyzed. The two differently colored bars were the results from duplicate experiments. CaP, prostate adenocarcinomas; bar, 50 μm.
The TRAMP mouse provides a prostate tumor model in which tumors develop through histologically distinct stages. The expression of certain angiogenic factors, such as VEGF, is elevated in poorly differentiated versus well-differentiated prostate adenocarcinoma. 18. Id1 and Id3 are strongly expressed in the endothelium of poorly differentiated tumors but not that of well-differentiated tumors, illustrating a difference in the genetic composition of tumor vasculature, depending on tumor grade. The reduction in Id gene dosage also induced tumor grade-dependent differential effects on prostate tumor vasculature. In Id-deficient mice, poorly differentiated but not well-differentiated prostate adenocarcinoma showed extensive hemorrhage, indicating that Id loss only induces angiogenic defects at a more advanced tumor stage, consistent with the tumor grade-dependent Id expression pattern in blood vessels. These observations also are consistent with the fact that macroscopic tumors (usually enriched for rapidly growing poorly differentiated lesions) are observed at lower frequency in the Id knockout background compared with wild-type controls.

The failure to see any survival benefit in TRAMP mice in the Id knockout backgrounds may be interpreted simplistically as evidence that the severe antiangiogenic stress imposed by Id loss on prostate tumors (and all of the autochthonous tumors known to express Id1 or Id3 in the vessels) is not likely to be an effective clinical strategy. However, the extensive hemorrhage and necrosis observed in the poorly differentiated tumors on even modest Id reduction is reminiscent of that observed in mouse mammary tumor virus-HER-2/neu tumors (5), and remarkably these tumors respond synergistically with chemotherapeutic intervention to effect the first complete remission of tumors (5), and remarkably these tumors respond synergistically with chemotherapeutic intervention to effect the first complete remission of tumors (5). The vessel development stage tumorigenesis in premalignant lesions and the origin of the vasculature in prostate tumors is grade specific. We propose that the extent of bone marrow incorporation is one component for such neovascular heterogeneity. Defining tumor angiogenesis according to tumor stages could significantly affect how we design and use angiogenesis inhibitors therapeutically. Further understanding of stage-specific neovascularization could provide important clues on how to target imaging agents and therapeutics to tumor vasculature in a more accurate and sensitive manner.

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