Cancer Surgery
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ABSTRACTS

Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity.

Ben Eliyahu S, Page GG, Yirmiya R, et al.

Int J Cancer. 1999 Mar 15; 80(6):880-8.

Stress and surgery have been suggested to compromise host resistance to infectious and malignant diseases in experimental and clinical settings. Because stress affects numerous physiological systems, the role of the immune system in mediating such effects is unclear. In the current study, we assessed the degree to which stress-induced alterations in natural killer (NK) cell activity underlie increased susceptibility to tumor development in F344 rats. Two stress paradigms were used: forced swim and abdominal surgery. Host resistance to tumor development was studied using 3 tumor models syngeneic to inbred F344 rats: CRNK-16 leukemia and the MADB106 mammary adenocarcinoma, both sensitive to NK activity, and the NK-insensitive C4047 colon cancer. Swim stress increased CRNK-16-associated mortality and metastatic development of MADB106 but not metastasis of C4047 cells. In both stress paradigms, stress suppressed NK activity (NKA) for a duration that paralleled its metastasis-enhancing effects on the MADB106 tumor. In vivo depletion of large granular lymphocyte/NK cells abolished the metastasis-enhancing effects of swim stress but not of surgical stress. Our findings indicate that stress-induced suppression of NKA is sufficient to cause enhanced tumor development. Under certain stressful conditions, suppression of NKA is the primary mediator of the tumor-enhancing effects of stress, while under other conditions, additional factors play a significant role. Clinical circumstances in which surgical stress may induce enhanced metastatic growth are discussed

Echinacea purpurea and melatonin augment natural-killer cells in leukemic mice and prolong life span.

Currier NL, Miller SC.

J Altern Complement Med. 2001 Jun; 7(3):241-51.

OBJECTIVE: We recently showed that daily dietary administration of Echinacea purpurea root extract to normal mice for as little as 1 week resulted in significant elevations of natural-killer (NK) cells (immune cells that are cytolytic to virus-containing cells and many tumor cells). Such boosting of this fundamental immune cell population suggests a prophylactic role for this herb in normal animals. Based on this evidence, our goal in the present work was to assess the role of dietary administration of this herbal extract to mice bearing leukemia, a type of tumor well known to be a target for NK cells. DESIGN: A commercially available root extract of E. purpurea, which we have already shown to be highly effective in mice, was administered daily for 50 days from the onset of leukemia (day 0). Control leukemic mice received no extract. Other leukemic mice received the NK-enhancing neurohormone, melatonin, administered precisely as above. In all treatment and control categories, some mice were sampled at 9 days after tumor onset, others were sampled at 3 months, and still others were left to assess treatment effect on life span. RESULTS: At 9 days (intermediate stage leukemia; death beginning by day 17-18), E. purpurea-treated mice had a 2.5-fold increase in the absolute numbers of NK cells in their spleens. By 3 months after leukemia onset, E. purpurea-treated mice still had 2-3 times the normal numbers of NK cells in their spleens. No leukemic, untreated (control) mice remained alive at 3 months, hence the comparison with normal animals. Moreover, at 3 months post-tumor onset, all the major hemopoietic and immune cell lineages in their bone marrow birth site, were recorded at normal numbers, in E. purpurea-consuming, leukemic mice. The survival advantage provided by administering these leukemic mice with E. purpurea was highly significant versus untreated, leukemic mice when analyzed by Kaplan-Meier survival statistics. CONCLUSION: The present study has provided the first systematic analysis, under controlled laboratory conditions, of the effect(s) of the botanical, E. purpurea, in vivo, in leukemic hosts. The profoundly positive effects of this herb in disease abatement observed in this study suggest the therapeutic potential of E. purpurea, at least with respect to leukemia, if not other tumors as well

Ipsilateral breast tumor recurrence following breast-conserving surgery for early-stage invasive cancer.

Fowble B.

Acta Oncol. 1999; 38 Suppl 13:9-17.

Ipsilateral breast tumor recurrence (IBTR) following conservative surgery and radiation for early stage invasive cancer occurs in approximately 15% of all patients at 10 years and is diminished with surgical excisions which achieve negative margins. Treatment strategies of breast-conserving surgery with or without radiation that result in IBTR rates of 30 40% will impact negatively on survival and the magnitude of this effect will be influenced by the predominant pattern of local failure as well as initial and subsequent distant metastases. Optimal local control in early-stage invasive breast cancer is important to minimize the risk of a salvage mastectomy and maximize the potential for long-term survival

Autologous tumor killing activity as a prognostic factor in primary resected nonsmall cell carcinoma of the lung.

Fujisawa T, Yamaguchi Y.

Cancer. 1997 Feb 1; 79(3):474-81.

BACKGROUND: Cytotoxic activity of peripheral blood lymphocytes obtained during surgery against autologous fresh tumor cells has been reported. However, the role of lymphocyte autologous tumor killing or natural killer activity during the postoperative period remains obscure. In this article, the authors describe the importance of postoperative autologous tumor killing activity as a prognostic factor in patients with primary resected nonsmall cell lung carcinoma (NSCLC) after long term follow-up. METHODS: Forty-two patients who had resection of NSCLC, with primary culture of autologous tumor cells taken successfully, were studied. Cytotoxic activity against autologous, allogenic NSCLC and K562 leukemia cells was examined using peripheral blood lymphocytes obtained during the 2 weeks immediately following surgery. Factors related to prognosis were analyzed by univariate and multivariate analyses. RESULTS: The overall 5- and 10-year survival rates for the NSCLC patients were 40.5% and 27.5%, respectively. Statistical analysis of survival curves revealed a significant difference with regard to T classification (P = 0.025), N classification (P = 0.0015), stage (P = 0.028), and postoperative autologous tumor killing activity (P = 0.0008); there were no significant differences in relation to age, gender, histology, differentiation, visceral pleural invasion, resectability, surgical method, allogeneic tumor killing activity, or natural killer activity. Multivariate analysis demonstrated a significant correlation between disease recurrence and N classification (P = 0.0003), T classification (P = 0.023), stage (P = 0.001), and autologous tumor killing activity (P = 0.007), indicating independent prognostic significance. The phenotypes of the effector cells involved in autologous tumor killing activity were CD3(+), CD4(-), CD8(+), and CD11b(-). Autologous tumor killing activity was inhibited by competing unlabeled autologous tumor cells. CONCLUSIONS: Autologous tumor killing activity during the 2 weeks immediately following surgery is an important prognostic factor in resected NSCLC

The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats.

Gaspani L, Bianchi M, Limiroli E, et al.

J Neuroimmunol. 2002 Aug; 129(1-2):18-24.

Surgery stress has been shown to be associated in rat with decreased natural killer (NK) cell activity and enhancement of tumor metastasis. We have previously shown that the analgesic drug tramadol stimulates NK activity both in the rodent and in the human. In the present study, we analyze, in the rat, tramadol ability to prevent the effect of experimental surgery on NK activity and on the enhancement of metastatic diffusion to the lung of the NK sensitive tumor model MADB106. The administration of tramadol (20 and 40 mg/kg) before and after laparatomy significantly blocked the enhancement of lung metastasis induced by surgery. In contrast, the administration of 10 mg/kg of morphine was not able to modify this enhancement. The modulation of NK activity seemed to play a central role in the effect of tramadol on MADB106 cells. In fact, both doses of tramadol were able to prevent surgery-induced NK activity suppression, while the drug significantly increased NK activity in normal non-operated animals. Morphine, that in normal rats significantly decreased NK cytotoxicity, did not prevent surgery-induced immunosuppression. The good analgesic efficacy of tramadol combined with its intrinsic immunostimulatory properties suggests that this analgesic drug can be particularly indicated in the control of peri-operative pain in cancer patients

Production of tumor necrosis factor-alpha and interferon-gamma from human peripheral blood lymphocytes by MGN-3, a modified arabinoxylan from rice bran, and its synergy with interleukin-2 in vitro.

Ghoneum M, Jewett A.

Cancer Detect Prev. 2000; 24(4):314-24.

Recently, we presented evidence for the role of MGN-3, an enzymatically modified arabinoxylan extracted from rice bran, in potent activation of human natural killer (NK) cell function in vivo and in vitro. In the current study, we examined the mechanism by which MGN-3 elevated NK cytotoxic activity. We did this by testing the action of MGN-3 on the levels of both tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) secretions and MGN-3 function on the expression of key cell surface receptors. Peripheral blood lymphocytes were treated with MGN-3 at concentrations of 0.1 mg/ml and 1 mg/ml, and

supernatants were subjected to enzyme-linked immunosorbent assay. Results showed that MGN-3 is a potent TNF-alpha inducer. The effect was dose-dependent. MGN-3 concentration at 0.1 and 1 mg/ml increased TNF-alpha production by 22.8- and 47. 1-fold, respectively. MGN-3 also increased production of IFN-gamma but at lower levels as compared to TNF-alpha With respect to key cell surface receptors, MGN-3 increases the expression of CD69, an early activation antigen at 16 hours after treatment. Furthermore, the interleukin-2 receptor CD25 and the adhesion molecule ICAM-1 (CD54) were upregulated after treatment with MGN-3. Treating highly purified NK cells with MGN-3 also resulted in increased levels of TNF-alpha and IFN-gamma secretion in conjunction with augmentation of NK cell cytotoxic function. Furthermore, addition of MGN-3 to interleukin-2-activated NK cells resulted in a synergistic induction of TNF-alpha and IFN-gamma secretion. Overall, our data suggest that MGN-3, a novel biological response modifier, can be used as a safe alternative or as an adjuvant to the existing immunotherapeutic modalities

Role of NK cells in the control of metastatic spread and growth of tumor cells in mice.

Gorelik E, Wiltrout RH, Okumura K, et al.

Int J Cancer. 1982 Jul 15; 30(1):107-12.

The ability of BALB/c nude and C57BL/6 mice to eliminate tumor cells from the blood stream was severely impaired after a single inoculation of 0.2 ml of anti-asialo BMI (asGMI) serum, diluted 1:40 to 1:320. The number of i.v.-inoculated YAC-I cells surviving in the lungs of BALB/c nude mice pretreated with anti-asGMI serum was 28 times higher than in the control nude mice. In this respect, nude mice treated with anti-asGMI behaved similarly to beige mice. The increase in the initial survival of tumor cells in the mice that was induced by pre-treatment with anti-asGMI resulted in a substantial increase in the number of artificial lung metastases that developed. In C57BL/6 +/+ mice treated with anti-asGMI and in C57BL/6 beige mice, i.v. inoculation of B16 melanoma cells induced 10 times more metastatic foci in the lungs than in the control C57BL/6 +/+ mice. In contrast, in nude mice which possess higher levels of NK reactivity, metastatic growth was suppressed 7-fold in comparison with intact C57BL/6 +/+ mice. In beige mice and in C57BL/6 +/+ mice treated with anti-asGMI, multiple metastatic foci developed in the liver, whereas in control C57BL/6 +/+ and nude mice, no extrapulmonary metastases were found. These data indicate that B16 melanoma cells are able to grow in the liver, but their growth is ordinarily prevented by NK cells. The antimetastatic defense of C57BL/6 mice treated by anti-asGMI could be restored by transplantation of 40 X 10(6) normal spleen cells. This antimetastatic effect of transplanted spleen cells was mediated by asGMI-bearing cells, since after in vitro pre-treatment of normal spleen cells with anti-asGMI and complement, they lost their ability to inhibit the development of artificial metastases in the lungs of C57BL/6 mice. Suppression of NK reactivity by multiple injections of anti-asGMI (every 4 to 5 days), in C57BL/6 mice inoculated intrafootpad (i.f.p.) with B16 melanoma or 3LL tumor cells, did not influence the growth of local tumors, but dramatically accelerated the development of spontaneous pulmonary metastases. These data demonstrate that NK cells may play an important role in resistance to the dissemination of tumor cells, and therefore contribute to the control of metastasis formation in mice

Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth.

Gupta K, Kshirsagar S, Chang L, et al.

Cancer Res. 2002 Aug 1; 62(15):4491-8.

Morphine is used to treat pain in several medical conditions including cancer. Here we show that morphine, in a concentration typical of that observed in patients' blood, stimulates human microvascular endothelial cell proliferation and angiogenesis in vitro and in vivo. It does so by activating mitogen-activated protein kinase/extracellular signal-regulated kinase phosphorylation via Gi/Go-coupled G protein receptors and nitric oxide in these microvascular endothelial cells. Other contributing effects of morphine include activation of the survival signal PKB/Akt, inhibition of apoptosis, and promotion of cell cycle progression by increasing cyclin D1. Consistent with these effects, morphine in clinically relevant doses promotes tumor neovascularization in a human breast tumor xenograft model in mice leading to increased tumor progression. These results indicate that clinical use of morphine could potentially be harmful in patients with angiogenesis-dependent cancers

The antitumoral effect of endostatin and angiostatin is associated with a down-regulation of vascular endothelial growth factor expression in tumor cells.

Hajitou A, Grignet C, Devy L, et al.

FASEB J. 2002 Nov; 16(13):1802-4.

Endostatin and angiostatin are known as tumor-derived angiogenesis inhibitors, but their mechanisms of action are not yet completely defined. We report here that endostatin and angiostatin, delivered by adenoviral vectors, reduced in vitro the

neovessel formation in the mouse aortic ring assay by 85 and 40%, respectively. We also demonstrated in vivo that both endostatin and angiostatin inhibited local invasion and tumor vascularization of transplanted murine malignant keratinocytes, and reduced by 50 and 90% the development of highly vascularized murine mammary tumors. This inhibition of tumor growth was associated with a reduction of tumor vascularization. Expression analysis of vascular endothelial growth factor (VEGF) carried out in the mouse aortic ring model revealed a 3- to 10-fold down-regulation of VEGF mRNA expression in endostatin-treated rings. A similar down-regulation of VEGF expression at both mRNA and protein levels was also observed in the two in vivo cancer models after treatment with each angiogenesis inhibitor. This suggests that endostatin and angiostatin effects may be mediated, at least in part, by their ability to down-regulate VEGF expression within the tumor. This work provides evidence that endostatin and angiostatin act on tumor cells themselves

The role of natural killer cells in the control of tumor growth and metastasis.

Hanna N.

Biochim Biophys Acta. 1985; 780(3):213-26.

Altered helper and suppressor lymphocyte populations in surgical patients. A measure of postoperative immunosuppression.

Hansbrough JF, Bender EM, Zapata-Sirvent R, et al.

Am J Surg. 1984 Sep; 148(3):303-7.

Although a wealth of evidence has suggested that cell-mediated immunity is suppressed after simple surgical trauma, there have been contradictory results using stimulation assays of lymphocyte function. We quantitated T-lymphocyte subsets in 11 patients undergoing routine cholecystectomy by immunofluorescence microscopy using specific monoclonal antibodies. T-helper to T-suppressor cell ratios were calculated on the preoperative day and the first postoperative day in all patients, and on the third or fourth postoperative day in five patients. Helper to suppressor ratios decreased in all patients on the first postoperative day (p greater than 0.01), but returned to within normal limits on subsequent days. Changes were due more to decreases in helper cells than to increases in suppressor cells, although changes in both populations were statistically significant. The measurement of T-cell subsets by antibody-specific labeling and immunofluorescence microscopy may prove to be a more sensitive, quantifiable, and reproducible assay of immune function in surgical or traumatized patients than use of stimulation assays. Measurements of specific helper and suppressor lymphocyte populations may prove useful in predicting morbidity and mortality, and may also help in studying the effect of immunomodulating agents on the immune response

Natural killer cells: their roles in defenses against disease.

Herberman RB, Ortaldo JR.

Science. 1981 Oct 2; 214(4516):24-30.

Natural killer cells are a recently discovered subpopulation of lymphoid cells that are present in most normal individuals of a range of mammalian and avian species. Natural killer cells have spontaneous cytolytic activity against a variety of tumor cells and some normal cells, and their reactivity can be rapidly augmented by interferon. They have characteristics distinct from other types of lymphoid cells and are closely associated with large granular lymphocytes, which comprise about 5 percent of blood or splenic leukocytes. There is increasing evidence that natural killer cells, with the ability to mediate natural resistance against tumors in vivo, certain virus and other microbial diseases, and bone marrow transplants, may play an important role in immune surveillance

Effect of melatonin and electroacupuncture (EA) on NK cell activity, interleukin-2 production and POMC-derived peptides in traumatic rats.

Huang YS, Jiang JW, Wu GC, et al.

Acupunct Electrother Res. 2002; 27(2):95-105.

The present study was to evaluate the effect of melatonin (MT) and EA on the cytotoxic activity of natural killer (NK) cells, the dynamic changes of the induction of interleukin-2(IL-2) and the content of POMC-derived peptides, beta-endorphins (betaE) and ACTH in spleen lymphocytes and in plasma of traumatic rats. The results showed that intraperitioneal (i.p.) injection of MT was able to recover the lower levels of NK cell activity and the induction of IL-2 production; MT could also decrease the higher betaE and ACTH levels induced by trauma in spleen lymphocytes and plasma. EA needling of Zusanli (St.36) and Lanwei (Extra.37) points obviously improved the immunosuppression produced by trauma and antagonized the elevation of betaE and ACTH

contents induced by trauma stress in spleen lymphocytes and plasma. MT + EA could further modulate the depressed immune function, and there was a significant difference compared with MT (i.p.) or EA alone. MT + EA group further decreased the betaE and ACTH contents in immune cells and plasma. Yet, the mechanisms of the attenuation of MT and EA on immunosuppression induced by trauma need further study

Preoperative natural killer cell activity: correlation with distant metastases in curatively research colorectal carcinomas.

Koda K, Saito N, Takiguchi N, et al.

Int Surg. 1997 Apr; 82(2):190-3.

The authors investigated whether host immunity contributes to the development of asynchronous distant metastases in colorectal carcinomas. The host immunity was examined 8 times, pre- and postoperatively during a one year period in 77 curatively operated cases. A prospective study was performed using obtained personal data. During the mean follow-up period of 920 days, 13 patients developed distant metastases. Among the immunological parameters, the preoperative natural killer (NK) cell activity differed significantly between the metastases positive and negative groups. On univariate analysis, dichotomous NK activity, presence of nodal metastases, and venous invasion correlated with metastases. The hazard ratios on multivariate analysis were 4.53, 3.82, and 4.81, respectively. No correlation was noted between NK activity and the progression stages of colorectal carcinomas. These data suggested that attenuated preoperative NK activity is an important background factor for the development of asynchronous distant metastases following curative resection of colorectal carcinomas

Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters.

Levy SM, Herberman RB, Maluish AM, et al.

Health Psychol. 1985; 4(2):99-113.

Although findings from recent animal studies suggest that behavioral factors such as "helplessness" play a role in cancer progression, very few such studies with humans have been carried out. The study investigated the predictive power of an immunologic effector cell, the natural killer (NK) cell, as well as selected psychological and demographic factors, to breast cancer prognostic risk status. It was found that NK activity predicted the status of cancer spread to the axillary lymph nodes. Patients who had low levels of NK activity were rated as well-adjusted to their illness; patients who had higher NK activity appeared to be distressed or maladjusted. These findings are discussed in the light of recent animal findings linking environmental stress and behavioral responsiveness to biological vulnerability via endocrine and immune pathways

Binding of opioids to human MCF-7 breast cancer cells and their effects on growth.

Maneckjee R, Biswas R, Vonderhaar BK.

Cancer Res. 1990 Apr 15; 50(8):2234-8.

The well characterized human breast cancer cell line, MCF-7, has been shown to possess membrane receptors for various opioid ligands, and these compounds have been shown to modulate the growth of the cells in culture. Using specific radioligands for the receptor types, we were able to demonstrate that the MCF-7 cells possess multiple opioid receptor types. Relatively high-affinity-binding sites are present for the mu- and kappa-specific ligands, while lower affinity sites are present for the delta-agonist. Opioid ligands specific for the different receptor types significantly inhibited the growth of the MCF-7 cells in a dose-dependent manner when grown in the presence of 10% fetal bovine serum. This inhibitory effect was reversed by the simultaneous administration of the opioid receptor antagonist, naloxone. However, the opioid effect appears to be restricted to the hormonally responsive fraction of the MCF-7 cell growth. Cells grown in the presence of charcoal-stripped fetal bovine serum are refractory to the effects of the opioids unless the media is supplemented with estradiol. The data presented here suggest an important regulatory role for opioids in the growth and development of human breast cancers

Analysis of local recurrence rates after surgery alone for rectal cancer.

McCall JL, Cox MR, Wattchow DA.

Int J Colorectal Dis. 1995; 10(3):126-32.

Local recurrence (LR) continues to be a major problem following surgical treatment for rectal cancer, and proposed ways of reducing this remain controversial. The aim of this study was to review results from published surgical series in which adjuvant therapies were not used. A Medline search identified series published between January 1982 and December 1992 with follow-up

on at least 50 patients with rectal cancer treated surgically for cure, without adjuvant therapy. Fifty one papers reported follow-up on 10,465 patients with a median LR rate of 18.5%. LR was 8.5%, 16.3% and 28.6% in Dukes' A, B and C patients respectively, 16.2% following anterior resection and 19.3% following abdominoperineal resection. Nine papers (1,176 patients) reported LR rates of 10% or less. LR was 7.1% in 1,033 patients having total mesorectal excision and 12.4% in 476 patients having extended pelvic lymphadenectomy. Routine cytocidal stump washout in 1,364 patients was associated with 12.2% LR, however a higher proportion (41%) also underwent total mesorectal excision. In 52% of cases, LR was reported to have occurred with no evidence of disseminated disease. Surgical technique is an important determinant of LR risk. LR rates of 10% or less can be achieved with surgery alone in expert hands

Symposium on rectal cancer: 2. Local recurrence after surgery for rectal cancer.

McLeod RS.

Can J Surg. 1997 Oct; 40(5):353-7.

Local recurrence is a serious complication in patients with rectal cancer because of the frequency with which it occurs, its impact on quality of life and the fact that treatment is rarely successful. Although local recurrence rates varying from 4% to 51% have been reported, recent series have reported rates of less than 10%. Various factors may affect the rate of local recurrence, including the stage and location of the tumour. Other prognostic factors may be of importance, but it is controversial whether they are independent risk factors. Finally, there is mounting evidence that the local recurrence rate varies with the surgeon. Whether this is due to the surgical technique or surgical expertise is not clear, but randomized controlled trials addressing the issue of extent of resection are indicated in order to optimize surgical results

Endostatin: an endogenous inhibitor of angiogenesis and tumor growth.

O'Reilly MS, Boehm T, Shing Y, et al.

Cell. 1997 Jan 24; 88(2):277-85.

We previously identified the angiogenesis inhibitor angiostatin. Using a similar strategy, we have identified endostatin, an angiogenesis inhibitor produced by hemangioendothelioma. Endostatin is a 20 kDa C-terminal fragment of collagen XVIII. Endostatin specifically inhibits endothelial proliferation and potently inhibits angiogenesis and tumor growth. By a novel method of sustained release, E. coli-derived endostatin was administered as a nonrefolded suspension. Primary tumors were regressed to dormant microscopic lesions. Immunohistochemistry revealed blocked angiogenesis accompanied by high proliferation balanced by apoptosis in tumor cells. There was no toxicity. Together with angiostatin data, these findings validate a strategy for identifying endogenous angiogenesis inhibitors, suggest a theme of fragments of proteins as angiogenesis inhibitors, and demonstrate dormancy therapy

Prebiopsy neo-adjuvant endocrine therapy for breast cancer to prevent post-surgery trauma-induced growth factor and immune-suppression mediated tumour progression.

Oliver RT, Tobias J, Gallagher C.

Eur J Cancer. 1996 Mar; 32A(3):396-7.

The role of LGL/NK cells in surgery-induced promotion of metastasis and its attenuation by morphine.

Page GG, Ben Eliyahu S, Liebeskind JC.

Brain Behav Immun. 1994 Sep; 8(3):241-50.

Painful stress such as surgery has been shown both to suppress immune function and to promote metastasis, although the degree to which alterations in immunity underlies the tumor-enhancing effects of surgery remains unclear. We recently reported that an experimental laparotomy results in a twofold increase in the number of lung metastases following iv injection of MADB106 tumor cells, a natural killer (NK)-sensitive mammary adenocarcinoma cell line, syngeneic to the Fischer 344 rats we studied. Further, the administration of an analgesic dose of morphine prevented these metastatic-enhancing effects of surgery. The aim of the present study was to investigate the role of NK cells in both the metastatic-enhancing effects of surgery and the attenuation of these effects by morphine. Using a simple 2 x 2 experimental design (surgery with anesthesia vs anesthesia only, and morphine vs vehicle), we found that surgery resulted in a decrease in both whole blood NK cytotoxic activity and number of circulating LGL/NK cells assessed 4 h postoperatively. In a second experiment involving an 18-h lung clearance assay, we used the mAb 3.2.3 to deplete rats of LGL/NK cells with the following rationale: if LGL/NK cells are necessary to mediate an event,

then in their absence, that event should not occur. Normal and LGL/NK-depleted animals were assigned to the same four experimental groups, and radiolabeled MADB106 tumor cells were injected iv 4 h after surgery. In normal animals, there was a significant interaction between surgery and morphine such that morphine attenuated the surgery-induced increase in tumor cell retention without affecting tumor cell retention in the anesthesia groups. In the LGL/NK-depleted animals, however, although the tumor-enhancing effects of surgery remained evident, morphine did not mitigate this outcome. These results suggest that: (a) both LGL/NK cell activity and other factors independent of LGL/NK cells play a role in the surgery-induced increase in tumor cell retention; and (b) LGL/NK cells play a critical role in morphine's attenuating effects on this outcome. Finally, these results reinforce concern about the pathogenic consequences of unrelieved pain

The development of sexual dimorphism in natural killer cell activity and resistance to tumor metastasis in the Fischer 344 rat.

Page GG, Ben Eliyahu S, Taylor AN.

J Neuroimmunol. 1995 Dec; 63(1):69-77.

The development of sexual dimorphism in the number and activity level of natural killer (NK) cells was studied in the inbred Fischer 344 rat from prepubescence to maturity. Additionally, in view of the biological significance of NK cells in controlling cancer, especially the metastatic process, we used a syngeneic mammary tumor (MADB106) to assess the host anti-metastatic activity. This tumor model was used because NK cells control the lung clearance of i.v.-injected MADB106 tumor cells, a process that critically affects the metastatic colonization of these tumor cells in the lungs. The results indicated that although prepubescent (36 days of age) males and females exhibited greater NK cytotoxicity (assessed in vitro) and higher anti-metastatic activity, evidenced by fewer tumor cells retained in the lungs. On the other hand, the mature males (140-170 days of age) displayed greater LGL/NK number and activity per ml blood, retained fewer tumor cells, and developed fewer lung tumor colonies compared to the females. During early postpubescence (63 days of age), a transitional stage between prepubescence and maturity, females and males exhibited equivalent numbers of circulating LGL/NK cells, and females displayed slightly greater NK cytotoxicity per ml blood yet retained somewhat greater numbers of tumor cells compared to the males. Overall, whereas the males exhibited increasing levels of NK number and activity throughout the age span tested, the females, despite displaying greater NK function compared to the males at prepubescence and slight improvement at postpubescence, fell behind the males in these indices of NK function at maturity

Mechanism of surgical stress impairment of human perioperative natural killer cell cytotoxicity.

Pollock RE, Lotzova E, Stanford SD.

Arch Surg. 1991 Mar; 126(3):338-42.

Natural killer (NK) cells are an important defense against intravascular tumor dissemination. Tumor embolization can occur at surgery, so we tested whether surgical stress decreased perioperative NK cell cytotoxicity, and examined the underlying mechanism of suppression. Patients with solid tumors underwent NK cell cytotoxicity assay just before and 24 hours after surgery in a 3-hour chromium 51 release assay. The NK cell cytotoxicity was significantly decreased postoperatively. We considered that surgical NK cell impairment might be due to (1) NK cell redistribution, (2) presence of suppressor cells, or (3) direct "toxic" effects on NK cells. Impaired NK cell cytotoxicity was not due to NK cell redistribution, because differential counts showed no significant changes in the percentage of large granular lymphocyte NK morphology. To isolate possible suppressor cells, postoperative cells from patients were selectively depleted of NK cells using anti-Leu-11b monoclonal antibody plus complement; these cells were then mixed with autologous preoperative cells. Postoperative NK cell cytotoxicity was markedly impaired, but the postoperative NK depleted cells did not suppress preoperative NK cells. We conclude that NK cell functional impairment from surgical stress is due to direct "toxic" effects on NK cells rather than either NK cell redistribution or the generation of NK-directed suppressor cells

Evidence for the role of natural immunity in the control of metastatic spread of head and neck cancer.

Schantz SP, Brown BW, Lira E, et al.

Cancer Immunol Immunother. 1987; 25(2):141-8.

Deficient natural killer (NK) cell activity may contribute to the development of distant metastases in the head and neck cancer patient. A total of 246 previously untreated patients expressed deficient NK activity against K562 target cells when compared to 110 age-matched healthy controls (70 +/- 48 lytic units (LU) versus 95 +/- 52 LU) (P less than 0.001). Some 164 consecutive patients have undergone definitive therapy subsequent to NK cell assessment and have been followed for a minimum of 12 months (median = 16 months), and 23 have developed recurrent disease in distant sites. The risk of subsequently (1) developing distant metastases, (2) developing regional metastases, and (3) dying of progressive cancer was inversely related to pretreatment NK LU values (P less than 0.02, less than 0.02, less than 0.005, respectively, by the Cox proportional hazards

model). NK cell function within the peripheral blood of the patient with head and neck cancer could be related to the percentage of Leu 11+ NK cell subsets (P less than 0.01 by linear regression analysis) as determined by both single-parameter and multiparameter flow cytometric assessment. Contrastingly, no relationship could be identified between NK function with the percentage of circulating Leu 7+ cell subsets. In vitro measured NK cell function identifies a population at increased risk for developing distant metastases, thus supporting the role of natural immunity as defense mechanism against blood-borne disease

The prognostic significance of natural killer cytotoxicity in patients with colorectal cancer.

Tartter PI, Steinberg B, Barron DM, et al.

Arch Surg. 1987 Nov; 122(11):1264-8.

We evaluate the prognostic significance of preoperative natural killer (NK) cytotoxicity for K562 cells and its relationship to other prognostic factors in 102 patients with colorectal cancer who underwent curative resections between February 1984 and February 1985. The 18 patients who had recurrences within two years of surgery had significantly higher numbers of preoperative peripheral blood suppressor/cytotoxic and NK cells and significantly lower preoperative NK cytotoxicity than disease-free patients. Low preoperative NK cytotoxicity was predictive of recurrence independent of age, sex, hematocrit, procedure, blood loss, duration of surgery, Dukes' stage, specimen length, tumor size, tumor differentiation, and post-operative therapy. Low levels of in vitro NK-cell cytotoxicity may identify a subgroup of patients at high risk for recurrence

Phase I pharmacokinetic and pharmacodynamic study of recombinant human endostatin in patients with advanced solid tumors.

Thomas JP, Arzoomanian RZ, Alberti D, et al.

J Clin Oncol. 2003 Jan 15; 21(2):223-31.

PURPOSE: Endostatin is the first endogenous angiogenesis inhibitor to enter clinical trials. Laboratory investigations with endostatin have indicated broad antitumor activity coupled with remarkably low toxicity. A phase I trial of recombinant human endostatin was designed to evaluate toxicity and explore biologic effectiveness in patients with refractory solid tumors. PATIENTS AND METHODS: Endostatin was administered as a 1-hour intravenous infusion given daily for a 28-day cycle. A starting dose of 30 mg/m2 was explored with subsequent dose escalations of 60, 100, 150, 225, and 300 mg/m2. Assessment of serum pharmacokinetics was performed on all 21 patients. Western blot assay and mass spectroscopy were employed to evaluate endostatin metabolism. Circulating levels of endogenous proangiogenic growth factors were examined. Tumor and tumor blood supply were imaged by dynamic computed tomography (CT), magnetic resonance imaging, ultrasound, and positron emission tomography. RESULTS: Endostatin given on this schedule was essentially free of significant drug-related toxicity. Two transient episodes of grade 1 rash were observed. No clinical responses were observed. Endostatin pharmacokinetics were linear with dose, and serum concentrations were achieved that are associated with antitumor activity in preclinical models. No aggregate effect on circulating proangiogenic growth factors were seen, although several patients exhibited persistent declines in vascular endothelial growth factor levels while enrolled in the study. A few patients demonstrated changes in their dynamic CT scans suggestive of a decline in microvessel density, although overall, no consistent effect of endostatin on tumor vasculature was seen. CONCLUSION: Endostatin given daily as a 1-hour intravenous infusion was well tolerated without dose-limiting toxicity at doses up to 300 mg/m2

Port-site recurrence following laparoscopic surgery in cervical cancer.

Tjalma WA, Winter-Roach BA, Rowlands P, et al.

Int J Gynecol Cancer. 2001 Sep; 11(5):409-12.

Port-site metastasis (PSM) after laparoscopic lymphadenectomy in cervical cancer is a new phenomenon. This situation creates potential therapeutic difficulties, especially in node-negative and early stages of disease. We report a case of port-site metastases following laparoscopic removal of para-aortic lymph nodes in a 74-year-old women with stage IIIb squamous cancer of the cervix, together with an update of all the previous published cases in the literature. None of the removed lymph nodes showed evidence of metastatic carcinoma. The patient received radiation therapy and a complete response was accomplished. Fifteen months after the operation, the patient presented with a suspicious lesion around the umbilical port-site. The lesion was excised and histology confirmed metastatic disease. The patient was further treated with cisplatin. However, she died of her disease after 24 months. The development of a port-site recurrence after laparoscopic surgery in cervical cancer could jeopardize use of this approach. Therefore, all patients undergoing laparoscopic surgery for malignancies should have careful follow-up with special attention to the port sites

Cancer prevention by bovine lactoferrin and underlying mechanisms--a review of experimental and clinical studies.

Tsuda H, Sekine K, Fujita K, et al.

Biochem Cell Biol. 2002; 80(1):131-6.

In experimental studies, bovine lactoferrin (bLF) has been found to significantly inhibit colon, esophagus, lung, and bladder carcinogenesis in rats when administered orally in the post-initiation stage. Furthermore, concomitant administration with carcinogens resulted in inhibition of colon carcinogenesis, possibly by suppression of phase I enzymes, such as cytochrome P450 1A2 (CYP1A2), which is preferentially induced by carcinogenic heterocyclic amines. Enhancement of the activities of their phase II counterparts, such as glutathione S-transferase might have also played a critical role in post-initiation suppression in a study of tongue carcinogenesis. Anti-metastatic effects were moreover detected when bLF was given intragastrically to mice bearing highly metastatic colon carcinoma 26 cells (Co 26Lu), with apparent enhancing influence on local and systemic immunity. Marked increase in the number of cytotoxic T and NK cells in the mucosal layer of the small intestine and peripheral blood cells was thus found, this in turn enhancing the production of Interleukin 18 (IL-18) and caspase-1 in the epithelial cells of the small intestine, with possible consequent induction of interferon (IFN)-gamma positive cells. Furthermore, bLF has been found to exert anti-hepatitis C virus (HCV) activity in a preliminary clinical trial in patients with chronic active hepatitis due to this virus, a main causative factor in hepatocellular carcinoma development in Japanese. More extensive clinical trials are now underway in the National Cancer Center Hospital and other institutes to further explore the preventive potential against colon carcinogenesis

Molecular response to surgical stress: specific and simultaneous heat shock protein induction in the adrenal cortex, aorta, and vena cava.

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Surgery. 1991 Dec; 110(6):1125-31.

The endocrine response to surgical stress results in activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. The cellular response to a wide variety of stresses results in the synthesis of a family of stress response proteins termed heat shock proteins. Potential interactions between endocrine and cellular stress responses have not been investigated in vivo. A surgical model was developed to define the genetic response to surgical stress. Wistar rats underwent ether anesthesia, laparotomy, hemorrhage, and variable recovery periods. Tissues were subsequently harvested and the RNA was isolated and probed for HSP70 messenger RNA levels. These studies showed a strong induction of HSP70 but only in the adrenal gland, aorta, and vena cava. This specific induction was rapid, occurring 30 minutes after surgery, and dramatic (greater than twentyfold induction). The induction occurred in parallel with HPA axis activation and was adrenal cortical specific as determined by in situ hybridization. These observations suggest a functional interaction between the molecular stress response and HPA axis activation

Role of organ-associated NK cells in decreased formation of experimental metastases in lung and liver.

Wiltrout RH, Herberman RB, Zhang SR, et al.

J Immunol. 1985 Jun; 134(6):4267-75.

Mice treated with anti-asialo GM1 (asGM1) serum exhibited increased formation of experimental metastases in lung and liver after i.v. challenge with B16 melanoma or Lewis lung carcinoma. This increased metastasis formation coincided with decreased splenic NK activity and increased survival of i.v. injected radiolabeled tumor cells. In contrast, the injection of mice with the pyran copolymer maleic anhydride divinyl ether (MVE-2) augmented NK activity in the spleen and significantly depressed the formation of experimental metastases in the lungs and liver. However, a single or double administration of anti-asGM1 antiserum to MVE-2-pretreated mice failed to inhibit the immunoprophylaxis associated with MVE-2 administration, although it did decrease splenic NK activity and also increased the survival of i.v.-injected radiolabeled tumor cells. To address the mechanism for this dichotomy, we examined NK activity not only in the spleen but also in the blood, lungs, and livers of MVE-2-treated mice. Levels of NK activity in the lungs and liver were several-fold higher than those observed in spleen and blood. However, MVE-2-augmented NK activity in lung and liver was more resistant to depletion by the standard regimen of anti-asGM1 treatment than was NK activity in blood and spleen, and required two high-dose administrations of a higher titered antiserum for depletion of the augmented response. This high-dose regimen removed all detectable NK activity from the lung and liver, and concomitantly eliminated the metastasis-inhibiting effect of MVE-2. These data are consistent with a role for organ-associated NK cells in inhibiting metastasis formation during the extravasation and/or early postextravasation phases of the metastatic process. The results also suggest that biologic effects of NK activity in spleen and blood can be dissociated from those mediated by NK activity in other organs by use of different treatment regimens with anti-asGM1 serum. Finally, because NK activity in target organs can be augmented to an even greater extent than in the blood and spleen by at least some biologic response modifiers (BRMs), organ-associated NK activity should be considered as a possible mechanism for the therapeutic effects of BRM treatment

The effects of surgery, with or without rhGM-CSF, on the angiogenic profile of patients treated for colorectal carcinoma.

Wu FP, Westphal JR, Hoekman K, et al.

Cytokine. 2004 Jan 21; 25(2):68-72.

Wound healing is a process with immunological and angiogenic aspects. rhGM-CSF is known to stimulate the immune system and angiogenesis via multiple pathways. In this study we investigated the combined effects of surgery, with or without rhGM-CSF, on angiogenic parameters in patients with a colorectal carcinoma. In this phase II randomized, placebo-controlled trial, 16 patients were assigned to perioperative rhGM-CSF (2.8 microg/kg body weight) treatment or saline. Patients received subcutaneous injections from three days before surgery until four days after. IL-6, VEGF, endostatin and angiostatin levels were measured perioperatively. rhGM-CSF enhanced the production of IL-6 and VEGF, but had no effect on the antiangiogenic agents endostatin and angiostatin. Surgery induced a transient decrease of endostatin. Two types of angiostatin (kringle 1-3 and kringle 1-4) became visible postoperatively. We conclude that this study demonstrated the immediate initiation of angiogenesis postoperatively, reflected by the increase of VEGF and a transient decrease of endostatin, followed by the appearance of two angiostatin bands, which confirms physiological wound healing in these cancer patients