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Targeting myeloid-derived suppressor cells by inhibiting hypoxia-inducible factor 1α could improve tumor progression

Qiying Xu, MD[a,b,c], Huifang Liu, MD[a,b,c], Xiaoyan Song, MD[a,b], Tana Wuren, PhD[a,b,*], Ri-li Ge, PhD[a,b,*]

Abstract

Myeloid-derived suppressor cells (MDSCs) are a subset of immature myeloid cells that inhibit anti-tumor immunity and contribute to poor cancer outcomes. In this study, the authors used multi-color flow cytometry to detect changes in MDSCs in patients with cancer and tumor-bearing mice. Then the authors studied changes in MDSCs ratio and mouse tumors after administration of hypoxia-inducible factor 1α (HIF-1α) inhibitor. The results showed that the ratio of MDSCs, specifically polymorphonuclear MDSCs (PMN-MDSCs), was higher in patients with cancer, and both PMN-MDSCs and monocytic MDSCs (M-MDSCs) ratio were higher in tumor-bearing mice. When provided with the HIF-1α inhibitor LW-6, the ratio of MDSCs decreased in tumor-bearing mice, particularly PMN-MDSCs, and the volume of liver metastases also decreased. The authors' findings suggest that reducing MDSCs by inhibiting hypoxia-inducible factor 1α may slow tumor progression.

Keywords: cancer outcomes, hypoxia-inducible factor 1 α, LW-6, myeloid-derived suppressor cells, tumor microenvironment

Introduction

Myeloid-derived suppressor cells (MDSCs) were identified as a subset of myeloid cells with immunosuppressive ability[1]. MDSCs consist of two large groups of cells, termed granulocytic or polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs), in both humans and mice, based on their phenotype and morphology. In humans, a distinct subgroup named "early-stage MDSC" (e-MDSC) is known. Elevated levels of MDSCs have been detected in many types of cancer[2–5], and they play a crucial role in anti-tumor immune inhibition, angiogenesis, and tumor metastasis. Moreover, high levels of circulating MDSCs are associated with advanced tumor stage and poor clinical outcomes[6,7]. Targeting MDSCs can reverse the poor clinical outcomes in patients with advanced cancer.

HIGHLIGHTS

- Myeloid-derived suppressor cells (MDSCs) increased in both patients with cancer and a murine tumor model, especially polymorphonuclear MDSCs (PMN-MDSCs).
- Hypoxia-inducible factor 1α (HIF-1α) inhibition attenuated MDSCs accumulation and impeded tumor metastasis in mice.
- Combining chemotherapy with MDSCs targeting would have better clinical outcomes.

Hypoxia is a crucial factor in the complex accumulation of MDSCs in tumors. Hypoxia via hypoxia-inducible factor 1α (HIF-1α) dramatically alters the function of MDSCs in the tumor microenvironment (TME) and redirects their differentiation toward tumor-associated macrophages[8,9]. Myeloid HIF-KO in mice leads to abrogated MDSC accumulation in the uterus and impaired suppressive activity of MDSCs, which are important for pregnancy[9].

Thus, in this study, we aimed to investigate the MDSC ratio in patients with cancer and tumor-bearing mice and evaluated the changes in the MDSC ratio and tumor progression after inhibiting HIF-1α in mice.

Materials and methods

Patients and clinical samples

Permission to proceed with data acquisition and analysis was obtained from the Affiliated Hospital of ** (approval number:

[a]Research Center for High Altitude Medicine, [b]Key Laboratory for Application of High-Altitude Medicine, Qinghai University and [c]Department of Gynecology, Affiliated Hospital of Qinghai University, Xining, China

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*Corresponding authors. Address: NO.16 Kunlun Road, Xining, Qinghai, 810001, China, 29 Tongren Road, Xining, Qinghai, China. Tel.: +152 9702 2118. E-mail: tana.wuren@qhu.edu.cn (T. Wuren), and Tel.: +139 970 164 41. E-mail: geriligao@hotmail.com (R-l. Ge).

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SL-2020091). Appropriate written informed consent was obtained from each patient, and their clinical data and blood samples were analyzed. Seventy patients with gastric, lung, liver, pancreatic, ovarian, and cervical cancer were analyzed. This study included 53 newly diagnosed patients and 17 patients treated with chemotherapy. The 53 newly diagnosed patients were all patients with advanced cancer including 10 lung cancer patients, 19 stomach cancer patients, 6 liver cancer patients, 6 rectal cancer patients, 3 pancreatic cancer patients, 5 esophageal cancer patients, 2 ovarian cancer patients, 1 nasopharyngeal carcinoma patient, 1 diffuse large B-lymphoma patient. Five patients were sampled after the first visit and after one cycle of chemotherapy, and two patients were sampled after the initial visit and after two cycles of chemotherapy. Therefore, 79 data points were collected.

Flow cytometry analysis of human blood samples

MDSC-like cells were collected from peripheral blood samples of the participants using ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes. The samples were centrifuged for 20 min at 410*g* before the red blood cells were removed using RBC lysis buffer (BioLegend, 420301, B337300). The remaining white blood cells were washed twice in phosphate-buffered saline (PBS) and diluted to a concentration of $1–5 \times 10^6$ cells/ml before evaluation using a BV510-Zombie Aqua Fixable Viability Kit (BioLegend, 77143, B324734), which facilitates live/dead staining, according to the manufacturer's instructions. We performed a five-color analysis to confirm MDSC identity, including staining for FITC-CD11b (BioLegend, 301330, B272326), BV421-CD33 (BioLegend, 366622, B310764), Percp/cy5.5-HLA-DR (BioLegend, 307630, B293514), PE-CD14 (BioLegend, 367104, B274117), and APC-CD15 (BioLegend, 301908, B270323). Flow cytometry was performed using Aria III (BD Biosciences, NJ, USA), and the data were analyzed using FlowJo software. The Aria III was used for MDSC-like cell sorting, which relied on $CD11b^+HLA\text{-}DR^{low/-}CD33^+$ identification. The studied cells were referred to as MDSC-like cells as they were measured using flow cytometry in whole blood instead of peripheral blood mononuclear cells, and because of the absence of sufficient functional assays, the surface markers of each subset used were as follows:

Total MDSC-like cells: $CD11b^+CD33^+HLA\text{-}DR^-$

PMN-MDSC-like cells: $CD11b^+CD33^+HLA\text{-}DR^-CD14^-CD15^+$

M-MDSC-like cells: $CD11b^+CD33^+HLA\text{-}DR^-CD14^+CD15^-$

e-MDSC-like cells: $CD11b^+CD33^+HLA\text{-}DR^-CD14^-CD15^-$

Animals and experimental models

Eight-week-old C57BL/6 male mice were provided by Beijing Huafukang Bio-technology Co., Ltd. (Production License: SCKK; Beijing, China; 2020-0004, Quality Certificate: 11032200101810883). All the animals were raised in a barrier environment in an animal room at the Research Center for High-Altitude Medicine of ** (Laboratory Animal Use Permit License: SYXK (QING) 2020-0001). Five animals were housed in plastic cages with sawdust bedding and maintained on a 12 h light/dark cycle at room temperature (20–26°C). B-16 cells were cultured in RPMI media containing 10% fetal bovine serum (Gibco, USA, 10099-141C, 2254375CP) and 1% penicillin-streptomycin at 37°C in 5% CO_2. For the metastasis assays, the cells were harvested during log phase growth, and subsequently, 10^6 cells were suspended in 100 µl sterile PBS for tail vein injection of mice to build a tumor model. For HIF-1α inhibition experiments, LW-6 (MCE, USA, HY-13671/CS-6439, 66990) was administered via intra-gastric administration (10 mg/kg). To study the changes of MDSCs in tumor-bearing mice, there were 4 mice in control group and 5 mice in both tumor-14 days and tumor-21 days group. To study the effect on inhibiting HIF-1αin tumor-bearing mice, there were 3 mice in control group and 8 mice in both tumor group and tumor + LW-6 group. The work has been reported in line with the ARRIVE criteria[10], Supplemental Digital Content 1, http://links.lww.com/MS9/A478.

Flow cytometry analysis of mice samples

Splenocytes were washed twice in PBS and diluted to a concentration of $1–5 \times 10^7$ cells/ml before evaluation using a BV510-Zombie Aqua Fixable Viability Kit (Bio-Legend, 423102, B327055), which facilitates live/dead staining, according to the manufacturer's instructions. Five-color analyses were conducted to confirm the identity of MDSCs, including staining for PerCP/Cy5.5-CD45 (BioLegend, 103132, B319286), FITC-CD11b (BioLegend, 101206, B333716), PE/Cy7-Ly-6G (BioLegend, 127618, B329031), PE-Ly-6C (BioLegend, 128008, B313796), and APC-F4/80 (BioLegend, 123116, B321485). Flow cytometry was performed using Aria III (BD Biosciences), and the data were analyzed using FlowJo software 6.0. The surface markers of each subset were as follows:

M-MDSCs: $CD45^+CD11b^+Ly\text{-}6G^-Ly\text{-}6C^+$

PMN-MDSCs: $CD45^+CD11b^+Ly\text{-}6G^+Ly\text{-}6C^-$

Macrophages: $CD45^+CD11b^+F4/80^+$

Tissue sampling

Tissue sampling was performed after the treatment. The mice were anesthetized with either sevoflurane or isoflurane using an animal gas anesthesia machine (RWD Life Science, China, R583S). Splenocytes were obtained using grinding and transferred to collection tubes containing EDTA at a maximum volume of 1 ml. Lung cells were collected by digestion with collagenase I (C0130-100MG, SLCH0219; Sigma-Aldrich). Red blood cells were extracted from the tissues using red blood cell lysis buffer (Bio-Legend, 420301, B337300) and analyzed using flow cytometry to observe metastatic nodules in the liver tissue.

Statistical analysis

GraphPad Prism version 9.0 was used for all statistical analyses. Data are presented as mean ± SED and were analyzed using independent sample *t*-tests, paired *t*-tests, and one-way analysis of variance (ANOVA) tests. A P value of less than 0.05 was considered significant.

Results

MDSC-like cells percentage in peripheral blood increased in patients with cancer

To study the three subsets of MDSCs in the peripheral blood of patients with cancer, we conducted six-color flow cytometry of whole blood from patients ($n = 70$) and healthy donors ($n = 24$) using all the previously mentioned markers. Figure 1A

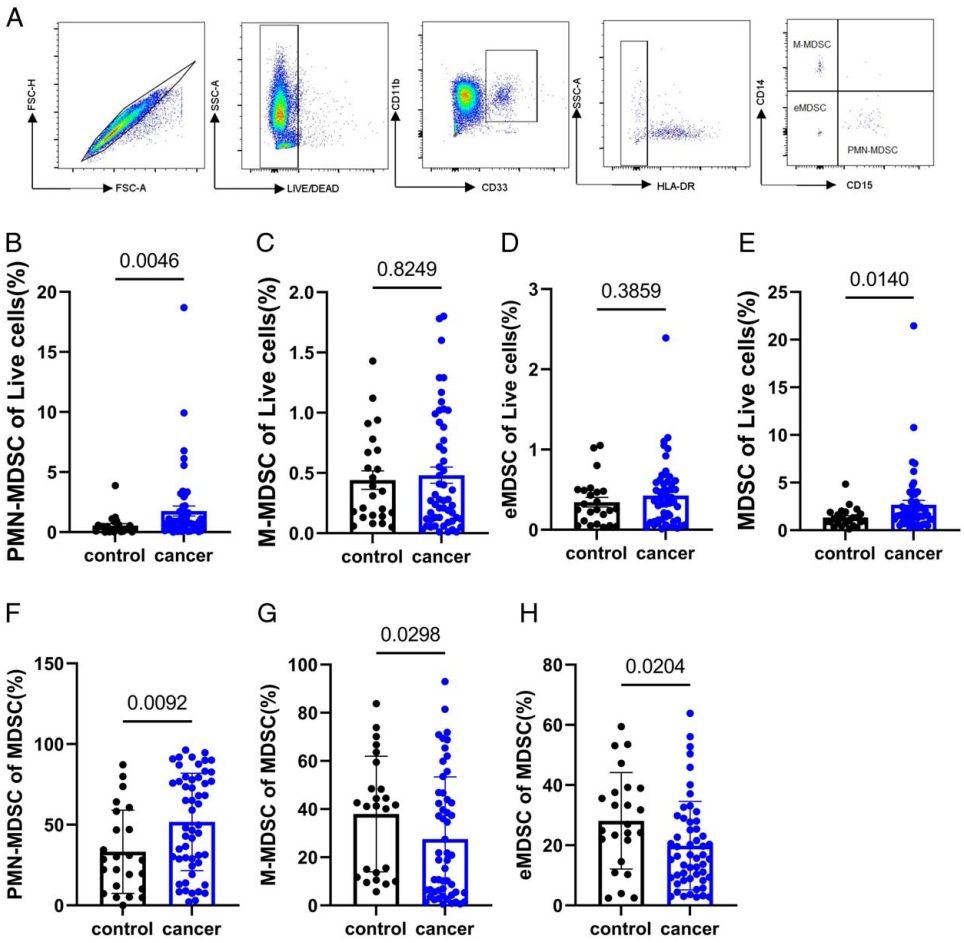

Figure 1. The change of MDSC-like, granulocytic-MDSC-like (PMN-MDSC-like), monocytic-MDSC-like (M-MDSC-like), and early-stage-MDSC-like (e-MDSC-like) cells. (A) The gating strategy for MDSC-like, PMN-MDSC-like, M-MDSC-like, and e-MDSC-like cells. The percentage of (B) PMN-MDSC-like, (C) M-like, (D) MDSC-like, and (E) e-MDSC-like cells within the live cell totals. The percentage of (F) PMN-MDSC-like, (G) M-like, and (H) e-MDSC-like cells within the total MDSC-like cells. Significance as determined using independent sample *t*-tests ($P < 0.05$). MDSC-like, myeloid-derived suppressor-like.

shows representative dot plots for one of the patients included in the study to illustrate the gating strategy used. We observed a significant increase in the total number of MDSC-like cells as a percentage of live cells in patients with cancer (Fig. 1E). This increase was particularly marked in PMN-MDSC-like cells (Fig. 1B), whereas the percentages of live M-MDSC-like and e-MDSC-like cells did not change (Fig. 1C and D). In addition, the proportion of PMN-MDSC-like cells increased significantly, whereas those of M-MDSC-like and e-MDSC-like cells decreased significantly (Fig. 1F-H). However, this change was not observed between the sexes (Supplementary Figure 1A-D, Supplemental Digital Content 2, http://links.lww.com/MS9/A479). We collected peripheral blood from a subset of patients with cancer who had undergone one or two cycles of chemotherapy, and the results revealed no difference in the proportion of the three subsets of MDSCs between patients who were initially diagnosed and those who were treated (Supplementary Figure 1E-H, Supplemental Digital Content 2, http://links.lww.com/MS9/A479). Data obtained from the same patient at the first visit revealed no changes compared with the data obtained after one or two cycles of chemotherapy (Supplementary Figure 1I-L, Supplemental Digital Content 2, http://links.lww.com/MS9/A479).

MDSCs percentage increased in B-16 tumor-bearing mice

Mice were injected with B-16 cells to assess the effect of tumors on the ratio of MDSCs. The percentage of MDSCs in the mouse spleen and lungs was examined at 14 and 21 days (Fig. 2A). We found that the weight of the mice decreased significantly after tumor cell inoculation (Fig. 2B). We observed that the ratio of both PMN-MDSCs and M-MDSCs in the spleen increased after 21 days of tumor-bearing (Fig. 2C and D). No significant difference was observed after 14 days of tumor-bearing. An upward trend was found in the ratio of macrophages on day 21 (Fig. 2E). Among the $CD11b^+$ cells, the ratio of PMN-MDSCs increased after 21 days of tumor-bearing, while the change in M-MDSCs was not apparent; a slight downward trend of macrophages was observed (Fig. 2F-H). In the lung tissue, the increase in PMN-MDSCs and decrease in macrophages were more evident (Supplementary Figure 2, Supplemental Digital Content 3, http://links.lww.com/MS9/A480).

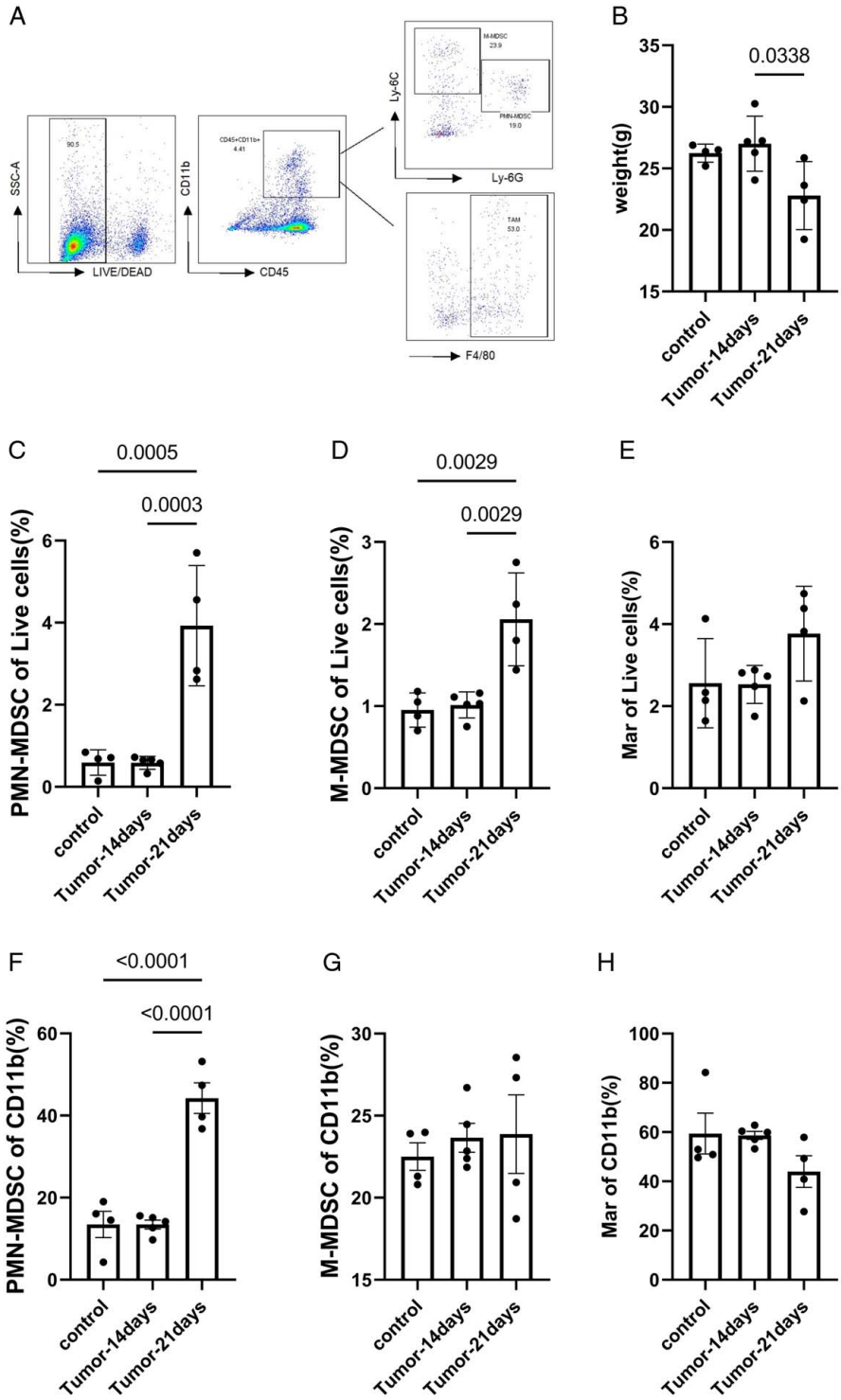

Figure 2. The change of PMN-MDSC, M-MDSC, and Mar after tumor cells were injected into the spleen. (A) The gating strategy for PMN-MDSC, M-MDSC, and Mar cells. (B) The changes in weight after tumor cell injection. The percentage of (C) PMN-MDSC, (D) M-MDSC, and (E) Mar cells within the live cells. The percentage of (F) PMN-MDSC, (G) M-MDSC, and (H) Mar cells within the total $CD45^+CD11b^+$ cells. Significance as determined using one-way ANOVA tests ($P < 0.05$). Mar, macrophage; M-MDSC, monocytic MDSC; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell.

Inhibition of HIF-1α reversed the increase in MDSCs and reduce tumor volume

Many studies have demonstrated the critical role of HIF-1α in MDSC differentiation, migration, and functional realization. In our other hypoxia-related studies, we found that administration of the HIF-1α inhibitor LW-6 can reverse the changes in the proportion of MDSCs due to hypoxia in mice (data was not published). Therefore, we hypothesized whether inhibition of

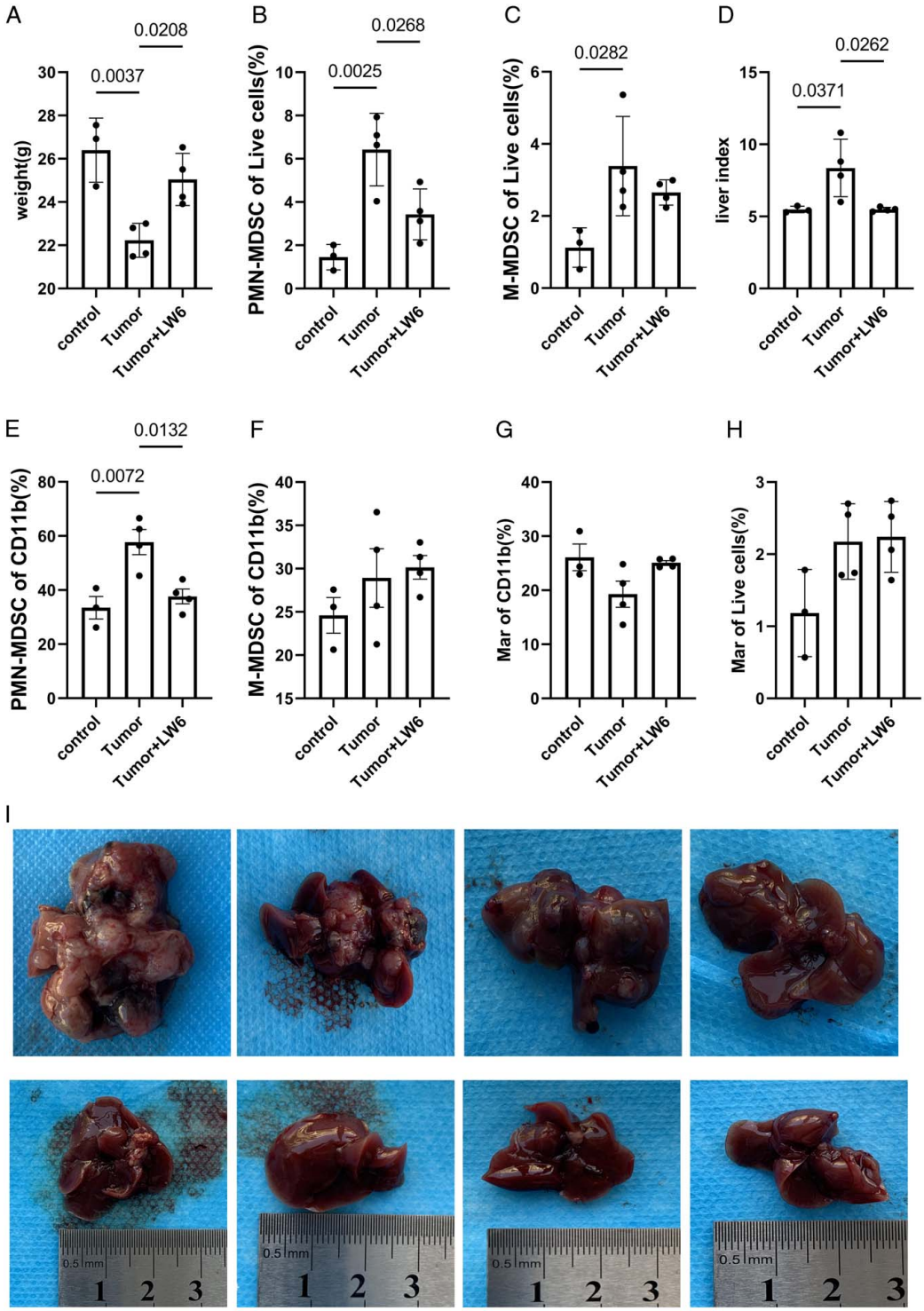

Figure 3. The change of PMN-MDSC, M-MDSC, and Mar after tumor cells injection and LW-6 intra-gastric into the spleen. (A) Weight changes. The percentage of (B) PMN-MDSC, (C) M-MDSC, and (H) Mar cells within the live cells. The percentage of (E) PMN-MDSC, (F) M-MDSC, and (G) Mar cells within the total $CD45^+CD11b^+$ cells. (D) Changes in liver index. (I) The liver of the tumor group (upper) and tumor + LW-6 group (lower). Significance as determined using one-way ANOVA tests ($P < 0.05$). Mar, macrophage; M-MDSC, monocytic MDSC; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell.

HIF-1α could also alter the changes in MDSCs in cancer models. We injected B-16 cells into the tail vein of mice to create a mouse model of metastasis. On the second day, we administered LW-6 to one group of mice by gavage for 10 days, and the endpoint was 21 days after tumor cell injection. The tumor group and the tumor + LW-6 group consisted of eight mice, with four mice in each group dying of tumors on days 18-20, meaning that at the end of the study, the mortality rates were consistent between these

two groups. We subsequently analyzed the remaining mice and found that the weight of the tumor-bearing mice was restored after LW-6 intervention, indicating a general improvement (Fig. 3A). We examined the percentage of MDSC in the spleen. After LW-6 administration, the percentage of PMN-MDSCs in mice decreased significantly and approached that of the control group (Fig. 3B). Moreover, the percentage of M-MDSCs decreased (Fig. 3C). Among the CD11b + cells, the ratio of PMN-MDSCs was restored after LW-6 intervention, while the change in M-MDSCs and macrophages was not apparent. However, a slight downward trend was observed (Fig. 3E–H). Notably, mice administered LW-6 had significantly fewer liver metastases and a much smaller liver index than that of the tumor group (Fig. 3D-I), which appeared to predict a better prognosis.

Discussion

The number of MDSCs increases in patients with cancer. Most current research focuses on one type of tumor, such as renal cell carcinoma, hepatocellular carcinoma (HCC), non-small cell lung carcinoma, cervical cancer, and melanoma[2–4,11–15]. Our study examined the frequency of MDSCs in the peripheral blood of patients with tumors without distinguishing tumor types for the first time. We confirmed that MDSCs increased during tumor attack, whereas PMN-MDSCs were predominant. An analysis of the proportions of the three subtypes of MDSCs showed that the proportions of M-MDSCs and eMDSCs in MDSCs decreased simultaneously with the increase of PMN-MDSCs; this may imply an interconversion between the three subtypes of MDSCs, that is to say, the phenotype of MDSCs changed under the influence of the TME, which further explained its immaturity and plasticity[1]. Our study found no differences in MDSC content between patients of different sexes, which may indicate that female hormones[16] have less influence on MDSCs than changes in the TME; therefore, more detailed experiments are needed to verify this aspect.

B-16 cells were used to create a mouse metastatic tumor model successfully. After 21 days after tumor injection, the mice lost weight and developed multiple metastases to the liver and lungs. We detected the proportion of MDSCs in the spleen and lung tissues. We found that the proportion of PMN-MDSCs in live cells increased at later stages of the tumor, similar to the results in patients with cancer, but with the difference that M-MDSCs were also elevated in the splenic live cells of mice. However, in CD45 + CD11b + cells, the proportion of PMN-MDSCs increased, whereas changes in M-MDSCs and macrophages were not evident. In lung tissue, the increase in PMN-MDSCs was accompanied by a significant decrease in macrophages, suggesting that macrophages may differentiate into PMN-MDSCs in the TME. Similar to the results in humans, the TME alters the differentiation of myeloid cells, making them more favorable for tumor progression as these changes are not observable 14 days after tumor cell inoculation, which becomes apparent as the tumor progresses. This may account for the fact that an increase in MDSCs is associated with tumor progression.

The hypoxic TME affects the proliferation and activation of MDSCs via the HIF pathway[8,9,17]. PMN-MDSCs have been shown to induce the stemness of colorectal cancer (CRC) cells that promote tumor progression through exosomal S100A9, which can be enhanced by hypoxia in a HIF-1α-dependent manner[18]. Our previous study found that the HIF-1α inhibitor LW-6 reduced MDSCs in mice (data not published); therefore, we proceeded to administer LW-6 in mice on the second day after B-16 cell inoculation. Remarkably, we observed that LW-6 administration reduced the number of MDSCs in the spleen of the mice while also decreasing the liver index of the mice and reducing the tumor metastases in the liver. However, using LW-6 did not improve tumor mortality in mice, as some mice died of tumors 1-3 days before reaching the study endpoint. This result was comparable to that obtained when LW-6 was not used, wherein the mortality rate was 50%. The reduction in the number and volume of metastatic tumors has been encouraging. However, the safety of LW-6 was also a point of concern. In our other studies, we gave mice with LW-6 for 10 days, and no weight loss or mortality was observed. While this finding partially supports the safety of LW-6, a comprehensive evaluation is still needed.

In clinical practice, neoadjuvant chemotherapy is commonly used to reduce tumor volume to increase the chances of successful surgical interventions and improve the prognosis of cancer patients. Therefore, similar to our study pertaining to the targeting of MDSCs through the inhibition of HIF-1α, reduction of the tumor volume can certainly benefit cancer patients. In this study, seven patients who underwent one or two cycles of neoadjuvant chemotherapy showed no significant change in MDSCs compared to their initial visit. This finding may indicate that chemotherapy is not targeted to MDSCs. Therefore, we speculated whether combining chemotherapy with MDSC targeting would have better clinical outcomes and reduce the required dose or frequency of chemotherapy to reduce its side effects.

The lack of relevant mechanism research is a limitation of our study. However, we believe this study offers a new perspective.

Conclusions

Based on the phenomenological description in this study, MDSCs increase in tumors, which is associated with poor prognosis. Reducing MDSCs by inhibiting HIF-1α may slow tumor progression. These findings may help to understand the pathophysiology of tumors better and lay the foundation for improving cancer outcomes.

Ethical approval

Permission to proceed with data acquisition and analysis was obtained from the Affiliated Hospital of Qinghai University (approval number: SL-2020091).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Q.X.: conceptualization, writing—original draft preparation, visualization. H.L.: conceptualization, writing—original draft preparation. X.S.: conceptualization, writing—original draft preparation. T.W.: supervision, writing—reviewing and editing. R.G.: supervision, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: not required.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Tana Wuren and Ri-li Ge.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Consent comments

The present study followed international, national and/or institutional guidelines for humane animal treatment and complied with relevant legislation.

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