Local and systemic inflammation triggers different outcomes of tumor growth related to infiltration of anti-tumor or pro-tumor macrophages

Xinghan Liu¹, Qi Jiang¹, Sunan Shen¹, Yayi Hou¹,²

¹The State Key Laboratory of Pharmaceutical Biotechnology, Division of Immunology, Medical School, Nanjing University, Nanjing, Jiangsu 210003, China; ²Jiangsu Key Laboratory of Molecular Medicine, Nanjing University, Nanjing, Jiangsu 210003, China.

Abstract
Background: Previous evidence suggests inflammation may be a double-edged sword with cancer-promoting and cancer suppressing function. In this study, we explore the impact of local and systemic inflammation on cancer growth.

Methods: Female BALB/C mice were subcutaneously implanted with foreign body (plastic plates) to build up a local inflammation and intraperitoneally injected with PolyIC or lipopolysaccharides (LPS) to build up a systemic inflammation, followed by subcutaneous injection of 5 × 10⁵ colon cancer cells. Immunohistochemistry and enzyme linked immunosorbent assay were utilized to detect the Ki67 and interleukin (IL) 6, IL-1β, and monocyte chemoattractant protein-1 expression in the tumor tissues and serum, respectively. The distributions of immune cells and expression of toll-like receptors (TLRs) were evaluated by flow cytometry (FCM) and quantitative real time-polymerase chain reaction.

Results: The results showed that local inflammation induced by foreign body implantation suppressed tumor growth with decreased tumor weight (P = 0.001), volume (P = 0.004) and Ki67 index (P < 0.001). Compared with the control group, myeloid-derived suppressive cells sharply decreased (P = 0.040), while CD4⁺ T cells slightly increased in the tumor tissues of the group of foreign body-induced local inflammation (P = 0.035). Moreover, the number of M1 macrophages (P = 0.040) and expression of TLRs, especially TLR3 (P < 0.001) and TLR4 (P < 0.001), were significantly up-regulated in the foreign body group. Contrarily, tumor growth was significantly promoted in LPS or PolyIC-induced systemic inflammation (P = 0.009 and 0.006). FCM results showed M1 type macrophages (P = 0.017 and 0.006) and CD8⁺ T cells (P = 0.031 and 0.023) were decreased, while M2 type macrophages (P = 0.002 and 0.007) were significantly increased in tumor microenvironment of LPS or PolyIC-induced systemic inflammation group. In addition, the decreased expression of TLRs was detected in LPS or PolyIC group.

Conclusions: The foreign body-induced local inflammation inhibited tumor growth, while LPS or PolyIC- induced systemic inflammation promoted tumor growth. The results suggested that the different outcomes of tumor growth might be attributed to the infiltration of anti-tumor or pro-tumor immune cells, especially M1 or M2 type macrophages into tumor microenvironment.

Keywords: Inflammation; Cancer; Macrophage; Toll-like receptor

Introduction

Inflammation is an adaptive response induced by endogenous or exogenous stimulation and is coordinated by multiple cells, inflammatory molecules, receptors and others. Exogenous stimuli consist of microbial factors (bacteria, virus and nematodes) and non-microbial factors (foreign bodies, radiation and mineral fibers), while endogenous stimuli are usually derived from stressed, damaged or malfunctioned tissues and cells, and degradation products of extracellular matrix. Stimulators of inflammation trigger immune or tissue cells to secrete numerous inflammatory mediators (cytokines, proteolytic enzymes, chemokines, and free radicals), which in turn affect the tissues and cells and inflammatory response.

Some epidemiological studies showed that inflammation increased the incidence of various types of cancer, such as bladder cancer, cervical cancer, gastric cancer, and bowel cancer. According to statistics, chronic infection and inflammation caused about 25% of cancer cases worldwide, and patients with inflammation had a significant increased risk of cancer. Apparently, inflammation not only directly initiates cancer, but also indirectly contrib-
utes to the progression and metastasis of cancer.\cite{7,8} In some situation, local inflammation may serve as a “fertile soil” to allow cancer growth and metastasis\cite{9,10}. For instance, physical trauma, which induced local inflammation and wound healing reaction, created an inflammatory milieu of cytokines, chemokines, and growth factors that augmented angiogenesis and favored cancer invasion and evasion of immune surveillance.\cite{11,12} Carrageenan-induced acute local inflammation also promoted cancer growth by generating the increased prostanooids and pro-inflammatory cytokines.\cite{13} Nevertheless, inflammation caused by toll-like receptor (TLR) agonists or Mycobacterium bovis, can be clinically used to suppress the growth and metastasis of cancer.\cite{14,15} In patients with colon cancer, local inflammation predicts a better prognosis,\cite{16,17,18,19} while systemic inflammation is opposite.\cite{18,19} All evidences suggest that inflammation may be a double-edged sword with cancer-promoting and cancer-suppressing function. Recently, more and more studies have found that the effects of inflammation on cancer are quite different according to the scope of inflammation. However, it is uncertain how local and systemic inflammation triggers different outcomes of tumor growth.

Thus, in the present study, we used foreign body (plastic plates) to build up a local inflammation and intraperitoneal injection of TLR3 agonist (PolyIC) or TLR4 agonist (LPS) to build up a systemic inflammation, and assessed the impact of both local and systemic inflammation on cancer.

**Methods**

**Ethical approval**

All of the animal protocols were approved by the Institutional Animal Care and Use Committee of Nanjing First Hospital, Nanjing Medical University (No. DW20200208) and conformed to the guidelines published by the National Institutes of Health.

**Cell culture**

CT26 colon cancer line was purchased from KeyGen BioTech (Nanjing, China) and cultured in Roswell Park Memorial Institute (RPMI)-1640 containing 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA) and 1% volume/volume (v/v) penicillin and streptomycin (Invitrogen) at 37°C in a 5% CO₂ incubator.

**Tumor mouse model under local or systemic inflammation**

Female BALB/C mice (5–6 weeks) were purchased from Model Animal Research Center of Nanjing University (Nanjing, China). The mouse tumor model under local inflammation was built as follows: plastic plates of foreign body were subcutaneously implanted into the right flank of female BALB/C mice (5–6 weeks).\cite{20} Five days later, 5 × 10⁵ CT26 cells were subcutaneously injected at the site of plastic plates. The mouse tumor model under systemic inflammation was built by intraperitoneal injection of LPS (Sigma-Aldrich, St. Louis, MO, USA; 2 mg/kg, every other day for a week) or PolyIC (Invivogen, San Diego, CA, USA; 2.5 mg/kg, every other day for two weeks) to female BALB/C mice, followed by subcutaneous injection of 5 × 10⁴ CT26 cells on the right flank. Indexes like body weight and tumor size were recorded every other day. Tumor volume was calculated by the formula: volume (V) = length (L) × width (W)^2 × 1/2.

**Analysis of tumor-infiltrating immunocytes**

Tumor tissues were peeled off from the mice, cut into pieces and digested with RPMI1640 medium containing 5% FBS, 2 mg/mL collagenase IV (Sigma-Aldrich, St. Louis, MO, USA), and 5 U/mL DNase I (Sigma-Aldrich) for 20 min by a 37°C shaker. After being neutralized with RPMI 1640 medium containing 5% FBS, cell suspension was filtered through a 70-µm nylon mesh into a centrifuge tube to get single cell suspensions. Scissors and 1 mL sterile syringes were used to separate the femurs and tibias and obtain the bone marrow cells. Then, the cells were lysed with red blood cell lysate, filtered through gauze, and resuspended in phosphate-buffered saline. For immunocyte detection, the following anti-mouse antibodies were used: CD45-phycoerythrin (PE) (103106, BioLegend, SanDiego, CA, USA), CD45-allophycocyanin (APC) (17-0451-83, ebioscience, CA, USA), CD11b-APC (101212, BioLegend), CD11b-peridinin-chlorophyll-protein complex (45-011282, ebioscience), glutathione reductase-1-fluorescein isothiocyanate (108406, BioLegend), F4/80-fluorescein isothiocyanate (FITC) (11-480182, ebioscience), inducible nitric oxide synthase-PE (125920-82, ebioscience), CD206-PE (12-2061-82, ebioscience), CD206-APC (17-2061-82, ebioscience), CD3-APC (17-0031-81, ebioscience), CD8-FITC (11-0081-81, ebioscience), CD4-Alexa Fluor 488 (100423, BioLegend). Stained cells were detected by a fluorescence-activated cell sorting Calibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA) and data were analyzed using FlowJo software (TreeStar, Ashland, OR, USA).

**Isolation of total RNA and quantitative real time-polymerase chain reaction (qRT-PCR)**

Total RNA from cells isolated from the tumor tissues was extracted by TRIzol reagent (Invitrogen) and reverse-transcribed to complementary DNA (cDNA) by HiScript II Q RT SynthesisMix Kit (Vazyme, Nanjing, China) following the manufacturer’s protocol. Then, SYBR Green SuperMix reagent (Bio-Rad, Hercules, CA, USA) was applied to polymerase chain reaction (PCR) quantification of cDNA. The expression of targeted genes was quantitatively calculated based on the ratio of target genes to the internal reference gene (glyceraldehyde-3-phosphate dehydrogenase) using the 2^(-ΔΔCt) method. Primers used in this study were displayed in Table 1.

**Enzyme linked immunosorbent assay (ELISA)**

First, blood was obtained from the eye socket of mice and allowed to stand at room temperature for 30 min. The blood serum was collected by centrifugation at 400 g for 20 min. The expression of interleukin (IL)-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) was determined according to the instructions of the mouse ELISA kit (Neobioscience, Shanghai, China).
mice, and then inoculated with CT26 cells in the same site [Figure 1A]. As seen in Figures 1B–1D, foreign body-induced local inflammation slightly suppressed tumor growth as evidenced by decreased average tumor weight (\(P = 0.001\)) and volume (\(P = 0.004\). Immunohistochemical staining of Ki67 showed foreign body reduced tumor proliferation to a great extent [Figures 1E and 1F]. Of note, foreign body implantation indeed induced the elevated level of IL6 in the mouse serum (\(P = 0.002\) [Figure 1G], indicating inflammation occurrence. However, the expression of IL-1β (\(P = 0.526\) and MCP-1 (\(P = 0.872\)) did not change significantly in the serum of mice with local inflammation [Figure 1G]. H&E images of tumor tissues showed the number of tumor cells in the mice with local inflammation was less than that in the control group [Figure 1H].

Local inflammation just affects the development of immature myeloid-derived cells

To assess the alteration of bone marrow, some immune cells from the bone marrow cells were obtained and analyzed. As shown in Figure 2, the proportion of myeloid-derived suppressor cells (MDCs; CD11b+Gr-1+; \(P = 0.010\)) in the bone marrow cells was lower in the group of foreign body [Figure 2A and 2B], although the percentages of granulocyte-MDSCs (G-MDSCs (\(P = 0.051\)) and monocytic-MDSCs (M-MDSCs, \(P = 0.771\)) stayed the same [Figure 2C and 2D]. In addition, the total macrophages [Figure 2E and 2F, CD11b+F4/80+, \(P = 0.196\)], M1 (CD11b+F4/80+iNOS+, \(P = 0.285\)) and M2 macrophages (CD11b+F4/80*CD206+, \(P = 0.610\) had not changed significantly [Figure 2G]. The number of CD4+ T cells (\(P = 0.238\)) was similar in the two groups, while the number of CD8+ T cells (\(P = 0.004\) was higher in the local inflammation group than control group [Figure 2H]. These results suggested that foreign body-induced local inflammation might mainly affect the development of immature myeloid-derived cells.

The suppression of tumor growth is related to infiltration of M1 type macrophages into tumor microenvironments under local inflammation

To assess the alteration of tumor microenvironment, some immune cells from tumor tissues were obtained and analyzed. The proportions of MDSCs (CD45+CD11b+Gr-1+, \(P = 0.040\)) in tumor tissues were significantly decreased in the foreign body group, accompanied with decreased percentages of G-MDSCs (\(P = 0.009\) and M-MDSCs (\(P = 0.001\) [Figures 3A–3D]. Total macrophages (CD45+CD11b+F4/80+, \(P = 0.013\), especially M1-type macrophages (CD45+CD11b+F4/80*CD206+, \(P = 0.004\) were significantly increased in foreign body-induced group, while the numbers of M2 type macrophages (CD45+CD11b+F4/80*CD206+, \(P = 0.731\) were similar between the two groups [Figures 3E and 3F]. In addition, CD4+ T cells (CD45+CD3+CD4+, \(P = 0.035\) slightly increased in the group with foreign body, while CD8+ T cells (CD45+CD3+CD8+, \(P = 0.760\) did not have a statistical difference between the two group [Figure 3G]. To explore the potential mechanism, single cells were extracted from tumor tissues and analyzed by qRT-PCR.

Surprisingly found that the expression of TLRs,
especially TLR3 \( (P < 0.001) \) and TLR4 \( (P < 0.001) \), was significantly elevated in the foreign body group [Figure 3H]. These data indicated that the suppression of tumor growth might be related to infiltration of antitumor M1 type macrophages into tumor microenvironments under foreign body-induced local inflammation.

**Tumor growth is promoted under condition of LPS or PolyIC-induced systemic inflammation**

Next, we wanted to explore the effect of systemic inflammation on tumor growth. PolyIC and LPS were intraperitoneally injected to induce systemic inflammation and then CT26 cells were subcutaneously injected at the
right flank of female BALB/C mice [Figure 4A]. The results showed that the systemic inflammation sharply promoted tumor growth, as evidenced by the increased average tumor weight \((P = 0.004 \text{ and } 0.002)\) and volume \((P = 0.009 \text{ and } 0.006)\) [Figure 4B–4D]. The systemic inflammation also enhanced the proliferation of tumor cells detected by Ki67 staining \((b o t h \ P < 0.001)\) [Figure 4E–4F]. Though the expression of IL-6 \((P = 0.119 \text{ and } 0.768)\) did not change significantly in PolyIC and LPS-treated mice, the levels of IL-1β \((b o t h \ P < 0.001)\) and MCP-1 \((b o t h \ P < 0.001)\) increased in the serum from PolyIC and LPS-treated mice when compared with the control group [Figure 4G]. H&E images of tumor tissues showed the number of tumor cells in the mice with PolyIC or LPS administration was more than that in the control group [Figure 4H].

**Systemic inflammation affects the polarization of macrophages in the bone marrow**

The distribution of immune cells in the bone marrow under condition of systemic inflammation was examined by FCM. The results showed that although the percentage of total MDSCs \((P = 0.852 \text{ and } 0.664)\) did not alter in the bone marrow cells [Figure 5A and 5B], the percentage of G-MDSCs \((P = 0.001)\) increased in the group treated with PolyIC and that of M-MDSCs \((P < 0.001)\) increased in the group treated with LPS [Figures 5C and 5D]. The percentage of macrophages \((P = 0.008 \text{ and } 0.003)\) was decreased [Figure 5E], but the percentage of M2-like macrophages \((P = 0.023 \text{ and } 0.011)\) was significantly increased [Figure 5F]. In addition, a significantly decreased number of CD4+ T cells \((P < 0.001)\) was observed in the mouse group treated with LPS [Figure 5G]. There was no significant difference in the distribution of CD8+ T cells in the PolyIC/LPS-treated mice when compared with the control group \((P = 0.255 \text{ and } 0.786)\). These results suggested that systemic inflammation could affect the polarization of macrophages into M2 type in the bone marrow.

**Infiltration of M2 type macrophages supports tumor growth in the condition of systemic inflammation**

The distribution of immune cells in the tumor microenvironment was analyzed by FCM. The results showed that total MDSCs \((P = 0.979 \text{ and } 0.746), \ G-MDSCs \((P = 0.230 \text{ and } 0.187)\) and M-MDSCs \((P = 0.591 \text{ and } 0.372)\) did not change statistically in both PolyIC and LPS-induced systemic inflammation groups compared with the control group [Figure 6A–6D]. Total macrophages \((P = 0.006 \text{ and } 0.004)\) were obviously decreased in the tumor tissues in the condition of systemic inflammation, accompanied with decreased percentage of M1 type \((P = 0.017 \text{ and } 0.006)\) and increased percentage of M2 type \((P = 0.002 \text{ and } 0.007)\) [Figure 6E–6F]. Though the distribution of CD4+ T cells \((P = 0.920 \text{ and } 0.614)\) in the Poly IC and LPS-induced groups was not significantly different from that in the control group, the proportion of CD8+ T cells \((P = 0.031 \text{ and } 0.023)\) slightly decreased in the systemic inflammation groups [Figure 6G]. Further more, the expression of TLRs obviously decreased in the mouse treated with PolyIC or LPS [Figure 6H]. These data indicated that LPS/PolyIC-induced systemic inflammation promoted tumor growth, which might be related to the polarization of macrophages into M2 type and decreased expression of TLRs in the tumor tissues.

**Discussion**

Macrophages are types of pleiotropic cells and are usually divided into two groups. The classic pro-inflammatory M1 macrophages can exert antigen presentation and tumor killing activity by expressing major histocompatibility complex I and II molecules and secreting cytokines such as tumor necrosis factor-α, IL-1β and IL6.[21,22] While M2 type macrophages are involved in the promotion of tissue remodeling and tumor progression, displaying an promoting function of tumor growth.[23,24] The phenotype of macrophages is plastic and regulated by the local tumor microenvironment.[25,26] In solid tumors, macrophages account for the majority of all immune...
Infiltrating macrophages in tumor microenvironment initially have an M1 phenotype. However, the persistence of various cytokines (such as C-C motif chemokine 2, vascular endothelial growth factor, and macrophage colony-stimulating factor) and hypoxic condition make macrophages polarize into M2-type or recruit circulating monocytes to differentiate into M2-like macrophages, thereby losing phagocytosis and the presentation ability of tumor-associated antigens to T cells. In this study, we found local inflammation induced by foreign body implantation significantly suppressed tumor growth with increased infiltration of macrophages especially M1 type in the tumor tissues. In contrast, systemic inflammation induced by intraperitoneal injection of PolyIC or LPS resulted in the reduction of tumoricidal M1 macrophages and the increase of suppressive M2 type, which may mediate its promotion of tumor growth.

Interestingly, the expression of all TLRs changed to varying degrees in the two mouse models. TLRs, one of the pattern recognition receptors, are expressed on the surface of immune cell surface and intracellular vesicles and can recognize pathogen/damage-related molecular patterns. Through myeloid differentiation factor 88 or Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF) pathways, TLRs induce the expression of inflammatory cytokines and chemokines thereby regulating immune responses and participating in the inflammation and cancer progression. Previous studies have reported that TLR3 and TLR4 could facilitate M1 macrophage polarization. TLR3 agonist (LPS) is traditionally used to polarize macrophages into M1 type. TLR4 was involved in the activation of nuclear factor-κB signaling, which participated in the M1 polarization of macrophages. Some TLR ligands, including TLR2, TLR7/8, and TLR9, can be used for tumor treatment by regulating immune cells. TLR9 ligand CpG strongly inhibited the suppressive function of MDSCs in tumor models. TLR7/8 agonist could promote MDSCs to differentiate into M1-like macrophages. Consistent with this, we found that compared with the control group, the expression of TLRs sharply increased in the local inflammation group, which suggested that activated TLRs may contribute to decreased MDSCs and increased M1-type macrophages in the tumor tissues. However, the expression of TLRs was down-regulated in the systemic inflammation group with the opposite macrophage infiltration. These results suggested the role of inflammation in cancer might depend on the status of TLRs.

In the present study, we found that the foreign body-induced local inflammation inhibited tumor growth, while LPS or PolyIC-induced systemic inflammation promoted tumor growth. The results suggested that the local inflammation-then-cancer and systemic inflammation-then-cancer models might lead to the opposite effects on cancer progression and induce different intra-cancer immune cell infiltration via changing the expression of TLRs.
Figure 5: Systemic inflammation affects the polarization of macrophages in bone marrow cells in vivo. (A–B) Quantitative data of the proportions (A) and FCM photographs of MDSCs (B) in the bone marrow cells from mice with indicated treatments. (C–D) Quantitative data of the proportions (C) and FCM photographs (D) of subgroups of MDSCs in the bone marrow cells from mice with indicated treatments. (E–G) Quantitative data of the proportions (E) of macrophages, subgroups of macrophages (F), and CD4+ and CD8+ T cells (G) in the bone marrow cells from mice with indicated treatments. *P < 0.01, †P < 0.05 vs. control. FCM: Flow cytometry; G-MDSCs: Granulocyte-myeloid-derived suppressor cells; Gr-1: Glutathione reductase-1; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharides; M-MDSCs: Monocytic-myeloid-derived suppressor cells.

Figure 6: Systemic inflammation enhances infiltration of M2 macrophages into tumor microenvironment in vivo. (A–B) Quantitative data of the proportions (A) and FCM photographs (B) of MDSCs in the tumor tissues from mice with indicated treatments. (C–D) Quantitative data of the proportions (C) and FCM photographs (D) of subgroups of MDSCs in the tumor tissues from mice with indicated treatments. (E–G) Quantitative data of the proportions (E) of macrophages, subgroups of macrophages (F), and CD4+ and CD8+ T cells (G) in the tumor tissues from mice with indicated treatments. (H) Single cells were extracted from the tumor tissues and used for qRT-PCR to determine the expression of targeted genes. *P < 0.01, †P < 0.05 vs. control. FCM: Flow cytometry; G-MDSCs: Granulocyte-myeloid-derived suppressor cells; Gr-1: Glutathione reductase-1; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharides; M-MDSCs: Monocytic-myeloid-derived suppressor cells; qRT-PCR: Quantitative real-time polymerase chain reaction; TLR: Toll-like receptor.
Chinese Medical Journal 2022;135(15) www.cmj.org

Conflicts of interest
None.

References
1. Medzhitov R. Origin and physiological roles of inflammation. Nature 2001;414:198–206. doi:10.1038/nature007201.
2. Rock KL, Kono H. The inflammatory response to cell death. Annu Rev Pathol. 2008;3:99–126. doi:10.1146/annurev.pathmech-dis.3.121806.151436.
3. Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, et al. Regulation of lung injury and repair by Toll-like receptors and hyaluronan. Nat Med 2005;11:1173–1179. doi:10.1038/nm1315.
4. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Trends Cardiovasc Med 2005;15:57–63. doi:10.1016/j.tcm.2005.02.002.
5. Balkwill F, Mantovani A. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:905–916. doi:10.1016/s1470-2045(14)70263-3.
6. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2011;29:610–612. doi:10.1016/s1470-2045(10)70263-3.
7. Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, et al. Extent of inflammation potentiates tumour growth or regression: powered by myeloid-derived suppressor cells to tumoricidal M1-macrophages. Cancer Lett 2020;469:173–185. doi:10.1016/j.canlet.2019.10.020.
8. Francescone R, Hou V, Grivennikov SI. Microbiome, inflammation and treatment effectiveness. Front Immunol 2019;10:2963. doi:10.3389/fimmu.2019.02963.
9. Korneev KV, Arretkhany KN, Drutskaya MS, Grivennikov SI, Kuprash DV, Niedoprosyov SA. TLR-signaling and proinflammatory cytokines as drivers of tumorgenesis. Cytokeine 2017;89:127–135. doi:10.1016/j.cyto.2016.01.021.
10. Ferrari A, Romani RA, Kasperek EM, Yu G, Kramer JM. Activation of MyD88-dependent TLRs mediates local and systemic inflammation in a mouse model of cancer, pyogenic, and sepsis syndrome. Front Immunol 2019;10:2963. doi:10.3389/fimmu.2019.02963.
11. Zou L, Zhao Q, Yang T, Ding W, Zhao Y. Cellular metabolism and macrophage functional polarization. Int Rev Immunol 2015;34:82–100. doi:10.3109/08936004.2014.968421.
12. Fujihara M, Muroi T, Tamamoto K, Suzuki T, Azuma H, Ikeda H. Molecular mechanisms of macrophage activation and deactivation by lipopolysaccharide: roles of the receptor complex. Pharmacol Ther 2003;100:171–194. doi:10.1016/j.pharmaco.2003.08.003.
13. Wang D, He S, Liu B, Liu C. MiR–27–p regulates TLR7/8 agonist reverses oxaliplatin resistance in colorectal cancer via targeting the myeloid-derived suppressor cells to tumoral M1-macrophages. Cancer Lett 2020;469:173–185. doi:10.1016/j.canlet.2019.10.020.
14. Akazawa T, Inoue N, Shime H, Kodama K, Matsumoto M, Seya T. Adjuvant engineering for cancer immunotherapy: development of a synthetic TLR2 ligand with increased cell adhesion. Cancer Sci 2010;101:1596–1603. doi:10.1111/j.1349-7006.2010.01583.x.
15. Zoglemier C, Bauer H, Norenberg D, Wedekind G, Bittner P, Sandholzer N, et al. CpG blocks immunosuppression by myeloid-derived suppressor cells in cancer patients. Cancer Res 2011;71:1765–1775. doi:10.1158/0008-5472.CCR-10-2672.
16. Liu Z, Xie Y, Xiong Y, Liu S, Qiu C, Zhu Z, et al. TLR 7/8 agonist reverses oxaliplatin resistance in colorectal cancer via targeting the myeloid-derived suppressor cells to tumoral M1-macrophages. Cancer Lett 2020;469:173–185. doi:10.1016/j.canlet.2019.10.020.

How to cite this article: Liu X, Jiang Q, Shen S, Hou Y. Local and systemic inflammation triggers different outcomes of tumor growth related to infiltration of anti-tumor or pro-tumor macrophages. Chin Med J 2022;135:1821–1828. doi:10.1097/CMA.0000000000001775

1828