Spontaneous Melanoma Model Cells and Chronic Inflammation in the Inhibition of Myeloid-Derived Suppressor Antitumor Effect of Paclitaxel Is Mediated by V. Shurin, Michael R. Shurin and Viktor Umansky

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Antitumor Effect of Paclitaxel Is Mediated by Inhibition of Myeloid-Derived Suppressor Cells and Chronic Inflammation in the Spontaneous Melanoma Model

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The antitumor effects of paclitaxel are generally attributed to the suppression of microtubule dynamics resulting in defects in cell division. New data demonstrated that in ultralow noncytotoxic concentrations, paclitaxel modulated in immune cells in vitro the activity of small Rho GTPases, the key regulators of intracellular actin dynamics. However, the immunomodulatory properties of paclitaxel in vivo have not been evaluated. In this study, using the ret transgenic murine melanoma model, which mimics human cutaneous melanoma, we tested effects of ultralow noncytotoxic dose paclitaxel on functions of myeloid-derived suppressor cells (MDSCs), chronic inflammatory mediators, and T cell activities in the tumor microenvironment in vivo. Administration of paclitaxel significantly decreased accumulation and immunosuppressive activities of tumor-infiltrating MDSCs without alterations of the bone marrow hematopoiesis. This was associated with the inhibition of p38 MAPK activity, TNF-α and production, and S100A9 expression in MDSCs. The production of mediators of chronic inflammation in the tumor milieu also was diminished. Importantly, reduced tumor burden and increased animal survival upon paclitaxel application was mediated by the restoration of CD8 T cell effector functions. We suggest that the ability of paclitaxel in a noncytotoxic dose to block the immunosuppressive potential of MDSCs in vivo represents a new therapeutic strategy to downregulate immunosuppression and chronic inflammation in the tumor microenvironment for enhancing the efficacy of concomitant anticancer therapies. The Journal of Immunology, 2013, 190: 000–000.

Conventional chemotherapy based on maximum-tolerated doses represents one of the major cancer treatments despite its severe toxicity, development of drug resistance, and strong immunosuppression. However, a growing body of evidence indicates that lowering the dose of antitumor cytotoxic agents and combining chemotherapy with other modalities may not only decrease the toxicity of chemotherapy but also upregulate the efficacy of different anticancer therapies by altering differentiation and activation of immune regulatory and effector cells (1).

Although the signaling pathways targeted by chemotherapeutic agents at low doses in immune cells are still unknown, new data suggest that the immunomodulating activity of these agents in noncytotoxic, noncytostatic concentrations is mediated by drug-specific activation of signal transduction pathways. For instance, paclitaxel can modulate the activity of small Rho GTPase family members that regulate the assembly and organization of actin-based structures in cells (1, 2).

Furthermore, certain drugs (e.g., paclitaxel or 5-fluorouracil) at ultralow noncytotoxic doses were reported to display the immunomodulating effects including the stimulation of maturation and functions of human and murine dendritic cells (DCs) in vitro (3, 4) and augmentation of the antitumor efficiency of DC vaccination in the transplantable mouse model of lung cancer (5). It has been recently demonstrated that low-dose paclitaxel blocked tumor-induced polarization of conventional DCs into immunosuppressive regulatory DCs (6), which was prevented by a small Rho GTPase inhibitor (H. Zhong, D.W. Gutkin, B. Han, Y. Ma, M.R. Shurin, and G.V. Shurin, submitted for publication).

However, it is still unknown whether paclitaxel can modulate homing and function of myeloid-derived suppressor cells (MDSCs), a key cell subset responsible for maintaining the immunosuppressive and tolerogenic tumor microenvironment in many cancers (7–9). This heterogeneous population of immature myeloid cells was reported to inhibit the antitumor immune cell responses via different mechanisms and markedly restrict the efficiency of antitumor immunotherapies (10–12). Malignant melanoma is characterized by a strong immunosuppression driven by chronic inflammation that induces the MDSC recruitment and activation (13–17). However, no clinically feasible strategies are developed...
so far to downregulate the emergence and function of MDSCs in the melanoma microenvironment.

In this study, we have tested how paclitaxel changes MDSC accumulation and activity in the ret transgenic mouse model of spontaneous melanoma that closely resembles human melanoma regarding histopathology and clinical development (18, 19). We also determine the signaling pathways in MDSCs that are involved in their inhibition and verified the involvement of chronic inflammation in the antitumor action of paclitaxel. Our results revealed that paclitaxel at a nontoxic dose reduced the number of tumor-infiltrating MDSCs and abrogated NO production by MDSCs in the metastatic lymph nodes (LNs) and bone marrow (BM) of melanoma-bearing mice without affecting hematopoietic stem cells. Tumor-derived MDSCs from paclitaxel-treated animals showed lower immunosuppressive activity associated with decreased expression of p38 MAPK and S100A9. The production of chronic inflammatory mediators such as TGF-β, GM-CSF, IL-1β, IL-10, TNF-α, and IFN-γ was reduced in primary tumors. The antitumor effect of paclitaxel was associated with the restoration of CD8 T cell activity and significantly increased survival of tumor-bearing mice. These results suggest that the reversal of immunosuppression in the tumor microenvironment induced by ultralow nontoxic doses of paclitaxel represents an efficient therapeutic approach and can be combined with immunotherapies for increasing their antitumor efficiency.

Materials and Methods

Mice

C57BL/6 mice expressing human ret transgene in melanocytes under the control of mouse metallothionein-I promoter–enhancer (18) were provided by Dr. I. Nakashima (Chubu University, Aichi, Japan). Animals were crossed and kept under specific pathogen-free conditions in the animal facility of German Cancer Research Center (Heidelberg, Germany). Experiments were performed in accordance with government and institutional guidelines and regulations.

Reagents and Abs

Paclitaxel was purchased from Hexal. Rat anti-mouse directly conjugated mAbs (CD3-PerCP-Cy5.5, CD4-FITC, CD8-PE, CD11b-PE, CD25-PE, and anti-CD28 mAbs (0.5 μg/ml each) and cocultured with MDSCs in triplicates (at the splenocytes:MDSC ratio 1:1) for 96 h. T cell proliferation was determined using FACS Canto II with FACS Diva software (both from BD Biosciences) with dead cell exclusion based on scatter profile or propidium iodide inclusion. FlowJo software (Tree Star) was used to analyze at least 100,000 events. Data were expressed as dot plots.

Bio-Plex assay

Snap frozen primary tumor samples were mechanically disrupted and treated with lysis solution (Bio-Rad). After sonication, samples were centrifuged at 4,500 × g for 10 min at 4°C. Protein concentration in lysates was determined using Pierce bicinecinonic acid protein assay kit (Thermo Scientific) and adjusted to 1000 μg/ml using serum diluent (Bio-Rad). Concentrations of inflammatory factors in tissue lysates were measured by multiplex technology (Bio-Rad).

In vitro proliferation assay

MDSCs were shown to be important regulators of chronic inflammation, tumorigenesis, and tumor progression (7, 10). Therefore, we tested the hypothesis that nontoxic ultralow dose of paclitaxel (1 mg/kg, weekly × 3) affected MDSCs in primary skin tumors and lymphoid organs (Fig. 1A, 1B; Supplemental Fig. 1A). Administration of Taxol caused a significant reduction (1.9-fold; p < 0.01) in frequencies of tumor-infiltrating MDSCs as compared with the PBS-treated group (Fig. 1B). MDSC frequency in the metastatic LN, spleen, and BM remained unchanged (Supplemental Fig. 1A). In contrast to MDSCs, the frequency of tumor-infiltrating DCs and macrophages was not significantly altered upon the paclitaxel treatment (Supplemental Fig. 1B).

The production of NO and elevated ARG-1 activity are the key factors of immunosuppression mediated by MDSCs (8, 10). To test, whether these pathways are involved in the effect of paclitaxel on MDSCs, we used an intracellular NO staining with
**FIGURE 1.** Paclitaxel downregulates the number and function of tumor-infiltrating MDSCs in vivo. Tumor-bearing *ret* transgenic mice were treated with ultralow-dose paclitaxel (1 mg/kg). CD11b+ Gr1+ MDSCs were assessed by flow cytometry. (A) A representative dot plot of primary tumor is shown. (B) Cumulative data from six independent experiments assessing MDSCs in primary tumors expressed as the percentage within live leukocytes (mean ± SD; 28 mice/group). (C and D) MDSCs were isolated from tumors followed by the coculture with normal splenocytes labeled with CPD eFluor 670 and stimulated with anti-CD3 and anti-CD28 mAbs. (C) A representative histogram from one experiment out of three with similar results. (D) Data (mean ± SD; nine mice per group) for the inhibition of T cell proliferation by MDSCs are presented as the percentage of divided T cells. Splenocytes (spl):MDSC ratio was 1:1. *p < 0.05, **p < 0.01.

diaminofluorescein-2 diacetate and found a significant reduction of NO-producing Gr1+CD11b+ MDSCs in metastatic LN from paclitaxel-treated melanoma-bearing mice as compared with PBS-treated control group (p < 0.05); however, the influence of paclitaxel on these cells in the BM was less pronounced (Supplemental Fig. 2). Levels of NO-producing MDSCs in primary skin tumors and the spleen of treated animals were not significantly different from those in PBS-treated mice (data not shown). In addition, we did not see significant inhibition of ARG-1 expression in MDSCs after paclitaxel administration (data not shown), suggesting that the effect of paclitaxel on MDSCs in vivo was tissue and signaling specific.

Next, to determine the immunosuppressive potential of MDSCs, we verified a direct impact of tumor-infiltrating MDSCs from melanoma-bearing mice on T cell proliferative activity. MDSCs isolated from primary tumors were cocultured with splenocytes from untreated syngeneic mice stimulated by anti-CD3 and anti-CD28 mAbs. Our results demonstrated a significant reduction (up to 1.4-fold; p < 0.05) in the capacity of tumor-infiltrating MDSCs from paclitaxel-treated mice to suppress T cell proliferation as compared with MDSCs from PBS-treated group (Fig. 1C, 1D). This suggests that paclitaxel inhibited the immunosuppressive activity of MDSCs in vivo.

In addition, analyzing how paclitaxel affected the BM hematopoiesis, we found no alterations in the levels of Lin"Sca-1"c-Kit" (LSK) and Lin"Sca-1"c-Kit" (LK) cells or in their proliferative capacity measured by the expression of Ki67 (Fig. 2), suggesting a selective effect of paclitaxel administration on MDSCs.

Paclitaxel modulates p38 MAPK, S100A8/A9, and STAT-3 signaling pathways in MDSCs

Signaling pathways involving p38 MAPK, S100A8/A9, and STAT-3 play an important role in the myeloid cell activation in chronic inflammatory tumor microenvironment (8). To determine which signaling pathways in MDSCs are affected by paclitaxel in vivo, we assessed the activity of p38 MAPK by measuring phosphorylation of threonine 180 and tyrosine 705 (pT180/pY182). The results revealed a significant downregulation of p38 activation (up to 1.5-fold; p < 0.05) in tumor-infiltrating MDSCs upon the paclitaxel treatment (Fig. 3A). Moreover, p38 phosphorylation was significantly reduced (p < 0.05) in MDSCs from the BM and spleen in paclitaxel-treated tumor-bearing mice (Fig. 3B). In contrast, no differences in the level of MDSCs expressing activated p38 MAPK were demonstrated in the metastatic LN (data not shown). Because p38 MAPK can regulate the TNF-α production (20), we measured its intracellular expression in tumor-infiltrating MDSCs. As expected, primary skin tumors contained a significantly less amount of MDSCs producing TNF-α upon the paclitaxel treatment as compared with control group (p < 0.05; Fig. 3C). Because p38 MAPK is also known to be activated by secreted S100A8/A9 complex (21, 22), we evaluated the intracellular expression of S100A9 and detected a strong reduction in the number of tumor-infiltrating MDSCs expressing S100A9 upon the treatment with paclitaxel as compared with untreated animals (26 ± 5 versus 14 ± 3% cells, respectively; p < 0.05; Fig. 3D). In contrast, the amount of S100A9-positive MDSCs in the metastatic LNs was not significantly altered (data not shown).

Because the STAT3 pathway is responsible for the regulation of MDSC-mediated immunosuppression (8, 10), we next analyzed the phosphorylation of tyrosine 705 in the STAT3 molecule (pY705). In the metastatic LN, a significant reduction (up to 2.3-fold; p < 0.05) of p-STAT3–positive MDSCs was detected upon the ultralow-dose paclitaxel treatment (Supplemental Fig. 3). However, STAT3 phosphorylation in tumor-infiltrating MDSCs was not profoundly altered, suggesting a tissue-specific effect of paclitaxel on MDSC signaling pathways in vivo (data not shown).

**Paclitaxel diminishes chronic inflammation and inhibits tumor development**

Recent reports by us and others have demonstrated that numerous chronic inflammatory mediators can attract and activate MDSCs in the tumor microenvironment (8, 10, 13, 23). In addition, we...
demonstrated in this study a positive correlation between intra-tumoral concentrations of TNF-α and tumor progression (Fig. 4). Because these inflammatory factors could be produced by myeloid cells upon the activation of p38 MAPK signaling (20–22, 24–26), we defined whether their levels were influenced by the ultralow-dose paclitaxel treatment in vivo. The results revealed a remarkable decrease in the levels of TGF-β, GM-CSF, IL-1β, IL-10, IL-5, IL-13, TNF-α, and IFN-γ in the primary skin tumor microenvironment (Fig. 5A). For instance, the concentration of IL-1β was 4.2 times lower upon paclitaxel administration (p < 0.001). These data are also in agreement with the abovementioned downregulation of TNF-α production by MDSCs infiltrating skin tumors (Fig. 2C). Moreover, the reduction of chronic inflammation was associated with a significantly decreased tumor burden estimated at day 21 after the beginning of the paclitaxel administration as compared with untreated group (from 593 ± 60 to 453 ± 57 mg of tumor weight, respectively; p < 0.05; Fig. 5B). In addition, we revealed a profound prolongation of the survival of treated tumor-bearing mice (p < 0.05; Fig. 5C). Importantly, using the proliferation marker Ki-67 and the TUNEL assay, we observed no direct cytostatic or cytotoxic effects of paclitaxel on tumor cells at day 2 after its administration in ultralow dose (Supplemental Fig.

**FIGURE 2.** Administration of ultralow-dose paclitaxel is not toxic for BM hematopoietic cells. C57BL/6 mice were treated with ultralow doses of paclitaxel as described in Materials and Methods. Hematopoietic early progenitor cells LSK and LK were analyzed by flow cytometry. (A) Results are presented as the percentage of LSK or LK cells among Lin− cells (eight mice per group). (B) Proliferation of hematopoietic cells is shown as the percentage of Ki67+ cells within a respective cell subset (mean ± SD; eight mice per group). Data of two independent experiments are depicted.

**FIGURE 3.** Paclitaxel modulates p38 MAPK and S100A9 signaling in tumor-associated MDSCs in vivo. Tumor-bearing mice were treated with ultralow doses of paclitaxel. Expression of p-p38 MAPK, S100A9, and TNF-α were detected in CD11b+Gr1+ MDSCs from skin tumors and lymphoid organs by flow cytometry. Data of three independent experiments are presented as the percentage of p-p38 MAPK expressing cells within total MDSCs in the tumor (A) and lymphatic organs (B) (mean ± SD; 13–17 mice/group). TNF-α–producing (C) and S100A9–expressing (D) tumor-infiltrating MDSCs were shown as the percentage of respective cells among total MDSCs (mean ± SD; 14 mice/group). *p < 0.05.
4). In contrast, paclitaxel at conventional dose (15 mg/kg) induced both effects on melanoma cells under the same conditions. These results suggest that paclitaxel in ultralow dose (in contrast to conventional therapeutic dose) is not able to directly suppress tumor cell proliferation or induce their apoptosis in vivo but affects immune regulators in the tumor milieu.

**Restoration of the antitumor activity of CD8+ T cells upon the treatment with paclitaxel**

Because the development of the antitumor immune response is associated with the accumulation and activation of tumor-infiltrating CD8+ T cells (TILs) in the tumor milieu (27) and MDSCs are known to suppress TILs activity (8), we next tested whether reduced chronic inflammation as well as MDSC amounts and suppressive functions could increase TIL frequencies and restore their functions in vivo. We detected a significant accumulation of CD8+ TILs in skin melanoma lesions from paclitaxel-treated mice as compared with the control group (16 6 3 versus 10 6 1% among total TILs, respectively; p, 0.05; Fig. 6A).

Because TCR C-chain expression is important for T cell functions (23), we estimated the ability of CD8+ TILs to accomplish their functions in situ by assessing C-chain levels in these cells. The results revealed a significant elevation of its expression in CD8+ TILs from paclitaxel-treated mice as compared with TILs from untreated animals (p < 0.05; Fig. 6B).

To determine the effect of paclitaxel on tumor-specific CD8+ TILs, we next measured the amount of CD8+ T cells specific for the melanoma-associated Ag tyrosinase-related protein-2 (TRP-2) that infiltrated melanoma lesions. Under the treatment conditions, we demonstrated a significant increase in the frequency of TRP-2–specific CD8+ T cells in the metastatic LN of paclitaxel-treated mice as compared with untreated animals (1.02 ± 0.17 versus 0.48 ± 0.14% among total CD8+ T cells; p < 0.05; Fig. 6C). In addition, we detected a strong tendency to the increase in the frequency of TRP-2–specific CD8+ TILs within total CD8+ TILs, despite a high variability in individual animals (p = 0.0765; Fig. 6C). These findings suggest that paclitaxel was able to increase not only the frequency of total CD8+ TILs but also that of TRP-2–specific CD8+ T cell subset in the tumor milieu in vivo.

**To directly prove the role of effector T cells in the antitumor activity mediated by the paclitaxel administration, we depleted CD8+ T cells during paclitaxel treatment (Fig. 6D, 6E). The depletion efficiency was checked at day 10 in the spleen, peripheral blood, and LN, showing >95% decrease in CD8+ T cell numbers. The results showed that the removal of CD8+ T cells in paclitaxel-treated mice resulted in the complete abrogation of the beneficial anti-melanoma effect of ultralow-dose paclitaxel documented by the absence of differences in survival with the control group of tumor-bearing mice (Fig. 6E).**

Taken together, paclitaxel applied at ultralow, nontoxic doses demonstrated a remarkable antitumor effect in vivo, indicated by a prolonged survival of melanoma-bearing mice and a reduced tumor burden. This effect was shown to be linked to the elevated...
CD8+ TIL numbers and activity in melanoma lesions associated with the downregulation of chronic inflammation, leading to diminished amounts and immunosuppressive functions of MDSCs in the tumor microenvironment.

Discussion

We have recently reported a novel immunomodulatory approach based on the application of various chemotherapeutic drugs (including paclitaxel) at ultralow noncytotoxic doses called chemoinmunomodulation (1, 2). In particular, the administration of ultralow-dose paclitaxel has been shown to enhance the maturation and immunostimulatory functions of mouse DCs in vitro and in the transplantable tumor model in vivo (1, 2, 5). In the current study, we highlight the complex effect of paclitaxel on the major myeloid cell subset with immunosuppressive functions, MDSCs, as well as on chronic inflammation in the tumor microenvironment in vivo.

MDSCs have been previously demonstrated by us and others to be recruited to the tumor site and activated both in cancer patients and tumor-bearing mice (8, 10–13, 16, 17). Moreover, it has been reported that a constant activation of inflammatory pathways in myeloid cells led to a systemic enrichment of MDSCs, development of chronic inflammation, and tumorigenesis (7). Using ret transgenic mice spontaneously developing skin melanoma with metastases in the LN, liver, lungs, and BM, we detected in this study a significant reduction of MDSC frequencies in melanoma lesions upon the paclitaxel treatment. Interestingly, a similar decrease of CD11b+Gr1+ immature myeloid cells in spleens and LNs was earlier observed in tumor-free C57BL/6 mice treated with the same nontoxic doses of paclitaxel (28). Furthermore, although MDSC numbers were not altered in the metastatic LN and BM of treated tumor-bearing mice, we revealed a reduction in frequencies of MDSCs producing NO that is involved in MDSC-mediated immunosuppression in these organs (10). Importantly, tumor-infiltrating MDSCs also displayed a significantly lower ability to suppress the proliferation of stimulated normal T cells, indicating their decreased immunosuppressive function after paclitaxel administration. The mechanisms of observed differences in the paclitaxel-mediated effects on MDSCs in skin tumors and metastatic LNs are currently under investigation.

Next, we addressed a question about signaling pathways in MDSCs affected by the paclitaxel-based chemoinmunomodulation. We demonstrated that the phosphorylation of p38 MAPK in MDSCs was strongly associated with reduction of TNF-α, IL-1β, IL-10, TGF-β, and IL-6 (24–26, 30, 31). Indeed, we have found in this study that a downregulation of the p38 MAPK signaling in MDSCs was strongly associated with reduction of TNF-α production by these cells and decreased levels of the above-mentioned factors in the chronic inflammatory tumor microenvironment. Furthermore, an autocrine regulation of p38 MAPK activation is possible because TNF-α and IL-1β were reported to activate p38 MAPK signaling (32, 33), stimulating thereby a production of IL-6 (34), an activation of inducible NO synthase (34, 35), and the accumulation of MDSCs (36). In agreement with these publications, our findings demonstrated that paclitaxel-mediated abrogation of p38 MAPK activation...
in MDSCs resulted in the decrease in their numbers in tumors as well as in their capacity to produce NO and suppress T cell functions. Decreased amounts of tumor-infiltrating MDSCs also could be due to an enhanced MDSC differentiation. Indeed, our recent in vitro studies demonstrated that paclitaxel in ultralow concentrations can promote the MDSC differentiation into functional conventional DCs (37). Because p38 MAPK is also involved in signaling pathways activated by secreted S100A8/A9 in autocrine manner (21, 22, 38), we evaluated the intracellular expression of S100A9 in MDSCs. A significant reduction in the number of tumor-infiltrating MDSCs expressing S100A9 was found after administration of paclitaxel, additionally highlighting the importance of the stimulation of p38 MAPK-S100A8/A9 pathways in MDSC-mediated immunosuppression.

Taking into account a critical role of MDSCs and chronic inflammatory mediators in supporting tumor progression, we also assessed the antitumor potential of nontoxic application of paclitaxel and revealed a significant delay in tumor development indicated by a prolonged survival of treated animals. Investigating the mechanism of this effect, we found an increased numbers of CD8+ TILs and TCR 3-chain expression in these cells upon the treatment. Importantly, in the metastatic LN, frequencies of TRP-2–specific CD8+ T cells were also significantly higher, although the total numbers of CD8+ T cells were not changed. Along this line, we have previously reported that administration of ultralow-dose paclitaxel in healthy C57BL/6 mice strongly increased the frequencies of TRP-2–specific spleen T cells upon the peptide vaccination (28). These results are in agreement with data reported by us and others that the reduction of MDSC numbers and/or immunosuppressive functions resulted in the restoration of effector functions of tumor-specific CD8+ T cells (13, 39). A selective depletion of CD8+ T cells led to the complete abrogation of the beneficial antitumor activity of paclitaxel, underlying a critical role of CD8+ T cells in this effect. In addition, a lack of direct toxic effect of paclitaxel in ultralow dose (in contrast to conventional doses) on melanoma cells in vivo further emphasizes its immunomodulating potential.

In conclusion, we demonstrated in this study that administration of ultralow nontoxic dose of paclitaxel caused a significant reduction of tumor-associated immunosuppression because of the decrease in MDSC numbers and functions in the tumor lesions. These effects were strongly related to the downregulation of p38 MAPK signaling in MDSCs associated with a decreased production of chronic inflammatory mediators in the tumor microenvironment. Abrogation of MDSC-driven immunosuppression strongly affected melanoma progression indicated by the prolonged survival of tumor-bearing animals through the CD8+ T cell–dependent mechanism. Taken together with our previous data on the stimulation of antitumor activities of DCs and modulation of intratumoral cytokine network (3–5), our findings in this study demonstrated that the paclitaxel-based chemoimmunomodulation could efficiently condition the tumor microenvironment, decreasing its immunosuppressive potential. This suggests that administration of paclitaxel in nontoxic doses can be considered as a novel therapeutic approach for decreasing the protumorigenic potential of the tumor microenvironment and increasing the efficacy of associated anti-cancer therapies.

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Disclosures
The authors have no financial conflicts of interest.

References


