Effects of Interleukin-1 Receptor Antagonist and Chemotherapy on Host–Tumor Interactions in Established Melanoma

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Abstract. Background: Interleukin-1 (IL-1) has been implicated in the vascular and immune suppressor cell responses that promote tumor progression. IL-1, however, has also been shown to inhibit tumor progression by promoting antitumor immune responses and by enhancing the activity of chemotherapy. Materials and Methods: The effects of IL-1 receptor antagonist (IL-1Ra), alone and combined with temozolomide and docetaxel chemotherapy, were examined in vitro and in vivo against microscopic and macroscopic mouse B16 melanoma. Results: IL-1Ra did not demonstrate antitumor activity in vitro, alone or combined with chemotherapy. When administered in vivo at the time when B16 cells were inoculated, IL-1Ra inhibited tumor growth. It did not affect growth when administered after tumors had established and were macroscopic. IL-1Ra increased M1 macrophage polarization and reduced myeloid-derived suppressor cells in mice with macroscopic tumors. Regulatory T-cells, tumor vascularity, and tumor interstitial fluid pressure were not significantly altered. Pre-treatment but not concurrent treatment with IL-1Ra enhanced the antitumor activity of chemotherapy in vivo against macroscopic tumors. Whereas chemotherapy reduced myeloid suppressor cells systemically, chemotherapy increased markers of myeloid suppressor cells intratumorally. These effects were attenuated by pre-treatment with IL-1Ra. Conclusion: The effects of IL-1 and chemotherapy in melanoma are complex. IL-1Ra modifies myeloid suppressor cell populations and may have a role with chemotherapy in the treatment of established melanoma.

Interleukin (IL-1) is a mediator of acute and chronic inflammatory conditions as well as a hematopoietin. Both isoforms, IL-1α and IL-1β, have been implicated in the development, growth, invasion, and metastasis of tumors, as well as in host responses that contribute to tumor progression, including angiogenesis and the ability to escape immune surveillance (reviewed in (1)). Malignant melanoma is a refractory malignancy. The chemotherapies currently applied are rarely effective and are limited by toxicity. In experimental models, IL-1 has been shown to be required for melanoma invasiveness, metastasis, and angiogenesis (2, 3). A naturally occurring antagonist, IL-1Ra, competitively blocks IL-1α and IL-1β at the receptor level. IL-1Ra has demonstrated antitumor activity in mouse B16 melanoma and human melanoma xenograft models, and there is interest in applying IL-1Ra clinically (4-6). As IL-1 has also been implicated in the clinical toxicity of several chemotherapeutics, combining IL-1Ra with chemotherapy has also been suggested to improve treatment outcome (7-10).

The antitumor activity of IL-1Ra has been demonstrated in mouse melanoma models when administered at the time of tumor implantation to inhibit invasion, angiogenesis, and/or metastasis (4-6). The effects of IL-1Ra on macroscopic melanoma tumors, where abnormal vascularity and immune escape mechanisms are present, have not been reported. Although IL-1 has been implicated in tumor angiogenesis and in the adverse effects of chemotherapy, IL-1 has also been reported to improve the cytotoxic effects of chemotherapy in vivo, an effect attributed to vascular effects that result in an increase in intratumoral chemotherapy concentration (11, 12). Furthermore, IL-1 has been shown to directly sensitize tumors to the cytotoxic effects of several cytotoxic chemotherapeutics (13). IL-1Ra is immunosuppressive, and although IL-1 can suppress antitumor immune responses by stimulating of M2-polarized macrophages and myeloid derived suppressor cells (MDSC) (14, 15), IL-1 can potentially promote antitumor immune responses by activating M1 macrophages and dendritic cells, and attenuating FoxP3+ regulatory T (T-reg) cells (16, 17). In fact, IL-1 has demonstrated antitumor activity in mice with macroscopic B16 melanoma, an effect attributed to its ability to activate immune effector mechanisms (18).

Human recombinant IL-1Ra (hrIL-1Ra) is used clinically to treat patients with rheumatoid arthritis and has been shown to inhibit B16 melanoma metastases when administered at the
time of tumor inoculation (5). Given the potential contradictory roles of IL-1 in tumor progression, we examined the effects of hrIL-1Ra on the vascularity and immune suppressor cells associated with established macroscopic B16 tumors. We also examined the combined effects of hrIL-1Ra and chemotherapy, focusing on the alkylation agent, temozolomide, and the taxane, docetaxel, chemotherapeutics currently being used to treat patients with melanoma (19).

Materials and Methods

Cell lines and animals. Mouse B16 melanoma cells (B16.F10; American Type Culture Collection, Manassas VA, USA) were maintained in Dulbecco’s modified Eagle’s medium (DMEM) with 10% heat-inactivated fetal calf serum, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 μg/ml streptomycin (Mediatech, Herndon, VA, USA). The cultures were grown at 37°C in 5% CO2 to confluence, passaged by treatment with 0.05% trypsin in EDTA at 37°C, and washed in media before being centrifuged at 200 x g for 10 minutes to form a pellet. Female C57BL/6 mice (aged 4 weeks) were obtained from Taconic Farms (Hudson, NY, USA) and were fed with commercial diet and water ad libitum. The animal use and care protocol was approved by the Institutional Animal Use and Care Committee.

Tumor model. Tumors were established by injecting 2x105 B16 cells in 100 μl of serumless DMEM subcutaneously into a flank. Tumors become macroscopic, i.e. visible/ palpable, after 5 to 7 days with this inoculation. rhIL-1Ra (Amgen, Thousand Oaks, CA, USA) was administered intraperitoneally (i.p.) at 5 mg/mouse per day. Temozolomide (Schering Corporation, Kenilworth, NJ, USA) was dissolved in dimethyl sulfoxide (DMSO), diluted in phosphate-buffered saline (PBS) and administered i.p. Docetaxel (Sanofi-Aventis U.S., Bridgewater, NJ, USA) was also administered i.p. Tumors were measured bidimensionally with calipers every two to three days, and tumor volume calculated by the formula (length x width²)/2. Mice were euthanized when tumors reached the size of 2000 mm³.

Cell proliferation. 3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) was added to B16 cell cultures in 96-well plates as recommended by the manufacturer (CelTiter 96 AQueous Non-Radioactive Cell Proliferation Assay; Promega, Madison, WI, USA) and absorbance was read at 492 nm. Data represent mean % proliferation ([(experimental absorbance – background absorbance)/(absorbance of control cultures – background absorbance)] x 100%). Controls of vehicle alone (DMSO) did not exhibit proliferation changes as compared to cells in culture medium alone.

Flow cytometry. Cells were washed twice in PBS with 1% bovine serum albumin plus 0.05% sodium azide and stained for 30 minutes on ice with phycoerythrin- or fluorescein isothiocyanate-conjugated monoclonal antibodies specific for CD11b and Gr1 (BD Biosciences, San Jose, CA, USA) and CD4 and FoxP3 (eBioscience Inc., San Diego, CA, USA). Appropriate isotype controls were used in all experiments. Cells were washed and fixed with 2% paraformaldehyde. All samples were analyzed using an EPICS Altra flow cytometer (Beckman Coulter, Fullerton, CA, USA).

Tumor RNA. RNA from B16 cell lines in vitro was obtained using the RNeasy method (Qiagen, Valencia, CA, USA) according to the manufacturer’s directions. Dissected tumors grown in vivo were placed in RNA Later (Ambion, Austin, TX, USA) and stored at −80°C. RNA was then extracted with RNeasy and stored at −80°C.

Quantitative real-time polymerase chain reaction (qRT-PCR). An ABI Prism 7500 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and pre-standardized primers and TaqMan probes were used. Mouse cytokines IL-1α, IL-1β, IL-6, IL-10, IL-12(p40), tumor necrosis factor α (TNF-α), granulocyte/macrophage colony stimulating factor (GM-CSF), and vascular endothelial growth factor (VEGF) and markers of suppressor cell activity, including arginine (Arg1), a product of MDSC and M2-polarized macrophage (20, 21); CD206, a marker of M2-polarization (22); IL 12(p40), a product of M1-polarized macrophages; CXCL10 (Mrc1), a marker of M1-polarization (22); and FoxP3, expression of which in mice is highly restricted to T-reg cells (23) were assessed. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the endogenous control (Applied Biosystems). The reverse transcription and PCR was accomplished using a one-step protocol and TaqMan Universal Master Mix (Applied Biosystems). Ct values were determined, and the relative number of copies of mRNA was calculated using the ΔΔCt method (24).

Interstitial fluid pressure (IFP). Tumor IFP was measured using the wick-in-needle technique (25). Mice were anesthetized using ketamine/xylazine. A 20-gauge Huber needle filled with 4-0 suture and PBS, supplemented with 0.5 mM EDTA, was inserted into the center of the tumor and connected to a pressure transducer. Fluid communication between the needle and the transducer was confirmed by compression and decompression of the tubing during each measurement. The recorded pressure had to return rapidly to the pressure prior to compression and not deviate by more than 0.5-1 mm Hg to be an acceptable reading.

Immunohistochemistry. Antibodies to mouse CD4, CD11b, CD31, CD140b, (BD Biosciences), and α smooth muscle actin (ASMA; Invitrogen, Carlsbad, CA, USA) were used. Tissue sections were incubated for 1 hour at 37°C with the primary antibody diluted 1:100 in PBS containing 2% rabbit serum. After washing with PBS, sections were incubated for 15 minutes at 37°C with biotinylated secondary rabbit antibody (anti-rat IgG), followed by streptavidin-peroxidase complex (Vector Laboratories, Burlingame, CA, USA). Slides were washed, developed with 3,3’ diaminobenzidine (Vector Laboratories) and hydrogen peroxide, and counterstained with hematoxylin. The intensity of the immunohistochemical reactions was quantified by a Leica Image Analysis System with Image Pro, version 6.2 (Media Cybernetics, Bethesda, MD, USA).

Statistical analysis. Tumor volume data were analyzed using ANOVA with testing (Wilcoxon test) when significant differences (p<0.05) were found. Standard errors of the mean (SEM) for each set of tumor measurements were calculated and represented as y-axis error bars on each graph. Determination of synergy or antagonism was determined using CalcuSyn software and quantified by the combination index (CI) (22): CI=1 indicates an additive effect, <1, synergy, >1, antagonism (26). Other parameters were analyzed with two-sided Student’s t-test with p<0.05 being considered statistically significant.
Results

rhIL-1Ra does not directly affect proliferation or cytokine production in vitro. hrIL-1Ra did not manifest antiproliferative activity in vitro, whereas both temozolomide and docetaxel manifested the expected antiproliferative activity (Figure 1). CIs were calculated for the combination of hrIL-1Ra and temozolomide and of hrIL-1Ra and docetaxel. No interactions were observed: all CIs were approximately 1. rhIL-1Ra also did not alter B16 cell production of the mRNA of cytokines implicated in the regulation of tumor angiogenesis and/or the development of immune suppressor cells (Figure 2). With the exception of VEGF, basal expression of these cytokines was low. Up to log-fold increases in GM-CSF, IL-6, and TNF-α and decreases in VEGF expression were, however, noted in response to temozolomide and docetaxel. Again, no interactions were observed: all CIs for cytokine production were approximately 1.

rhIL-1Ra inhibits the growth of microscopic but not macroscopic tumors in vivo. A dose and schedule that is effective in mouse arthritis models and that mimics current clinical application, i.e., 1 mg/day was used (27). Confirming observations made in previous reports (4-5, 28), B16 tumor growth inhibition was observed when hrIL-1Ra was started at the time of tumor cell inoculation (p=0.001, Figure 3). The same dose and schedule, however, had no effect on tumor growth when injections started 7 days after tumor implantation, when tumors had established and were macroscopic.

hrIL-1Ra modifies the microenvironment of macroscopic tumors. Whether or not the 1 mg/day administration of hrIL-1Ra had any effects in vivo on macroscopic B16 tumor was then examined. Effects on intratumoral cytokines were examined using qRT-PCR. Whereas in vitro hrIL-1Ra had no direct effect on B16 cell cytokine production, in vivo it reduced the expression of GM-CSF, IL-1α, IL-1β, IL-6, IL-10, and TNF α in macroscopic B16 tumors (all p<0.05; Figure 4A). VEGF levels, however, did not significantly decrease. Standard immunohistochemical techniques were used to examine changes in intratumoral cellular constituents (Figure 4B). The frequency of CD11b+ macrophages and granulocytes significantly decreased intratumorally with hrIL-1Ra (p<0.01); changes in CD4+ lymphocytes, CD31+ blood vessels, CD140b+ fibroblasts and pericytes, and ASMA+ pericytes were not significant.

IL-1Ra has been shown to reduce tumor IFP, a physiologic measure of abnormal tumor vascularity (29). Obtaining reproducible measures of tumor IFP using the wick-in-needle technique required a minimal tumor volume. Treatment was thus started at day 10, and these experiments were performed at day 15 when the tumors had reached diameters of approximately 5 mm. As expected, the IFP of normal subcutaneous tissue was –6 to 0 mm Hg, whereas B16 tumor IFP was in the 9 to 13 mm Hg range. A slight but insignificant decrease in tumor IFP was observed: IFP after 5 days of hrIL-1Ra at 1 mg/mouse/day=7.4±2.3 (mean±SEM) mm Hg compared to 10.5±2.8 after 5 days of PBS.

qRT-PCR was also used to examine changes in markers of intratumoral suppressor cell activity. The decreases in arginase and CD206 and the increases in IL-12(p40) and CXCL10 observed in response to hrIL-1Ra (all p<0.05) were consistent with a decrease in MDSC and M2 macrophage polarization and an increase in M1-polarization (Figure 4C). Intratumoral levels of FoxP3 did not change significantly.

rhIL-1Ra modifies melanoma-associated MDSC but not T-reg cells systemically. Establishment of B16 tumors in C57Bl/6 mice has been associated with an increase in splenic
Whether hrIL-1Ra could modulate systemic immune suppressor cells was initially tested using spleens harvested at day 10 from mice with tumors established and treated as above. At this time point, tumor volumes were approximately 150 mm$^3$. These spleens did not manifest a significant increase in the frequency of MDSC or T-reg cells, and hrIL-1Ra treatment, using the same dose and the 5-day schedule, had no effect (Figure 5). A similar study was then performed harvesting tumors at day 17 after the 5-day course of hrIL-1Ra, when tumors were larger, with volumes $>1000$ mm$^3$. Increases in splenic MDSC and T-reg cells were observed in mice bearing these larger tumors. The frequency of MDSC did decrease with hrIL-1Ra ($p<0.001$, Figure 5); the frequency of T-reg cells was not altered.

**Pretreatment with hrIL-1Ra improves the antitumor activity of chemotherapy.** The combined effects of hrIL-1Ra and chemotherapy were examined *in vivo* against macroscopic B16 tumors. The dose and schedule of hrIL-1Ra that modified the tumor microenvironment in the studies described were first tested with a partially effective dose and three-day schedule of temozolomide used in other studies in B16 melanoma (32). rhIL-1Ra enhanced the activity of temozolomide. Enhancement was schedule dependent: pre-treatment ($p=0.001$) but not concurrent treatment with hrIL-1Ra enhanced the growth inhibitory effects (Figure 6A). The combined effects of hrIL-1Ra and docetaxel were then examined, again using a partially effective dose of docetaxel previously applied in B16 melanoma (33). Studies of temozolomide were repeated using a single dosing and not a three-day schedule. These studies are summarized in Figure 6B. rhIL-1Ra enhanced the growth inhibitory effects of docetaxel ($p=0.02$) and temozolomide ($p=0.001$), but only when applied before the chemotherapeutic. rhIL-1Ra treatment alone again did not affect tumor growth in these experiments.
rhIL-1Ra pretreatment attenuates the intratumoral immune regulatory response to chemotherapy. The effects of temozolomide and docetaxel, alone and combined with hrIL-1Ra pretreatment, on CD11b+Gr1+ MDSC and CD4+FoxP3+ T-reg cells in mice bearing macroscopic B16 tumor were examined using flow cytometry (Figure 7A). As had previously been reported (34, 35), decreases in both populations were observed in spleens in response to the chemotherapy. Pretreatment with hrIL-1Ra did not significantly modulate these effects. The combined effects of chemotherapy, alone and combined with hrIL-1Ra pretreatment, on markers of immune suppressor activity (Figure 7B) and relevant cytokines (Figure 7C) intratumorally were examined using qRT-PCR. In contrast to the spleen studies, there was evidence that myeloid suppressor cell populations increased intratumorally in response to chemotherapy. Pretreatment with hrIL-1Ra pretreatment, on markers of immune suppressor activity (Figure 7B) and relevant cytokines (Figure 7C) intratumorally were examined using qRT-PCR. In contrast to the spleen studies, there was evidence that myeloid suppressor cell populations increased intratumorally in response to chemotherapy. Both temozolomide and docetaxel increased arginase and increased CD206 levels. Temozolomide also reduced CXCL10. Both temozolomide and docetaxel increased intratumoral GM-CSF. Docetaxel increased IL-6, IL 10, IL-12(p40), and TNF-α levels, whereas temozolomide did not. In contrast, temozolomide reduced FoxP3, whereas docetaxel did not. In all cases, pretreatment with hrIL-1Ra attenuated the changes effected by the chemotherapeutic intratumorally, although only the attenuation of increases effected by temozolomide on arginase (p=0.001) and CD206 (p=0.02) and the increases effected by docetaxel on IL-6 (p=0.0001), IL-10 (p=0.001), and TNF α (p=0.001) were statistically significant.
Discussion

Multiple studies indicate that IL-1 plays a role in tumor development and progression, and inhibiting IL 1 with IL-1Ra has demonstrated antitumor activity in tumor models (1). There is also evidence supporting the use of IL-1Ra to improve chemotherapy tolerability (8, 9). IL 1, however, has also demonstrated antitumor activity, including the ability to enhance antitumor immune responses and chemotherapy cytotoxicity (13, 16, 18). Furthermore, the antitumor activity of IL-1Ra in mouse melanoma models has been demonstrated only against microscopic tumor and has been incomplete (4-6). To better mimic the more common clinical situation and application, we examined the effects of hrIL-1Ra against established mouse B16 melanoma tumors, alone and combined with chemotherapy. Our studies indicate that hrIL-1Ra can modify the host response to macroscopic tumor and enhance the antitumor activity of chemotherapy.

rhIL-1Ra did not demonstrate significant antitumor activity in vitro, alone or combined with chemotherapeutics. IL-1 may serve as an autocrine growth factor for some tumors. IL-1Ra has been shown to directly inhibit...
proliferation of skin and head and neck carcinoma (36, 37). There is, however, little evidence that IL-1 functions as an autocrine growth factor in melanoma. In contrast, hrIL-1Ra has been shown to block the IL-1-mediated reduction in growth in vitro of prostatic and hepatic carcinoma and glioblastoma cells (38-40). Consistent with previous reports, hrIL-1Ra manifested antitumor activity against B16 melanoma in vivo, albeit modest, when administered at the time of tumor cell inoculation. When administered when tumor had established and was macroscopic, hrIL-1Ra did not significantly inhibit growth. Significant changes in host tumor had established and was macroscopic, hrIL-1Ra did not significantly inhibit growth. Significant changes in host response, were, however, effected.

IL-1 promotes M2-polarization and MDSC development, which suppress antitumor immune response by a variety of mechanisms (15, 41). rhIL-1Ra has been shown to reduce splenic CD11b+Gr1+ MDSC in mice implanted with fibrosarcoma cells transfected with IL-1β (14). Our study confirms this effect and extends this observation. We also observed reduced infiltration of CD11b+ cells, as well as reduced levels of arginase and CD206, and increased levels of IL-12(p40) and CXCL10 intratumorally, which are consistent with decreases in MDSC and M2-polarization and increases in M1 polarization. The ability of hrIL-1Ra to reduce the levels of other cytokines implicated in the generation of myeloid suppressor cell populations, such as GM-CSF, IL-6, and TNF-α, may have contributed to these effects. Reduction of MDSC and induction of M1-polarized macrophages facilitate the regression of mouse breast cancer (42). The changes in MDSC and macrophage polarization we observed were not associated with mouse melanoma regression. Alternative doses and schedules of hrIL-1Ra may have been more effective. B16 melanoma, however, is poorly immunogenic. We also did not observe significant alterations in T-reg cells systemically or intratumorally. Although MDSC induce T-reg cells (43), IL-1 has been shown to attenuate T-reg cells function though effects on dendritic cells (16).

IL-1 has been shown to enhance the activity of cancer chemotherapeutics by direct and indirect mechanisms. Although ineffective in vitro and although IL-1Ra can block the ability of IL-1 to enhance chemotherapy cytotoxicity (44), we found that hrIL-1Ra was able to enhance the antitumor activity of both temozolomide and docetaxel in vivo. Enhancement was schedule dependent. Pretreatment but not concurrent or post-treatment with hrIL-1Ra enhanced antitumor activity. It has also been reported that the modulation of cisplatin cytotoxicity by IL-1 is schedule dependent: synergistic antitumor activity is observed with concurrent administration; treatment with IL-1 before cisplatin produced drug resistance, an effect attributed to the ability of IL-1 to induce antioxidant enzymes (45, 46). Preclinical and clinical studies have indicated that the immune response contributes to the efficacy of chemotherapy (47, 48). There is evidence that supports the possibility that a decrease in MDSC improves chemotherapy efficacy (49, 50). The mechanism of this improvement and whether MDSC and/or tumor-specific immune responses are enhanced will require further study.

We did observe decreases in splenic T-reg cells with both temozolomide and docetaxel, consistent with previous reports (34, 35). We also observed a decrease in intratumoral FoxP3 with temozolomide treatment. In contrast, the effects of the chemotherapeutics on myeloid suppressor cell populations differed systemically compared to intratumorally. In spleens, MDSC cells decreased; intratumorally, there was evidence MDSC and M2 macrophage polarization increased. rhIL-1Ra attenuated these effects. The ability of the chemotherapeutics to directly increase tumor production of cytokines, such as GM-CSF, which we demonstrated in vitro and in vivo, may have contributed to these observations. Assessing myeloid suppressor cell populations intratumorally by cell surface markers is complicated. MDSC become Gr1− within tumors (51), and M1- and M2-type markers are simultaneously expressed on identical macrophages within tumors (52). Intratumoral expression of CD206 and CD11c as assessed by qRT-PCR has been correlated with immune suppressor activity (22). The intratumoral immune effects of temozolomide and docetaxel also differed. Docetaxel and related taxanes display a variety of immunomodulatory effects, which in mice is attributed to their ability to mimic lipopolysaccharide. These include the ability to promote M1 polarization and macrophage cellular toxicity (reviewed in (53)). The increases observed in, for example, intratumoral IL-12(p40) production with docetaxel but not temozolomide may be a manifestation of this.

Altering tumor vascularity can improve the activity of chemotherapy, and when applied in the setting of microscopic B16 tumors, hrIL-1Ra has been shown to reduce vascularization (5). Using immunohistochemical methods we did not observe effects on tumor blood vessel density nor in tumor-infiltrating fibroblasts and pericytes when hrIL-1Ra was applied in the setting of established, macroscopic B16 tumor. Furthermore, we did not observe the decrease in tumor VEGF production previously reported with hrIL-1Ra in vitro and in vivo (6, 54). That VEGF is constitutively produced by B16 melanoma cells and was not directly inhibited by hrIL-1Ra may have played a role in this observation. Many solid tumors show an increased IFP that forms a barrier to transcapillary transport and results in inefficient uptake of therapeutic agents. Changes in tumor IFP can occur in the absence of changes in VEGF levels or the frequency of blood vessels supporting pericytes and fibroblasts. The 1 mg/day dose and schedule we used did not significantly lower IFP in this syngeneic model. Treatment of athymic mice bearing human thyroid carcinoma xenografts with 15 mg/day of hrIL-1Ra significantly reduced IFP (29).
The results of our studies underscore the complexity of cytokine action in tumor progression. IL-1 can modify the host response and may have a role with other agents in the treatment of melanoma; however, it is apparent this is also true of inhibition of IL-1 with hrIL-1Ra. That application of a cytokine and its inhibitor can both contribute antitumor activity is not without precedent. Whereas IL-2 is a potent activator of cytolytic lymphocytes, anti-IL-2 antibody can reduce T-reg cells, and the antitumor efficacy of IL-2 in vivo has been reported to be enhanced by an anti-IL-2 antibody (55). The results of our studies support the testing of hrIL-1Ra in patients with established melanoma tumors to modify myeloid suppressor cell populations. Several studies have suggested that macrophages may be critical for progression toward an aggressive phenotype and a poor prognosis (56). MDSC equivalents have also been described in patients with melanoma (57). Furthermore, elevated levels of IL-1 can be observed in patients with melanoma, which may help identify potentially responsive patients (58).

References

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