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Dexmedetomidine alleviates the pro-tumor activity of perioperative stress in tumor-bearing mice: an alternative approach of psycho-physiological intervention

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Abstract

Background The immediate perioperative period (IPP) usually is highly stressful and has significant effects on the postoperative recurrence/metastasis of tumors. Effective methods for limiting the impact of the IPP on postoperative recurrence/metastasis of tumors remain scarce. We aimed to determine the effects of dexmedetomidine (DEX) treatment during the IPP on postoperative recurrence/metastasis of tumors and the stress response.

Materials and methods The clinical perioperative setting was mimicked via tumor resection and perioperative restraint stress in tumor-bearing mice with or without DEX during the IPP. The stress response was assessed using stress hormone and interleukin (IL)-6 levels in peripheral blood. Tumor cell growth was measured via in vivo bioluminescent imaging, cell viability assay, wound-healing assay, and Western blotting.

Results In tumor-bearing mice, DEX during the IPP limited the growth of implanted tumor cells and stress response in a dose-dependent manner. The serum from mice without DEX promoted cultured tumor cell growth, which was alleviated by beta-adrenergic receptor blocker propranolol or IL-6 antibody. Relative to the serum from mice without DEX, the serum from mice with DEX had lower stress hormone and IL-6 levels, as well as weaker effects on tumor growth promotion. Dexmedetomidine supplementation during culture had no significant effects on tumor cells.

Conclusions Dexmedetomidine alleviates the pro-tumor activity of perioperative stress in abdominal tumors.

Keywords Dexmedetomidine, Long-term outcomes, Perioperative stress, Tumor metastasis

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Introduction

In solid tumors, surgical excision of the primary tumor is the foremost treatment with curative intent [1–4]. The postoperative recurrence/metastasis of tumors is a common concern [5, 6]. Chemotherapy or immunotherapy is commonly administered before or after surgery to prevent postoperative recurrence/metastasis by eliminating residual tumor cells from the proximal to excisional locations, lymphatic system, blood circulation, and distal organs [7]. However, the postoperative recurrence/metastasis of tumors remains a therapeutic challenge.

Recent evidence has shown that the immediate perioperative period (IPP), spanning a few days before and after surgery and including the surgical period itself, is a critical time for preventing the postoperative recurrence/metastasis of tumors [7, 8]. During the IPP, Patients are usually highly stressed because of their concerns about the disease and its subsequent treatment, as well as physiological responses to surgery and anesthesia [1, 9–12]. High stress levels over-activate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system; increase levels of blood catecholamines, glucocorticoids, and inflammatory cytokines; decrease the antitumor activity of natural killer (NK) and $CD8^+$ T cells; and promote Treg cell proliferation [7, 11, 12]. Thus, targeting the stress response system and its downstream signals may be effective in alleviating the IPP'S effects on tumor recurrence/metastasis [8]. In fact, the combined perioperative pharmacological blockade of Beta-adrenergic [13, 14] and COX2 signaling [15, 16] seem promising in improving long-term cancer outcome, based on ample translational studies and recent clinical trials. However, most patients have medical contraindications for the use of β-blockers and or COX2 inhibitors, and the pharmacological blockade can't prevent other responses, including increased cortisol and IL-10 levels before surgery [13, 14]. Thus, alternative approaches are needed. Psychophysiological interventions can help patients cope with stress and reduce psychological perioperative stress, and have been found effective as the alternative approaches [17, 18]. Their effectiveness depends on long intervention time and has significant inter-individual difference, which limits their use during IPP [18, 19].To date, effective methods for limiting the IPP's effects on tumor recurrence/metastasis remain scarce.

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist, and can exert sedative and anxiolytic effects by modulating the norepinephrine neurons in locus coeruleus and GABA-related pathways [4]. Recent studies have shown that Dexmedetomidine can protect surgical patients' immune function and attenuate perioperative stress and inflammation, suggesting that dexmedetomidine is a good candidate for alleviating the IPP's effects on tumor recurrence/metastasis [4, 20, 21]. However, a previous study showed that dexmedetomidine promoted the metastasis of breast, lung, and colon cancers in BALB/c mice, F344 rats, and C57BL/6 mice with acute and transient stress [22]. In contrast, a recent preclinical study reported that activation of the alpha-2 adrenoceptor showed significant antitumor effects in an immune-dependent manner [23], causing confusion about the consequences of dexmedetomidine use during the IPP for tumor recurrence/metastasis. Thus, we tested the antitumor effect of dexmedetomidine administration during the IPP in tumor-bearing mice.

Materials and methods

Animal study

All experiments were performed in accordance with the guidelines for experimental animal use of the Central South University in Changsha, China, and the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guideline. The protocol (CSU-2022-0086) was approved by the Central South University Ethics Committee. C57BL/6 female mice (8 weeks old, 20–25 g) were purchased from Central South University. All mice were housed in pathogen-free cages with free access to food and water in the unit, for which the temperature (24 ± 0.5), humidity (60%), and 12-hour dark-light cycle were tightly controlled. The study was conducted in accordance with the 5Fs and the 3Rs.

Grouping of animals

Experiment 1, the goal was to explore the effects of perioperative stress response on tumor growth and the regulatory role of dexmedetomidine. Mice were randomly divided into Con, SS, SSS, SSD-10, SSD-20, and SSD-30 groups ($n = 16$/group; 4 mice /group for in vivo imaging, and 12 mice /group for stress response assessment). Con group was the normal control. SS group was intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and intraperitoneally injected with 100 μl of saline three times a day. SSS group was intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 100 μl saline from day 1 before surgery to day 2 after surgery. SSD-10 or SSD-20 or SSD-30 group was intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 10 or 20 or 30 μg kg^{-1} dexmedetomidine from day 1 before surgery to day 2 after surgery.

Experiment 2, the goal was to investigate the underlying antitumor mechanisms of dexmedetomidine. Mice were randomly divided into Con, SS, SSS, and SSD-20 groups($n = 8$/group). The treatments of each group were

the same as described above. The serum of each group was collected to treat cultured ID8 cells.

Modeling perioperative stress and tumor surgery

To simulate the clinical setting of patients undergoing tumor surgery, 5×10^5 ID8 ovarian surface epithelial cells [24, 25] derived from C57BL/6 mice were injected subcutaneously to induce solid tumors in each C57BL/6 mouse. Then, 14 days later, these tumor-bearing mice received 100 μl of 1×10^5 ID8-Luc cells, mimicking residual malignant cells after surgery and following subcutaneous tumor resection under anesthesia with 2–2.5% sevoflurane. To imitate the perioperative stress of concerns about surgery and postoperative movement limitations, mice also received 3 h at a time of restraint stress in transparent tubes at 8:00, 12:00, and 16:00 from day 1 before surgery to day 2 after surgery.

Dexmedetomidine administration

Dexmedetomidine (10 μg kg^{-1}, 20 μg kg^{-1}, or 30 μg kg^{-1}) was administrated via intraperitoneal injection 30 min before each restraint stress session, as in previous studies [4, 22, 26].

In vivo propagation imaging of ID8-Luc tumor cells

In vivo bioluminescent imaging was performed with Xenogen IVIS on days 7 and 14 after surgery to evaluate the propagation of ID8-Luc tumor cells ($n = 4$ per group). Each mouse was first injected intraperitoneally with 0.2 mL of 15 mg mL-1 d-luciferin (Promega; Madison, WI) in sterile phosphate-buffered saline (PBS), according to the manufacturer's protocol, and placed in the imaging system's anesthesia induction chamber, which contained 1.5–2.0% isoflurane in medical-grade oxygen, delivered at a rate of 2.0 L min-1. Animals were immediately transferred to the system's heated specimen stage to await imaging. Imaging began 10 min after luciferin administration, when each mouse's average bioluminescence had previously been found to reach maximal intensity. Post-acquisition image analyses were performed using PerkinElmer's Living Image software (version 4.2) and graphed to obtain absolute photon fluence (photons/s/steradian/cm2) in well-defined regions of interest.

Stress response evaluation

Levels of stress hormones (i.e., epinephrine, norepinephrine, and corticosterone) and inflammatory factor (i.e., IL-6) in peripheral blood ($n = 6$ per group) were tested via enzyme-linked immunosorbent assay (ELISA), following reported methods of assessing the stress response [9, 11]. Briefly, mice were deeply anesthetized with 5% sevoflurane on the day of surgery or 2 days later. Peripheral blood was collected from the right atrial appendage and centrifuged, and serum was collected for further analysis. According to ELISA kit protocols, levels of epinephrine and norepinephrine (KA1877; Abnova; Taiwan), corticosterone (H094-1-2; Nanjing Jiancheng Bioengineering Institute; Nanjing, China), and IL-6 (H002-1-2, Nanjing Jiancheng Bioengineering Institute) were detected.

Cell culture and treatment

The mouse ID8 cells(Millipore Cat# SCC145, RRID: CVCL_IU14) and ID8-luc cells (Cat.No: M-C2011, Mcellbank Biotechnology) were purchased from companies. Cell cultures were monitored for mycoplasma contamination, and only mycoplasma-negative cells were used for experiments. ID8 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco) with 10% serum from mice with or without DEX treatment plus 1 μM of propranolol (MedChemExpress)/PBS, 200 μg ml^{-1} of tocilizumab (Roche)/IgG (Bio X Cell), or 0.1 μM dexmedetomidine (Jiangsu Hengrui Pharmaceuticals) at 37 °C.

Wound-healing assay

The wound-healing assay was performed as previously described, with minor modifications. Briefly, 2×10^5 ID8 tumor cells were seeded on 12 well plates for 24 h in DMEM containing 1% penicillin-streptomycin (Gibco) and 10% serum from mice with or without DEX treatment. Cell monolayers were then scraped into straight lines with a P10 pipette tip, and debris was removed by washing the monolayers with fresh serum-free culture medium. Images were captured using a Nikon Eclipse TE300 microscope at 0 h and 24 h after scraping. ImageJ software (v1.46; National Institutes of Health; Bethesda, MD, USA) was used to analyze the images, and the scratched areas were determined using the Polygonal Selection Tool for each time point and treatment. The results were normalized to the scratched areas at 0 h.

Cell viability assay (CCK-8)

The CCK-8 assay kit (Dojindo; Kumamoto, Japan) was prepared according to the manufacturer's instructions. Briefly, ID8 cells were cultured in DMEM containing 1% penicillin-streptomycin and 10% serum from mice with or without DEX treatment at 37 °C in a humidified incubator containing 5% CO2. After culturing for 0, 24, 48, or 72 h, the prepared reagents of the CCK-8 test kit were added to the well plates and detected at a 450-nm wavelength.

Western blotting

Cell samples were homogenized in a lysis buffer containing protease inhibitor cocktails (CW2333S; CWBio). Samples' protein quantity was determined using a BCA protein assay kit (CW0014S; CWBio) according to the manufacturer's instructions. Equal amounts of

protein samples were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride membranes. The membranes were blocked with 5% skim milk in TBST buffer for 2 h and then incubated with primary antibodies, p53 (Proteintech Cat# 60283-2-Ig, RRID: AB_2881401), vimentin(ProteintechCat# 10366-1-AP, RRID: AB_2273020), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH: Proteintech Cat# 60004-1-Ig, RRID: AB_210743660004-1-Ig) overnight at 4 °C. After three washes, membranes were incubated with secondary antibodies (goat anti-rabbit IgG [Abcam Cat# ab216773, RRID: AB_2925189]) at room temperature for 2 h. Finally, protein visualization was accomplished with the Odyssey CLx Imaging System (LI-COR), and relative protein expression levels were normalized using the ratio of target protein (i.e., p53 and vimentin) to GAPDH.

Statistical analysis

All experiments were independently repeated at least three times. GraphPad Prism 8 (GraphPad Software; La Jolla, CA, USA) was used for figure generation and statistical analysis. Data were presented by means ± SEM (Standard Error of the Mean). The results of the in vivo imaging, stress response evaluation, wound healing assay, and western blotting assay were statistically analyzed using one-way analysis of variance (ANOVA) after the Shapiro-Wilk test for normality distribution. If the data didn't follow the normal distribution, the Kruskal-Wallis test was performed for statistical analysis. The significance level was set at $P < 0.05$.

Results

Perioperative dexmedetomidine treatment limited the stress response and growth of implanted tumor cells in tumor-bearing mice in a dose-dependent manner

To simulate the clinical setting of patients experiencing preoperative fasting and concerns about anesthesia and surgery, tumor-bearing mice received subcutaneous tumor resection, intraperitoneal tumor cell implantation, and restraint stress from day 1 before surgery to day 2 after surgery (Fig. 1A). In vivo bioluminescence imaging showed that tumors in mice who had surgery, restraint stress, and saline treatment (SSS group) grew faster on days 7 and 14 after surgery ($P < 0.010$ for day 7 and 0.071 for day 14) (Fig. 1C and D) compared with mice who had surgery and saline (SS group), suggesting an important role for perioperative stress in tumor growth. In contrast, tumor growth in mice who had surgery, restraint stress, and dexmedetomidine treatment (SSD group) was significantly slower than that of the SSS group and had no significant difference compared with the SS group (Fig. 1C and D), suggesting an antitumor effect of dexmedetomidine. We also found that the antitumor effects of dexmedetomidine were different at doses of 10 μg kg^{-1}, 20 μg kg^{-1}, and 30 μg kg^{-1}, especially on day 14 after surgery (Fig. 1D).

Stress response was evaluated via levels of stress hormones (e.g., epinephrine, norepinephrine, and corticosterone) and inflammatory factor (IL-6) in peripheral blood [9, 11]. Corresponding to tumor growth differences (Fig. 1B-D), the levels of stress hormones and IL-6 in the peripheral blood of the SSS group were significantly higher than that of the SS and SSD groups on days 0 and 2 after surgery (Fig. 2B-E). There was a slight but not statistically significant difference in the levels of stress hormones and IL-6 in mice treated with dexmedetomidine doses of 10 μg kg^{-1}, 20 μg kg^{-1}, and 30 μg kg^{-1} (Fig. 2B-E). These data showed that perioperative dexmedetomidine treatment limited the stress response and the growth of implanted tumor cells in tumor-bearing mice in a dose-dependent manner.

Blocking stress response signaling partly mimicked the effects of dexmedetomidine-treated mice's serum on cultured tumor cells

To test the underlying antitumor mechanisms of dexmedetomidine, serum from different groups in the above experiments were used to treat cultured tumor cells with or without beta-receptor blocker propranolol and IL-6 antibody tocilizumab (Fig. 3A). Corresponding to tumor growth (Fig. 1), the levels of stress hormones and IL-6 in the peripheral blood (Fig. 2B-E) differences, ID8 cells treated with day 0 serum from SSD-20 group. Compared with that of the normal control, serum from the SSS group promoted tumor cell proliferation in the CCK8 assay (Fig. 3B), migration in the wound-healing assay (Fig. 3C), and expression of the migration-related protein vimentin (Fig. 3D and E), and it decreased the expression of tumor suppressor p53 (Fig. 3D and E), which was significantly alleviated by propranolol and tocilizumab (Fig. 3D and E). Similarly, the tumor cells treated with serum from the SSD group also showed slower proliferation, slower migration, less vimentin, and higher P53, relative to that treated with serum from the SSS group (Fig. 3D and E). Combining the changes of stress hormones and inflammatory factor in peripheral blood (Fig. 2), it is reasonable to that perioperative dexmedetomidine limited the growth of cultured tumor cells by alleviating the stress response.

Perioperative dexmedetomidine limited tumor cell growth not by directly acting on tumor cells

To test whether dexmedetomidine has direct effect on tumor cells, the effects of dexmedetomidine supplementation during culture were detected. We found there is no significant difference in proliferation and migration of tumor cells treated with serum of SSS group or serum

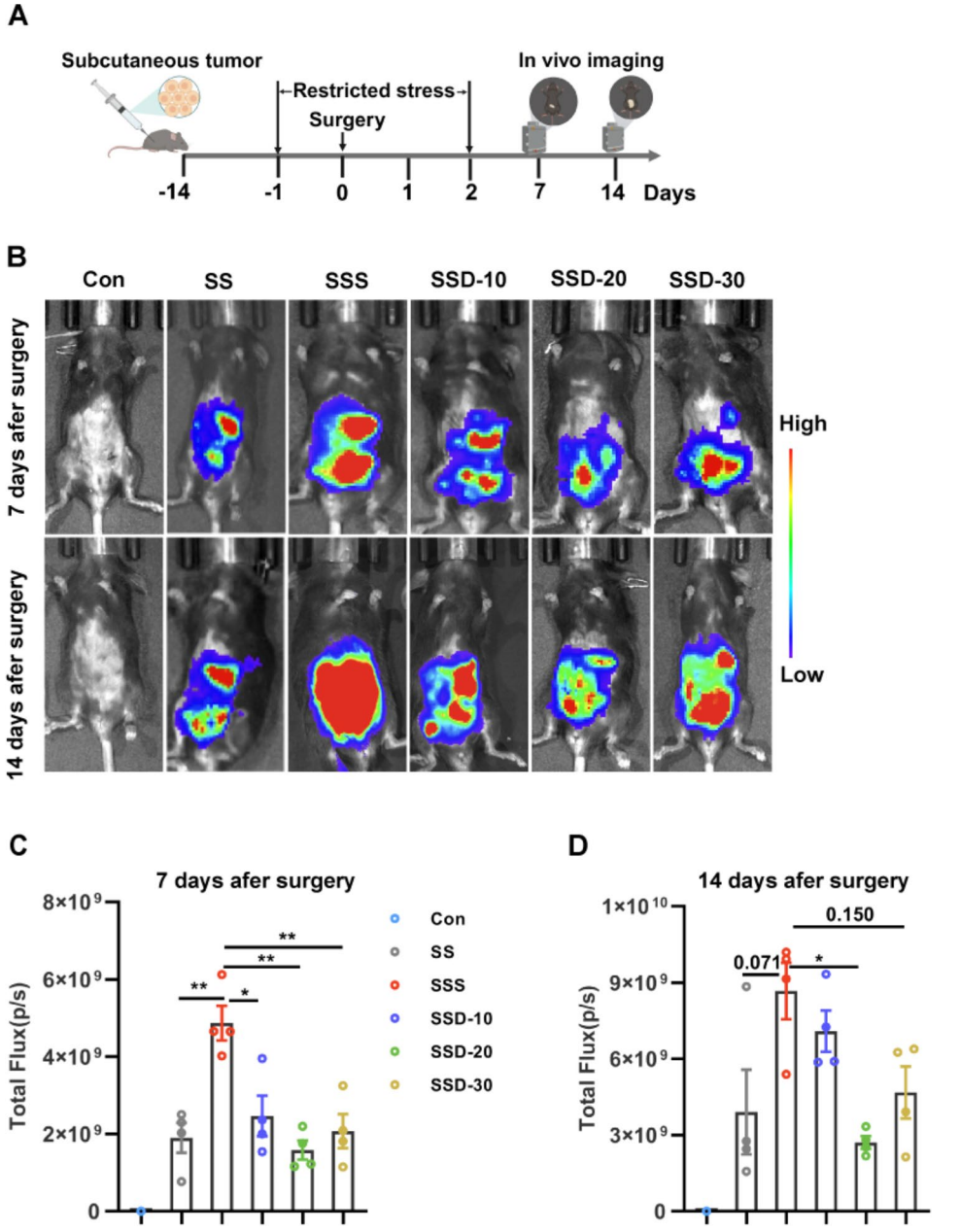

Fig. 1 Perioperative dexmedetomidine treatment limited the growth of implanted tumor cells in tumor-bearing mice. (**A**) Time schedule for subcutaneously transplanted tumor, restraint stress, surgery, and in vivo bioluminescence imaging. (**B**) Representative bioluminescent images on days 7 and 14 after surgery. (**C**) Total luminescent units on day 7 after surgery ($n=4$ per group). (**D**) Total luminescent units on day 14 after surgery ($n=4$ per group). Data are expressed as mean ± SEM; $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}01$; one- way ANOVA followed by Tukey's multiple comparisons test for comparison. Con, normal control group; SS, mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and intraperitoneally injected with 100 μl of saline three times a day; SSS, mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 100 μl saline from day 1 before surgery to day 2 after surgery; SSD-10 or SSD-20 or SSD-30,mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 10 or 20 or 30 μg kg^{-1} dexmedetomidine from day 1 before surgery to day 2 after surgery

of SSS group plus dexmedetomidine (Fig. 4). In contrast, the tumor cells treated with serum from the SSD group showed slower proliferation and migration, relative to that treated with serum from the SSS group or serum from the SSS group plus dexmedetomidine (Fig. 4).

Discussion

In this study, we found that dexmedetomidine treatment during the immediate perioperative period (IPP) limited the growth of implanted tumor cells and the stress response in tumor-bearing mice in a dose-dependent

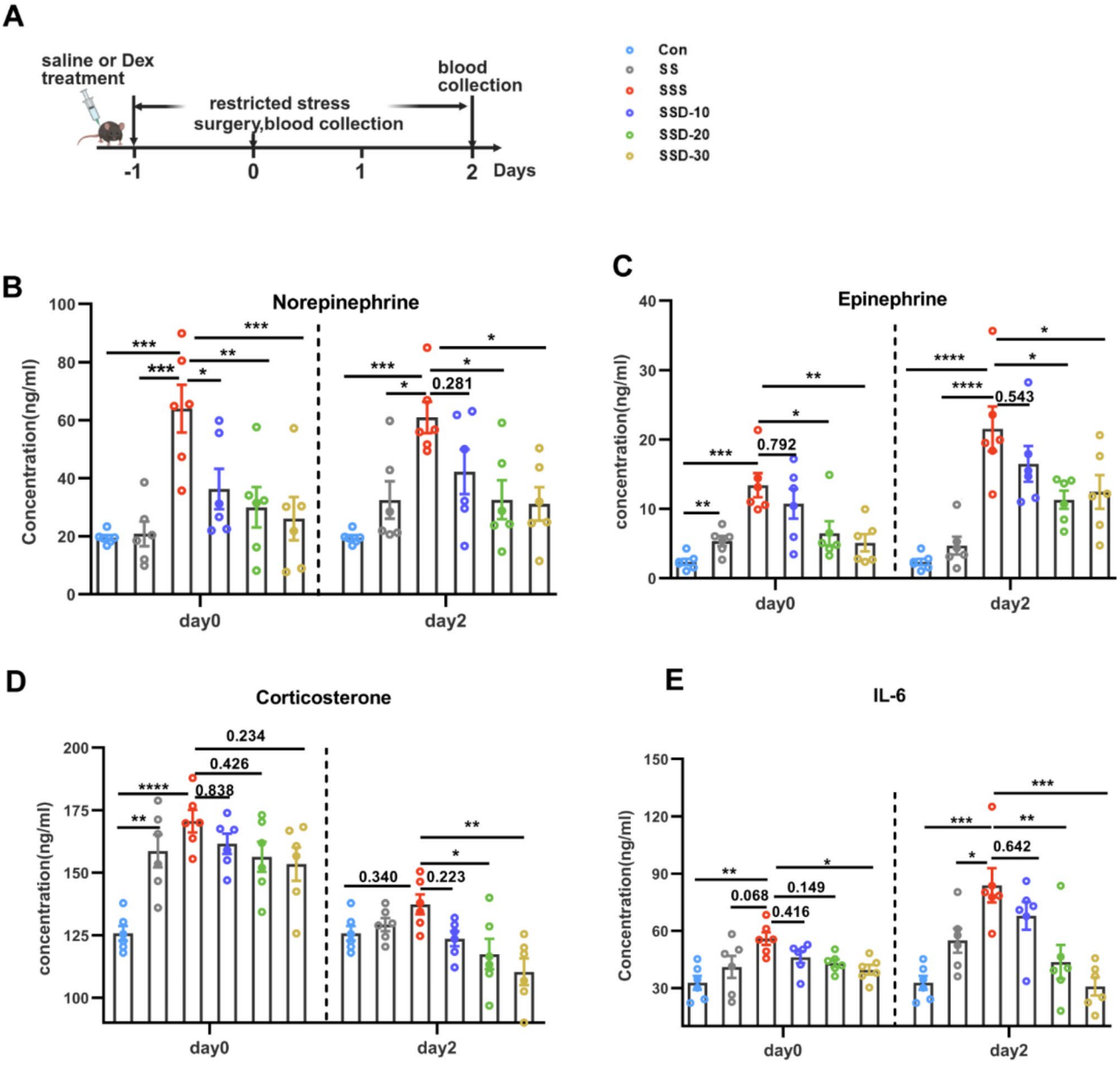

Fig. 2 Perioperative dexmedetomidine treatment limited the stress response in tumor-bearing mice. (**A**) Time schedule for restraint stress, surgery, and blood collection. (**B-E**) Concentrations of norepinephrine, epinephrine, corticosterone, and interleukin-6 (IL-6) in peripheral blood on days 0 and 2 after surgery ($n=6$ per group). Data are expressed as mean ± SEM; *$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$; one-way ANOVA followed by Tukey's multiple comparisons test for comparison. Con, normal control group; SS, mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and intraperitoneally injected with 100 μl of saline three times a day; SSS, mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 100 μl saline from day 1 before surgery to day 2 after surgery; SSD-10 or SSD-20 or SSD-30,mice intraperitoneally injected with 100 μl of 1×10^5 ID8-Luc cells after subcutaneous tumor resection and administered restraint stress 30 min after intraperitoneal injection of 10 or 20 or 30 μg kg^{-1} dexmedetomidine from day 1 before surgery to day 2 after surgery

manner. Perioperative dexmedetomidine limited tumor cell growth by alleviating the stress response rather than directly acting on tumor cells. These data are consistent with a recent preclinical study that reported the significant antitumor effects of alpha-2 adrenoceptor activation in an immune-dependent manner [23], and a previous retrospective study of 55 patients undergoing laparoscopic colorectal resection. Patients treated with dexmedetomidine showed a trend toward increased overall and disease-free survival: 1-year overall survival, 96.4% vs. 88.9%; 2-year overall survival, 89.3% vs. 74.1%; 3-year overall survival, 89.3% vs. 70.4%; and 5-year overall survival, 78.6% vs. 59.3% [27]. In addition, in 620 older patients with major noncardiac surgery mainly for

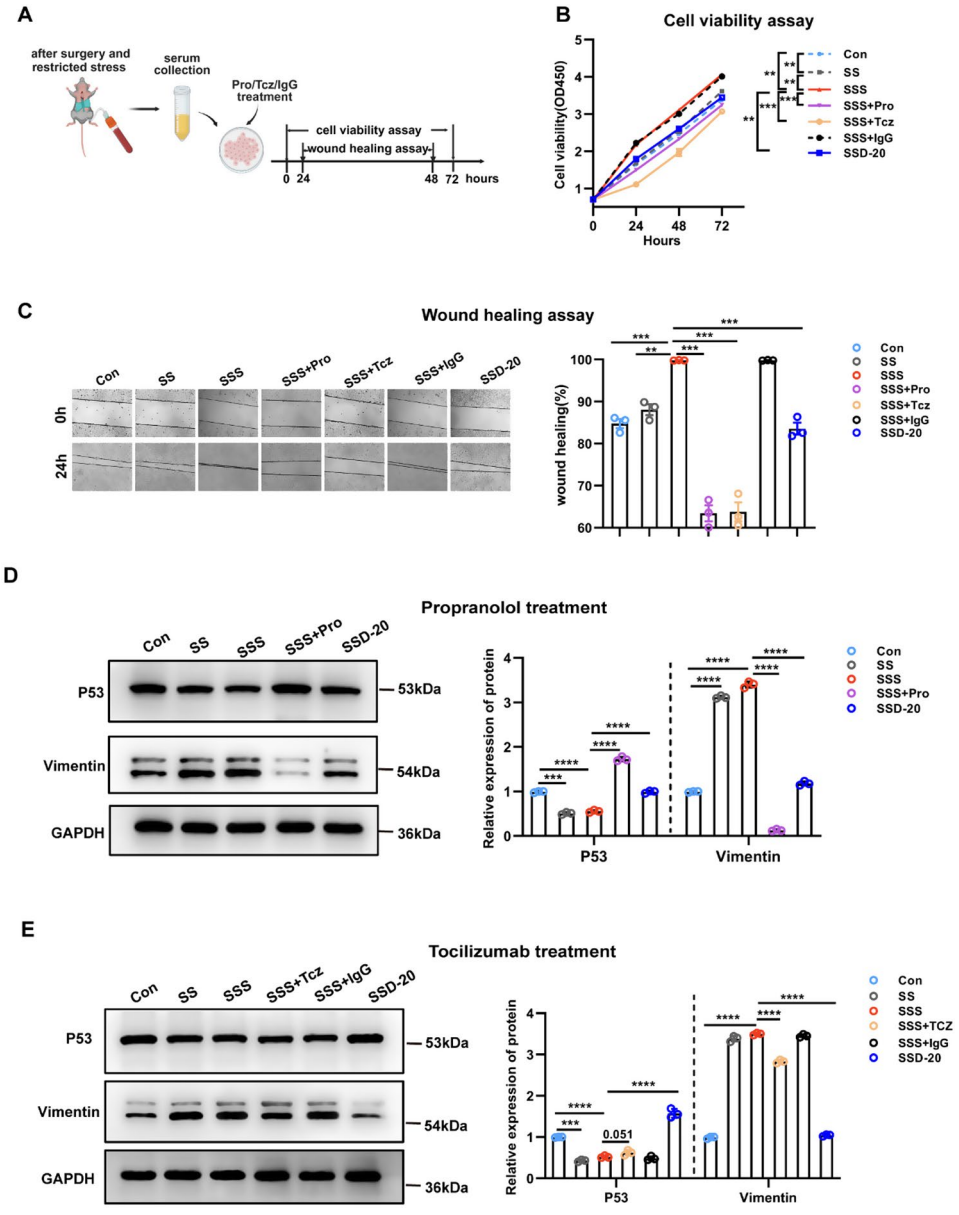

Fig. 3 Perioperative dexmedetomidine limited the growth of cultured tumor cells by alleviating the stress response. (**A**)Time schedule for serum collection on day 0 after surgery, beta-receptor blocker propranolol treatment (Pro), IL-6 antibody tocilizumab (TCZ), IL-6 antibody isotype control antibody IgG treatment, cell viability assay, and wound-healing assay. (**B**) Cell viability assay of day 0 serum-treated ID8 cells. (**C**) Representative images and quantification of wound-healing assay for ID8 cells treated with day 0 serum. (**D**) Western blot and corresponding quantification of tumor suppressor p53 and migration-related protein vimentin for cultured ID8 cells with or without propranolol treatment (Full-length blots/gels are presented in Supplementary Fig. 1A). (**E**) Western blot and corresponding quantification of tumor suppressor p53 and migration-related protein vimentin for cultured ID8 cells with or without tocilizumab treatment(Full-length blots/gels are presented in Supplementary Fig. 1B). Data are expressed as mean ± SEM ($n = 5$ per group for CCK8 assay and $n = 3$ per group for wound healing assay and WB); *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$, ****$P < 0{\cdot}0001$; one- way ANOVA followed by Tukey's multiple comparisons test for comparison. Con, normal control group; SS, ID8 cells treated with 10% serum from SS group on day 0 after surgery; SSS, ID8 cells treated with 10% serum from SSS group on day 0 after surgery; SSS + Pro, ID8 cells treated with 10% serum from SSS group on day 0 after surgery and 1 μM propranolol; SSS + TCZ, ID8 cells treated with 10% serum from SSS group on day 0 after surgery and 200 μg ml^{-1} tocilizumab; SSS + IgG, ID8 cells treated with 10% serum from SSS group on day 0 after surgery and 200 μg ml^{-1} IgG; SSD-20, ID8 cells treated with 10% serum from SSD-20 group on day 0 after surgery

cancer, intraoperative dexmedetomidine improved the recurrence-free and event-free survivals [28]. The protective effects of dexmedetomidine on brain, kidney, lung, and intestinal function during the perioperative period have been widely reported [4, 20, 29]. This information suggests that dexmedetomidine may be a simple, effective, and safe strategy for limiting the effects of the IPP on the postoperative recurrence/metastasis of abdominal

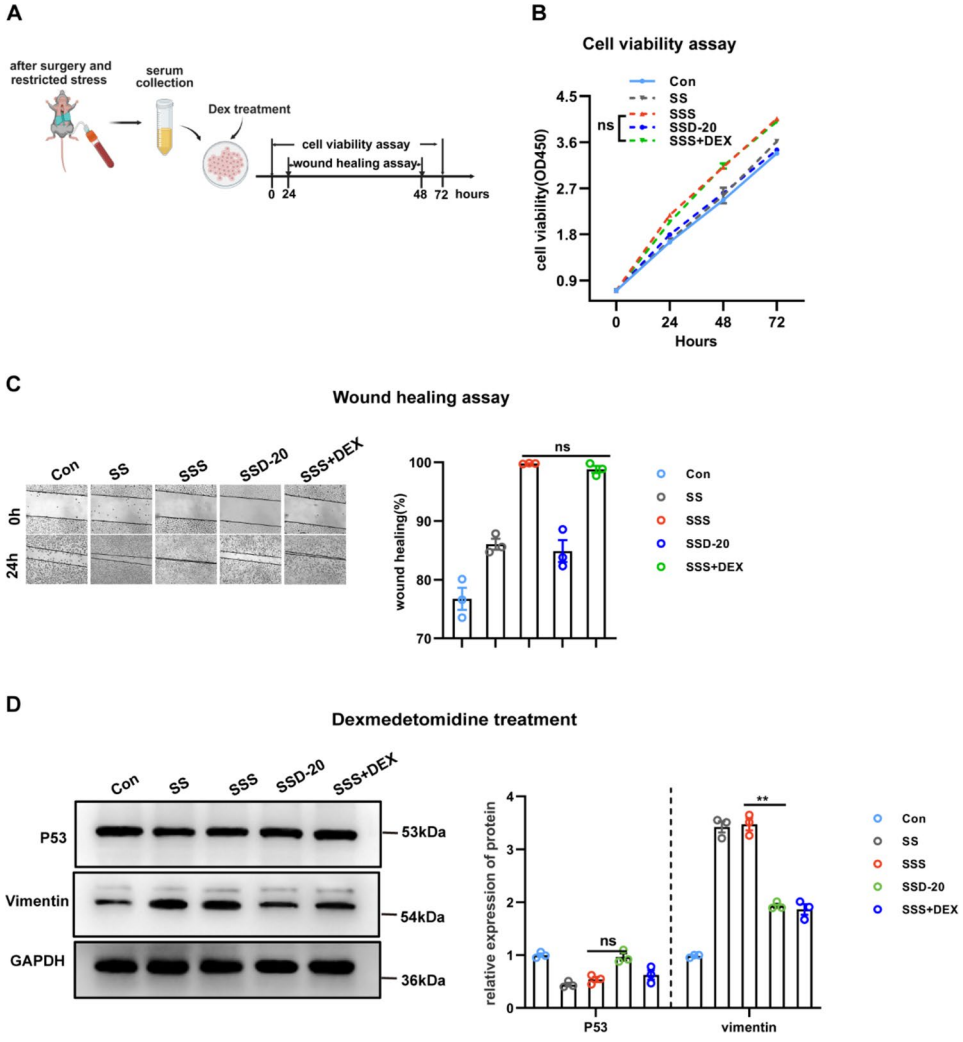

Fig. 4 Perioperative dexmedetomidine limited tumor cell growth not by directly acting on tumor cells. (**A**)Time schedule for serum collection on day 0 after surgery, dexmedetomidine treatment (Dex), cell viability assay, and wound-healing assay. (**B**) Cell viability assay of day 0 serum-treated ID8 cells (**C**) Representative images and quantification of wound-healing assay for ID8 cells treated with day 0 serum. (**D**) Western blot and corresponding quantification of tumor suppressor p53 and migration-related protein vimentin for cultured ID8 cells with or without Dexmedetomidine supplement(Full-length blots/gels are presented in Supplementary Fig. 1B). Data are expressed as mean ± SEM ($n = 5$ per group for CCK8 assay and $n = 3$ per group for wound healing assay and WB); $^{*}P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$; one- way ANOVA followed by Tukey's multiple comparisons test for comparison. Con, normal control group; SS, ID8 cells treated with 10% serum from SS group on day 0 after surgery; SSS, ID8 cells treated with 10% serum from SSS group on day 0 after surgery; SSD-20, ID8 cells treated with 10% serum from SSD-20 group on day 0 after surgery, SSS + Dex, ID8 cells treated with 10% serum from SSS group on day 0 after surgery and 0.1 μM dexmedetomidine

tumors. A prospective clinical study is warranted to evaluate the true situation.

During the immediate perioperative period (IPP), many perioperative factors may affect the recurrence/metastasis of tumors, including stress and medical treatments. These factors can over-activate the stress response system, inducing immunosuppression and changing the biological characteristics of residual tumor cells. The alpha-2 adrenoceptor is the highly selective dexmedetomidine receptor widely expressed in immune cells and the nervous system [23]. By activating the alpha-2 adrenoceptor, dexmedetomidine can modulate the number and function of immune cells and the levels of stress hormones and inflammatory factors in patients undergoing surgery [30–32] and in animals with surgical and restraint stress [33]. In our study, the levels of stress hormones (e.g., epinephrine, norepinephrine, and corticosterone) and inflammatory factor (interleukin-6 [IL-6]) in peripheral blood increased after surgery. Serum from mice without perioperative dexmedetomidine treatment promoted the growth of cultured tumor cells, which was alleviated by the addition of the beta-receptor blocker propranolol or IL-6 antibody tocilizumab [34]. These results showed an important role for stress hormones and IL-6 in promoting tumor growth during the perioperative period. In line with these findings, serum from mice with perioperative

dexmedetomidine treatment had weaker effects on tumor growth promotion and lower levels of stress hormones and IL-6, relative to serum from mice without perioperative dexmedetomidine treatment. Dexmedetomidine supplementation during culture had no significant effect on cultured tumor cells. This finding is consistent with a recent study, which reported that alpha-2 adrenoceptor agonists exerted antitumor effects by upregulating the innate and adaptive immune response pathways of macrophages and T cells, rather than directly targeting tumor cells [23]. Previous studies have shown that dexmedetomidine can act on DC cells, NK cells, neutrophils, monocytes, and T cells, and affect the release of pro-inflammatory cytokines and anti-inflammatory cytokines [4]. Taken together, the attenuation of the perioperative stress response may be an important mechanism for dexmedetomidine to limit the IPP's effects on postoperative recurrence/metastasis of tumors. Adrenergic receptors are a class of G-protein-coupled receptors [23]. Activating β-adrenergic receptors can increase adenylate cyclase activity and cyclic AMP (cAMP) levels through Gs, resulting in activation of protein kinase A (PKA) and downstream transcription factors. Activating α2-adrenergic receptors can inhibit adenylate cyclase through Gi, and modulate cAMP and PKA [23]. Thus, adenylate cyclase and its downstream molecules cAMP and PKA maybe contribute to anti-tumor of dexmedetomidine during perioperative period. The real mechanisms need further study.

During the IPP, patients are usually highly stressed because of their concerns about the disease and its subsequent treatment, as well as physiological responses to surgery and anesthesia [9–12]. Psycho-physiological interventions are commonly recommended for psychological perioperative stress management and prevention of postoperative recurrence/metastasis of tumors in patients [17, 18]. However, the effectiveness of these interventions depends on long intervention time and has significant inter-individual difference, which limits their use during IPP [18]. In this study, we found that dexmedetomidine supplement significantly alleviated stress response. In addition, dexmedetomidine is water-soluble and effective for all individuals. Nasal inhalation of dexamethasone is available today. It is recommended for an alternative approach of psycho-physiological intervention during IPP.

This study detected the pro-tumor activity of perioperative stress and the anti-stress of dexmedetomidine only in a pre-clinical tumor model. Other pre-clinical tumor model studies and a prospective clinical study are warranted to evaluate the true situation. The mechanisms underlying the dexmedetomidine's anti-tumor by limiting perioperative stress remains elusive, although dexmedetomidine decreased the levels of stress-related factors and blocking the downstream signaling of stress-related factors partly mimicked the anti-tumor effects of dexmedetomidine.

Conclusions

In conclusion, we demonstrated that dexmedetomidine treatment during the IPP alleviates the pro-tumor activity of perioperative stress in tumor-bearing mice. Dexmedetomidine may be recommended to limit the effects of the IPP on the postoperative recurrence/metastasis of tumors as an alternative approach of psycho-physiological intervention.

Limitations of the study

This study detected the pro-tumor activity of perioperative stress and the anti-stress of dexmedetomidine only in a pre-clinical tumor model. Other pre-clinical tumor model studies and a prospective clinical study are warranted to evaluate the true situation. The mechanisms underlying the dexmedetomidine's anti-tumor by limiting perioperative stress remains elusive, although dexmedetomidine decreased the levels of stress-related factors and blocking the downstream signaling of stress-related factors partly mimicked the anti-tumor effects of dexmedetomidine.

Abbreviations

IPP the immediate perioperative period
DEX dexmedetomidine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03665-w.

Supplementary Material 1

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Author contributions

Study design and data analysis: JB Tong, YZ Tang, SQ Xu. Project administration: SQ Xu, YZ Tang, JB Tong. Writing: SQ Xu, JB Tong. Revising manuscript: all authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study and included experimental procedures were approved by the institutional animal care and use committee of Central South university (approval no. CSU-2022-0086). All animal housing and experiments were conducted in strict accordance with the institutional guidelines for care and use of laboratory animals.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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