Brain, Behavior, and Immunity 30 (2013) S32–S40

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Surgery and stress promote cancer metastasis: New outlooks on perioperative mediating mechanisms and immune involvement

Elad Neeman, Shamgar Ben-Eliyahu *

Neuroimmunology Research Unit, Department of Psychology, Tel Aviv University, Tel Aviv 69978, Israel

ARTICLE INFO

Article history:
Available online 4 April 2012

Keywords:
Perioperative
Metastasis
Immunity
Stress
Surgery
Cancer
Catecholamines
Prostaglanids
Glucocorticoids
Anesthesia

ABSTRACT

Surgery for the removal of a primary tumor presents an opportunity to eradicate cancer or arrest its progression, but is also believed to promote the outbreak of pre-existing micrometastases and the initiation of new metastases. These deleterious effects of surgery are mediated through various mechanisms, including psychological and physiological neuroendocrine and paracrine stress responses elicited by surgery. In this review we (i) describe the many risk factors that arise during the perioperative period, acting synergistically to make this short timeframe critical for determining long-term cancer recurrence, (ii) present newly identified potent immunocyte populations that can destroy autologous tumor cells that were traditionally considered immune-resistant, thus invigorating the notion of immune-surveillance against cancer metastasis, (iii) describe *in vivo* evidence in cancer patients that support a role for anti-cancer immunity, (iv) indicate neuroendocrine and paracrine mediating mechanisms of stress- and surgery-induced promotion of cancer progression, focusing on the prominent role of catecholamines and prostaglandins through their impact on anti-cancer immunity, and through direct effects on the malignant tissue and its surrounding, (v) discuss the impact of different anesthetic approaches and other intra-operative procedures on immunity and cancer progression, and (vi) suggest prophylactic measures against the immunosuppressive and cancer promoting effects of surgery.

1. The perioperative period as a critical timeframe for metastatic progression

In cancer patients, surgical removal of the primary tumor is commonly the first and most important step toward abrogating the disease or controlling its progression. While this treatment has been utilized in cancer patients for several millennia (starting with the ancient Egyptians), its shortcomings have become clearer in the last decades. An epidemiological historical study (Demicheli et al., 2001) had compared two databases of breast cancer patients, showing that while untreated patients exhibited only one peak of mortality 3–4 years after diagnosis, operated patients showed an additional distinct peak at 7–8 years after surgery, suggesting that beside its important beneficial outcomes, surgery may indeed have long-term deleterious effects. Given that this notion cannot be directly tested in cancer patients, researchers and clinicians have to rely on animal models and human correlative or indirect findings in determining the potential role of surgery in metastatic progression.

Starting at mid-20th century, using various animal models, researchers have shown that surgery or various stress responses can increase susceptibility to experimental and spontaneous metastases of both solid and hematological tumors (Glasner et al., 2010; Goldfarb et al., 2011; Inbar et al., 2011; Kinsey, 1961). In the following years, animal and human studies have proposed several underlying mechanisms for this phenomenon. First, in humans, it had been repeatedly shown that surgery increases shedding of malignant cells into the blood and lymphatic circulations due to mechanical manipulations of the tumor and its vasculature (Eschwege et al., 1995; Weitz and Herfarth, 2001; Yamaguchi et al., 2000). Second, surgery was shown to increase malignant cell proliferation and resistance to apoptosis: for example, post surgical sera of cancer patients were reported to stimulate *in vitro* tumor proliferation (Kirman et al., 2002). Third, surgery was found to potentiate invasion capacity and motility of free malignant cells by inducing the release of matrix metalloproteinases (MMP) (Kirman et al., 2006), and by enhancing adhesion-molecule expression on tumor cells (Reviewed in (van der Bij et al., 2009). Fourth, factors related to tumor vascularity were also shown to be affected by surgery. Specifically, removal of the primary tumor was reported to cause a drop in levels of tumor-related anti-angiogenic factors (e.g. angiostatin and endostatin) (O'Reilly et al., 1997, 1994), and resulted in increased levels of pro-angiogenic factors (e.g. VEGF) (Svendsen et al., 2002), thus "turning on" the angiogenic switch in latent preexisting micro-metastases. Finally, tissue damage

* Corresponding author. Tel.: +972 3 640 7948/7266; fax: +972 3 640 9520/9547.
E-mail address: shamgar@post.tau.ac.il (S. Ben-Eliyahu).

0889-1591/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbi.2012.03.006

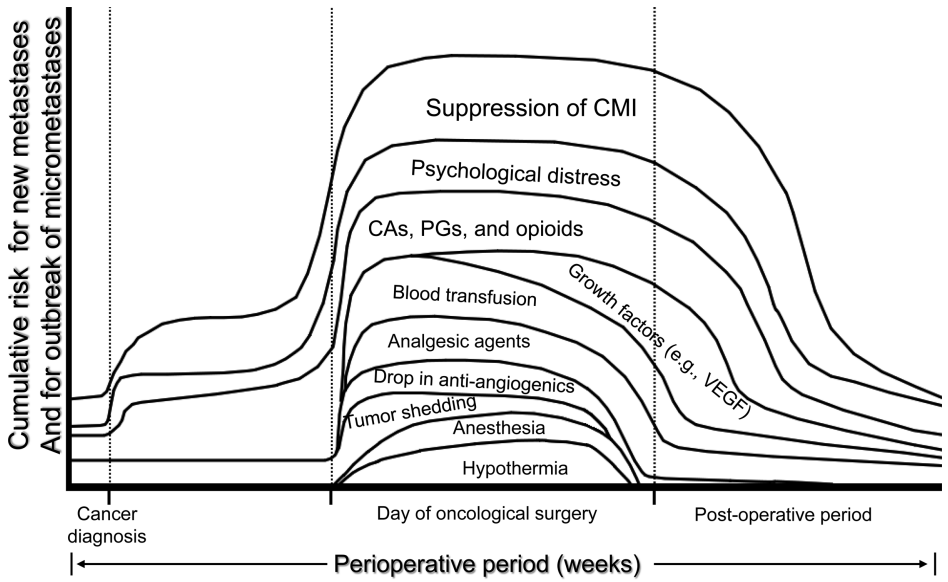

Fig. 1. A schematic representation of the cumulative kinetics of several perioperative risk factors for the initiation of new metastases and the outbreak of preexisting micrometastases in cancer patients (reviewed in Section 1). Each risk factor is represented by a horizontal layer, whose height at different time points along the perioperative period signifies its theoretical contribution to the overall risk. *Not indicated are the direct effects of many of the soluble factors, including catecholamines (CA), prostaglandins (PG), and opiates/opioids on malignant tissue proliferation, invasion capacity, secretion of VEGF, etc, which are reviewed in Sections 3 & 4.

caused by surgery, and specifically the subsequent local pro-inflammatory and wound-healing responses, were shown to increase levels of growth factors (e.g. EGF) (Abramovitch et al., 1999; Pascual et al., 2011), endorsing local and distant recurrence.

Additional aspects inherent to the surgical setting may also play a role in metastatic progression. Anesthetic and analgesic agents, nociception, and pain, were all shown to markedly suppress several aspects of immunity and to promote cancer progression. These effects are discussed below at length. Additionally, perioperative blood transfusions were causally linked, in animals (Atzil et al., 2008) and humans, to greater recurrence rates. Specifically, a recent meta-analysis, combining seven randomized controlled trials (RCTs) in colorectal cancer patients, had re-confirmed this finding and indicated a 42% percent increased risk for recurrence (Amato and Pescatori, 2006). Severe hypothermia was shown in animal studies to increase susceptibility to metastasis (Ben-Eliyahu et al., 1999), although milder hypothermia, which is more common in cancer patients, was not associated with cancer recurrence (Yucel et al., 2005).

An often disregarded additional perioperative risk factor for cancer recurrence is psychological distress: starting with cancer diagnosis, throughout and following surgical and adjuvant treatments, patients experience anxiety, stress, and depression, which translate, among others, to activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (Seok et al., 2010; Thornton et al., 2010), and the consequent release of stress hormones. Importantly, psychological stress was reported to down-regulate cellular immune indices, including NK and CTL activity, and macrophage motility and phagocytosis (Ben-Eliyahu et al., 2000; Li et al., 2005; Palermo-Neto et al., 2003; Stefanski, 2001). Stress hormones, specifically catecholamines, opioids, and glucocorticoids, were repeatedly shown in animal models to causally promote metastatic progression through various mechanisms, immunological and non-immunological (Benish et al., 2008; Goldfarb et al., 2009; Inbar et al., 2011; Lee et al., 2009; Page et al., 1998; Shahzad et al., 2010; Shakhar and Ben-Eliyahu, 1998; Shavit et al., 2004; Thaker et al., 2006). In fact, it was shown in animals that even a single exposure to stress or stress hormones during a critical period of tumor progression, could increase cancer mortality (Inbar et al., 2011).

Lastly and importantly, it is well acknowledged that surgery itself profoundly suppresses cell-mediated immunity (CMI) (Shakhar and Ben-Eliyahu, 2003). In patients, surgery and its associated neuroendocrine and paracrine responses were shown to increase secretion of immune suppressing hormones (e.g. cortisol), decrease numbers and activity of NK, Th1 and CTL cells, and reduce the pro-CMI type-1 cytokines (e.g. IL-12 and IFN-γ) (Bartal et al., 2010; Greenfeld et al., 2007). These phenomena commence even before surgery, are exacerbated following surgery, and dissipate during the few post-operative days or weeks (Faist et al., 1996; Greenfeld et al., 2007). The role of CMI, and its recently discovered unique lymphocyte populations, in controlling minimal residual disease (MRD), is extensively discussed below, providing the rationale for considering immunosuppression as a significant perioperative risk factor for cancer recurrence.

Taken together, the risk factors described above, which are all common in oncological surgery, occur simultaneously during the short perioperative period. Specifically, shedding of malignant cells, increased tumor-cell proliferation, excess release of pro-angiogenic/pro-invasive factors, accelerated spreading of tumor cells, abundant release of growth factors, psychological distress, and suppression of CMI, may act in synergy to render the patient temporarily vulnerable to metastases which could have been controlled otherwise. Therefore, the short perioperative period seems to have a non-proportionally high impact on long-term recurrence rates (Fig. 1), and thus presents an important and unexplored window of opportunity to improve prognosis.

2. Newly-acknowledged tumor-controlling leukocyte populations, and evidence from cancer patients, invigorate the notion of anti-metastatic immune-surveillance

The ability of the immune system to prevent cancer and control metastasis had been originally hypothesized by Paul Erlich more than a century ago. Fifty years later, Burnet & Thomas have coined the term *immune surveillance* to describe the ability of the immune system, especially CMI, to recognize and destroy transformed cells (Burnet, 1967), and numerous studies in animals have supported this notion. For example, it was repeatedly shown that depletion

of NK cells dramatically increased tumor load and metastatic formation of some syngeneic malignancies, while adoptive transfer of large granular lymphocytes (NK cells) restored normal tumor resistance (Barlozzari et al., 1985, 1983; Shakhar and Ben-Eliyahu, 1998); in mice, anti-IFN-γ treatment, IFN-γ deficiency, or RAG-2 knock-out (preventing T, B, and NK cell-genesis) promoted spontaneous tumor development and metastasis (Smyth et al., 2001). However, animal tumor models, including those based on human malignancies implanted in immune-deficient mice, have been justifiably criticized (Shakhar and Ben-Eliyahu, 2003) for not comprehensively simulating the initiation, immune-editing, and progression of human cancer, and for being based selectively on immune-sensitive tumor lines.

However, new evidence based on studies conducted in cancer patients, have since emerged, and have clearly indicated the role of immune-surveillance in cancer progression. Firstly, numerous immune-escape mechanisms revealed in human malignancies indicate a profound immune-tumor interaction, and tumor destruction and selection by the immune system (reviewed in (Kim et al., 2006)). The prevalence of escape mechanisms are greater in metastatic foci than in the primary tumor, indicating a higher selection pressure during the metastatic process (See (Shakhar and Ben-Eliyahu, 2003)). Secondly, in operated cancer patients, an indication for pre-existing immune-tumor interaction in the form of *in vitro* mixed lymphocyte responses against the excised autologous tumor, was reported to predict long-term survival rates even better than tumor stage and grade (McCoy et al., 2000; Uchida et al., 1990). Third, there is an increased frequency of certain malignancies, and a dramatic increase in metastatic progression in immune-compromised patients, including those receiving immunosuppressant therapy (Detry et al., 2000; Penn, 1993), patients with AIDS (Bernstein and Hamilton, 1993), and patients carrying anti-lymphocyte antibodies (Decaens et al., 2006). Lastly, and despite prior disappointing results, recent advances in immunomodulatory therapy also support the role of immunity in tumor resistance. For example, the newly FDA-approved CTLA-4 receptor blocker, ipilimumab, which enhances T-cell mediated anti-tumor immunity, was recently shown to increase survival time of patients with metastatic or unresectable melanoma, adding to the known benefits of recombinant IL-2 therapy in such patients (Postow et al., 2011). Taken together, these findings unequivocally indicate interactions of immunocytes with autologous malignancies in cancer patients, including cancer cell destruction, and a significant control over the metastatic process.

Still, despite the *in vivo* clinical evidence described above, for many years scientists had failed to directly demonstrate significant *in vitro* immune cytotoxic activity against many autologous tumors, in humans or in animals (Melamed et al., 2005). This apparent contradiction has elicited the hypothesis that yet undiscovered unique leukocyte populations that control MRD do exist *in vivo*. Indeed, in recent years, modern harvesting, phenotyping, and sorting techniques have led to the identification of several new leukocyte populations (some also found in humans), which display a unique ability to lyse "immune-resistant" autologous tumor cells. These populations are described below, and functionally resemble *in vitro* activated lymphocytes (e.g., by various Th1 cytokines), which had long been shown to exhibit superior and distinct tumor-lysing capabilities (Rosenberg and Lotze, 1986).

Marginating pulmonary (MP) leukocytes are defined as white blood cells adhering to the endothelium of the lung vasculature. These cells have been discovered and studied in rats (Melamed et al., 2005), and more recently also in mice (Unpublished data from our lab). When compared with circulating leukocytes, MP leukocytes naturally exhibit a continuous state of activation. Specifically, MP-leukocytes show a twofold higher cytotoxicity against xenogeneic tumor lines, and three- to tenfold increased cytotoxicity against syngeneic allegedly "NK-resistant" tumor lines (Melamed et al., 2010b, 2005; Shakhar et al., 2007). Morphologically, the proportion of large NK cells in the MP compartment is threefold higher than in the blood and spleen (Shakhar et al., 2007), and the MP cellular composition is characterized by a twofold greater proportion of "innate" leukocytes (granulocytes, monocytes, and NK cells) (Melamed et al., 2010b). Finally, MP leukocytes exhibit an increased production of IL-1β, IL-6, IL-10 and TNF-α in response to immunostimulation by poly I:C, CpG, and LPS (Melamed et al., 2010a). Additionally, specific leukocyte subsets within the MP compartment exhibit several characteristics of activation, including (i) significantly higher percentage of intracellular IFN-γ positive NK cells, (ii) elevated CD11b expression on NK cells, granulocytes and monocytes, (iii) elevated CD161 (also known as NKR-P1/NK1.1) on monocytes, (iv) twice as many CD80 positive dendritic cells (DCs), and (v) a significantly lower CD4/CD8 T-cell ratio (Melamed et al., 2010b).

Notably, the MP-population was reported to be very susceptible to immunosuppression following surgery or behavioral stress, or following exposure to corticosterone, catecholamines, or prostaglandins (Ben-Eliyahu et al., 2010; Benish et al., 2008; Inbar et al., 2011; Melamed et al., 2005). However, this population was also found to be highly responsive to *in vivo* immune stimulation with poly I:C (Rosenne et al., 2007; Shakhar et al., 2007) or CpG-C (Goldfarb et al., 2011), which enhanced tumor-lysis by MP leukocytes, and increased lung tumor-resistance.

Liver pit cells are activated hepatic NK cells with a potential wide range of anti-metastatic activity. These cells constitute a relatively rare population (approximately one tenth of Kupffer cells), and inhabit the liver sinusoids, adhering to the endothelial cells. Pit cells were initially described in rats in 1976 by (Wisse et al., 1976), and later also in mice (Luo et al., 2000) and humans (Hata et al., 1990). However, their potential significance to tumor resistance was only lately acknowledged. Pit cells are considered NK cells as they express high levels of NKR-P1, and specific patterns of CD2, CD18, and CD54, which are identical to those of circulating NK cells. Notably, all pit cells are CD8 positive, as opposed to only 40% of blood NK cells, and none of the NKT cells (Luo et al., 2000). Interestingly, and similarly to MP leukocytes, when compared to circulating/spleen NK cells, pit cells demonstrate characteristics of immune activation. These cells exhibit (i) a greater number of intra-cellular granules, (ii) a larger size, (iii) an increased NK activity against xenogeneic cells and syngeneic-NK resistant tumor cells, (iv) an elevated expression of the NK-activation markers gp42, CD25, and ANK44 antigen, and (v) high mRNA expression levels of perforin, granzymes, INF-γ, and tumor necrosis factor (TNF)-α (Luo et al., 2001, 2000). Pit cells are not a homogenous NK population, and can be divided to high-density (HD) and low-density (LD) pit cells, the latter demonstrating an even greater NK cytotoxicity and increased levels of activation-related mRNAs (i.e., perforin, granzymes, INF-γ, and TNF-α). It is believed that pit cells originate as blood NK cells, and when reaching the specific micro-environment of the liver sinusoids differentiate into HD, and later into LD pit cells (Vanderkerken et al., 1993).

We have recently studied the marginating hepatic (MH)-leukocyte population in its entirety, which contains pit cells and other leukocytes. Compared to circulating leukocytes, and much like MP leukocytes (Melamed et al., 2010a), MH-leukocytes exhibited greater cytotoxicity against xenogeneic and syngeneic tumor cells, and also greater levels of mRNA and induced-production of IL-1β, IL-6, IL-10, and TNF-α (manuscript in preparation).

Type 1 NKT cells, also known as invariant or classical NKT cells, are a subset of NKT lymphocytes with anti-tumor capabilities, extensively studied during the recent years (reviewed in (Hegde et al., 2010)). Initially, NKT cells had been defined as T cells

expressing NK markers (CD161 and/or CD56), but functionally this definition was found to be neither inclusive of all NKTs, nor exclusive of other populations. In recent years NKTs have been re-defined as T cells expressing CD1d, a non-classical MHC-I molecule. NKT cells are subdivided into two distinct populations: type1 NKT cells, which express an invariant Vα14 (in mice)- or a Vα24 (in humans)-T cell receptor (TCR), and bind to the α-GalCer glycolipid; and Type2 NKTs (non-classical NKTs) which express a variant TCR, and do not bind to α-GalCer. Type 1 NKT cells in humans typically comprise only 0.01–0.1% of peripheral blood mononuclear cells (PBMCs), ~1% of liver lymphocytes, and ~10% of lymphocytes in the omentum (Berzins et al., 2011). In recent years, type 1 NKT cells had been shown to secrete IFN-γ, promote IL-12 secretion by DCs, promote DC maturation, and, similarly to NK cells, to directly lyse tumor cells via the perforin, FasL, and/or TRAIL pathways (Seino et al., 2006) following recognition of specific glycolipids (Metelitsa et al., 2001, 2003). Interestingly, in numerous studies, defects in type 1 NKT cells were causally linked in mice (and associated in humans) to the promotion of both solid and hematological cancers (Berzins et al., 2011). Several phase-I clinical studies have already began to utilize α-GalCer injections, or adoptive transfer of type 1 NKT cells or of α-GalCer-loaded DCs in cancer patients (Motohashi and Nakayama, 2009).

Dendritic Epidermal T cells (DETC) are skin-specific γδ T-cells which express an invariant canonical Vγ3 Vδ1 TCR (Macleod and Havran, 2011), as well as the NKG2D activating receptor for tumor killing (Ebert et al., 2006). DETCs were discovered and mainly studied in mice, and their presence was also confirmed in humans. Their primary role appears to be in maintaining epidermal homeostasis – balancing keratinocyte proliferation and apoptosis. DETCs were shown to secrete TNF-α, IFN-γ, and CCL1 in response to stimulation, to produce intra-cellular perforin and to exhibit significant cytotoxicity against melanoma cells, similarly to skin NK cells and in contrast to the more abundant skin αβ T cells (Macleod and Havran, 2011).

Killer dendritic cells are a bi-phenotypic population of DCs found in mice, rats, and humans, which can express typical markers of DCs (e.g., MHC-II, CD11c) and NK cells (e.g., NK1.1). These cells have been identified in the spleen, lymph-nodes, thymus, liver, and lungs. Based on their unique traits, these cells were termed NKDCs or, by a different group, interferon-producing killer DCs (IKDC) (Larmonier et al., 2010). This population is unique in its ability to transform, after lysing tumor cells, from a naïve NK-like state (with up-regulated NKG2D, TRAIL, and killing capabilities) to a mature DC-like antigen-presenting cell state (with up-regulated MHC-II and co-stimulatory molecules). The *in vivo* significance of NKDCs in controlling tumor progression has rarely been studied, though they were recently shown to delay the development of the syngeneic B16-melanoma (Larmonier et al., 2010).

Taken together, these unique leukocyte populations (and other yet undiscovered) with anti-tumor capacities can explain the discrepancy between the *in vivo* evidence for anti-metastatic immune-surveillance and the *in vitro* apparent inability to lyse some malignant cells. Importantly, most of these populations inhabit strategic locations, specifically lung and liver capillary vasculature, fostering tight interactions with all circulating aberrant cells, and constituting an important barrier against metastatic dissemination. Overall, the discovery of these populations suggests a greater role than previously assumed for CMI in controlling circulating malignant cells and other aspects of MRD, even though immunity had failed to prevent the development of the primary tumor. It is also noteworthy that the removal of a primary tumor often terminates malignancy-related immunosuppression (Serafini et al., 2006), potentially allowing improved post-operative immune activity against MRD.

3. Catecholamines and prostaglandins are key mediators suppressing anti-metastatic immunity and acting directly on MRD to promote metastatic progression

Despite the removal of the primary tumor, and despite the ability of CMI to restrict or eliminate MRD, many patients exhibit cancer recurrence. Given the above-discussed significance of the perioperative period in determining long-term prognosis, and the marked paracrine, endocrine, and immunological perturbations that occur during this period, it is our hypothesis that certain surgery-related stress responses (i) reduce patient immune resistance to MRD, and (ii) directly facilitate MRD capacity to survive and progress, synergistically increasing the risk of cancer recurrence. While similar hypotheses have been suggested years ago, specific soluble factors and mechanisms have only recently been identified, and include catecholamines, prostaglandins, glucocorticoids, various cytokines, pro-angiogenic factors, and opioids. Indeed, human and animal studies have reported that a variety of physiological and psychological stressors perturb immune indices, including cytokine levels and their induced production, number and distribution of leukocyte subtypes, and cellular and humoral immune functions (Ben-Eliyahu, 2003; Maes et al., 1998; Segerstrom and Miller, 2004; Stefanski, 2001; Viswanathan and Dhabhar, 2005). A substantial amount of research has focused specifically on catecholamines and prostaglandins, which also mediate the secretion of most of the other pro-tumor and anti-CMI compounds described above (Giguere and Labrie, 1983; Glass and Ogawa, 2006; Rettori et al., 2009). Lastly, excess release of catecholamines and prostaglandins can be safely targeted pharmacologically in the perioperative context, and we propose that such an intervention may constitute a novel and easy approach to reduce recurrence rates in oncological patients.

3.1. Prostaglandins - direct effects on malignant tissue and its microenvironment

Ample scientific evidence implicates prostaglandins, especially prostaglandin E_2 (PGE_2), in promoting neoplastic progression. COX-2, a member of the cyclo-oxygenase enzyme family that produces prostaglandins (mostly PGE_2), is usually undetectable in most healthy human tissues (Reader et al., 2011). However, this enzyme is upregulated in many human malignant and pre-malignant tumors (Howe, 2007), especially colorectal and mammary carcinomas (Reader et al., 2011). Transgenic mice over-expressing the PGE_2 receptor, EP1, were reported to be significantly more prone to malignant skin tumors. PGE_2 administration was shown to facilitate macrophage differentiation toward the pro-tumoral M2 phenotype (Sica et al., 2006), contributing to tumor angiogenesis (Brecht et al., 2011). In colorectal cancer patients, tumor COX-2 expression levels (but not COX-1) were associated with tumor size, stage, depth of invasion, lymph node metastasis, blood vessel invasion, recurrence, and overall survival rates (Soumaoro et al., 2004). Blocking the COX-2 pathway in patients or animals was shown to facilitate tumor cell apoptosis (Cao et al., 2000; Roche-Nagle et al., 2004; Sinicrope and Gill, 2004; Zha et al., 2004), to reduce levels of pro-angiogenic agents (Jones et al., 1999; Sinicrope and Gill, 2004; Wei et al., 2004), to decrease tumor microvascular density (Roche-Nagle et al., 2004), and to lower neoplasm vascular invasive capacity by reducing local inflammation and vascular permeability (Condeelis and Pollard, 2006; Goswami et al., 2005).

3.2. Catecholamines - direct effects on malignant tissue and its microenvironment

The following and additional direct effects of catecholamines are comprehensively reviewed elsewhere (Cole and Sood, 2012) (also

see in this volume). Shortly, several lines of evidence demonstrate that activation of tumor β-adrenoceptors can promote malignant progression by facilitating tumor survival, angiogenesis, migration, proliferation, and resistance to anoikis (Antoni et al., 2006; Bernabe et al., 2011; Sood et al., 2010, 2006; Thaker et al., 2006; Wong et al., 2011). A pioneering study (Schuller et al., 1999) had shown that the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) promoted murine pulmonary tumor-cell DNA synthesis and proliferation by stimulating tumor β1 and β2 adrenoceptors. Other studies have shown that norepinephrine enhances *in vitro* production of several metastatic promoting factors, including VEGF, MMP2/9, IL-6, and IL-8, by a variety of human tumor lines (Bernabe et al., 2011; Sood et al., 2006; Thaker et al., 2006; Wong et al., 2011; Yang et al., 2009) – effects that were blocked by the β-antagonist propranolol (Lutgendorf et al., 2003). In mammary tumors, activation of β-adrenoceptors was linked to accelerated tumor growth (Antoni et al., 2006), and in a colon carcinoma cell line, norepinephrine was found to induce *in vitro* locomotion in a β_2-adrenoceptor-dependent manner (Masur et al., 2001). Lastly, a blockade of beta-adrenergic receptors had induced apoptosis of several human and animal carcinoma cell lines (Liao et al., 2010; Zhang et al., 2009).

3.3. Catecholamines and prostaglandins: effects on anti-tumor CMI

In addition to their direct effect on malignant tissue and its micro-environment, catecholamines and prostaglandins have been repeatedly shown to suppress many aspects of CMI *in vitro* (Hellstrand and Hermodsson, 1989; Koren and Leung, 1982), and *ex vivo* (Benish et al., 2008; Inbar et al., 2011; Levi et al., 2011; Shakhar and Ben-Eliyahu, 1998). Most lymphocytes express receptors for catecholamines and prostaglandins (Landmann, 1992; Uotila, 1996), and the intracellular cascades triggered by these substances that lead to immunosuppression have been extensively studied, and are mainly based on the cAMP-PKA pathway (Masera et al., 1989; Torgersen et al., 1997; Whalen and Bankhurst, 1990). Our studies in animals clearly indicate that administration of catecholamines (Ben-Eliyahu et al., 2000; Shakhar and Ben-Eliyahu, 1998) or prostaglandins, at presumably physiological levels, or the endogenous excess release of these compounds by stress or surgery, suppress NK activity *in vivo* (Benish et al., 2008; Melamed et al., 2005; Yakar et al., 2003). Furthermore, we provided causative evidence that this immunosuppression can compromise resistance to experimental metastasis (Shakhar and Ben-Eliyahu, 1998; Yakar et al., 2003). Last, our findings also support a role for this immunosuppression in reducing long-term survival rates in animals undergoing primary tumor excision (Benish et al., 2008; Glasner et al., 2010; Goldfarb et al., 2011; Inbar et al., 2011; Melamed et al., 2003). Catecholamines and prostaglandins are also known to shift the Th1/Th2 balance toward the anti-CMI Th2 dominance (Elenkov and Chrousos, 2002; Kalinski, 2012), and to increase ACTH and glucocorticoid levels(Giguere and Labrie, 1983), potentially suppressing several aspect of CMI through these responses (also see below). Lastly, specific anti-tumor leukocyte populations (described above), including MP-leukocytes (Benish et al., 2008; Melamed et al., 2005), DETCs (Martinet et al., 2009), and type 1 NKTs (Prigione et al., 2009), were all shown to be suppressed by β-adrenergic and/or prostanoid stimulation.

3.4. Synergistic effects of catecholamines and prostaglandins

In addition to the beneficial effects of blocking either catecholamines or prostaglandins on immunity and on resistance to tumor progression, recent studies emphasize the synergistic effects of blocking both factors. For example, only a combined treatment with a β-blocker and a COX-2 inhibitor attenuated the NK suppressive effects of surgery (Benish et al., 2008), and in two models of spontaneous metastasis only the combination of the two blockers, but none alone, improved survival rates following the removal of a primary metastasizing tumor (Benish et al., 2008; Glasner et al., 2010). We ascribe this synergism to the fact that both catecholamines and prostaglandins are elevated during the perioperative period, and that they can each alone cause immunosuppression and/or promote metastasis through non-immunological mechanisms described above. Indeed, both catecholamines and prostaglandins independently activate the same cAMP-PKA intracellular pathways on immune, malignant, and other host relevant cells, eventually promoting metastasis. Thus the blockade of only one receptor system could be ineffective.

3.5. Glucocorticoids: impact on immunity and tumor progression

Traditionally, glucocorticoids were considered as major mediators of the deleterious effects of stress on anti-tumor immunity. Indeed, glucocorticoids are potent *in vitro* suppressors of many aspects of CMI (Ashwell et al., 2000), including NK activity (Cox et al., 1983), and pharmacological doses of glucocorticoids in patients often lead to immunosuppression (Oehling et al., 1997). Like others before us (Tseng et al., 2005), we too observed *in vitro* and some *ex vivo* suppressive effects of exogenous and surgery-induced elevated glucocorticoid levels on NK activity (Shakhar and Blumenfeld, 2003). Nevertheless, our studies in rats have provided evidence that the *in vivo* role of glucocorticoids in the NK-suppressive and tumor-promoting effects of acute stress or surgery is rather limited. Physiologically relevant doses of corticosterone (3–9 mg/kg in rats) did not increase susceptibility to MADB106 metastasis or CRNK-16 leukemia (Inbar et al., 2011; Shakhar and Blumenfeld, 2003), although both models indicated significant impacts of other stress hormones (Inbar et al., 2011; Shakhar and Ben-Eliyahu, 1998). Correspondingly, interventions that did not markedly affect the HPA-axis responses almost completely abolished the *ex vivo* and *in vivo* effects of stress and surgery on NK activity and on tumor resistance (Benish et al., 2008; Glasner et al., 2010). Taken together, we suggest that an acute *in vivo* exposure to physiological high levels of glucocorticoids in rats is not sufficient to suppress levels of NK activity *in vivo*, and some studies in humans had reached a similar conclusion (Bodner et al., 1998). One hypothesis as to the apparent contradiction between the *in vitro* and *in vivo* findings addresses a potential difference in the effective concentrations of glucocorticoids used in the two approaches, and the fact that approximately 95% of glucocorticoids are bound *in vivo* to glucocorticoid binding globulins (CBGs), which further decrease their effective *in vivo* levels (Henley and Lightman, 2011).

On the other hand, it seems that longer *in vivo* exposures to elevated glucocorticoids can decrease Th1 cytokines, and through this mechanism induce a delayed reduction in CMI functioning. For example, we recently found that various prolonged stress paradigms reduced plasma IL-12 levels, beginning 5–10 h after stress initiation, and that this reduction was mediated through the release of adrenal corticosterone and activation of the GR receptors (Shaashua et al., 2011). However, it is worthy to note that *in vivo* high levels of catecholamines and prostaglandins can increase glucocorticoid levels (Giguere and Labrie, 1983; Rettori et al., 2009), and that their blockade perioperatively was shown to reduce delayed surgery-induced elevation in corticosterone levels (i.e., at 12, but not at 2 h post-operatively) (Glasner et al., 2010). Thus, the blockade of prostaglandins and catecholamines may also reduce delayed immunosuppressive effects of glucocorticoids that are secondary to catecholamine and prostaglandin release. Last, employing two models of prolonged stress and comparing the relative contribution of corticosterone to those of catecholamines and prostaglandins in causing *in vivo* suppression of NK activity, we

found that the blockade of corticosterone had a smaller effect than the blockade of catecholamines and prostaglandins. When adding corticosterone blockade to the two other interventions, no improvement was evident (Ben-Eliyahu et al., 2010). Overall, we suggest that elevated levels of glucocorticoids are of minor significance in suppressing NK activity *in vivo* relative to other responses to stress and surgery, and that prophylactic measures should focus on catecholamines and prostaglandins, which can also lead to reduced glucocorticoid levels, and are more feasible for clinical use during the perioperative period.

4. Anesthesia, analgesia, and pain: impact on immunity and tumor progression

Inherent to almost every surgery is the use of various anesthetic and analgesic agents administered through various approaches. It is now becoming clear that some common anesthetic and analgesic approaches are associated with an increase in cancer recurrence rates, as was shown regarding colorectal (Gupta et al., 2011), breast (Exadaktylos et al., 2006), melanoma (Schlagenhauff et al., 2000), ovarian (de Oliveira et al., 2011; Lin et al., 2011), and prostate (Biki et al., 2008) cancer. Generally, most of these studies reported that the common approach of employing general anesthesia combined with an opiate-based analgesia (the "GA approach") was linked to a poorer prognosis compared to various approaches which are exclusively based on, or include, regional or local blockade of nerve conduction (RA). Interestingly, supporting the clinical significance of the perioperative period, is the finding that epidural anesthesia (in addition to GA) in ovarian cancer patients was associated with improved recurrence-free survival, but only when administered intra-operatively, and not post-operatively (de Oliveira et al., 2011). Additionally, and as elaborated below, many of the deleterious effects of various aspects of anesthesia are based on mechanisms described above, including neuroendocrine responses, immunosuppression, and direct effects on the malignant tissue. Notably, a cautionary note is needed - all the above clinical studies are retrospective, and in few studies the adjustment for prognostic factors had eliminated significant differences between the anesthetic approaches (Melchi et al., 1995). In the only prospective study that was conducted, no significant differences were detected, but the study had a markedly limited statistical power (Myles et al., 2011).

The differences between the GA and the RA approaches can hint at specific factor(s) and mediating mechanisms underlying the alleged differences in long-term cancer outcomes. The GA approach commonly involves an induction phase (usually with thiopental or with propofol), and a maintenance phase utilizing a volatile anesthetic (e.g., sevoflurane or halothane), combined with the use of analgesics to relieve intra- and post-surgical pain, which are most commonly opiates. On the other hand, the RA approach employs administration of a local anesthetic (e.g. lidocaine or bupivicaine) in specific anatomic regions and in small quantities, to block peripheral or spinal nerve conduction (e.g., neuroaxial, paravertebral, or epidural block). This approach efficiently prevents nociception and pain, while, unlike the GA approach, also halting ascending neural transmission to CNS nuclei that otherwise may initiate HPA and sympathetic responses.

Animal studies had pointed at all factors differentiating between the two approaches as potential contributors to the poorer prognosis seen in patients subjected to GA. These include the utilization of specific induction agents, volatile anesthetics, opiate analgesics, and the centrally-mediated stress responses to nociception and pain. These factors, or the stress responses they elicit, eventually affect tumor progression either by impairing anti-tumor immunity, or directly by impacting the malignant tissue. For example, in a rat model of experimental metastasis, thiopental, ketamine, and halothane were all shown to reduce NK cytotoxicity, and to increase susceptibility to metastasis, some through activation of β-adrenoceptors (Melamed et al., 2003). Additionally, several volatile anesthetics, including isoflurane and desflurane, were shown to directly activate hypoxia inducible factors (HIFs) in tumor cells, increasing their resistance to cell death under hypoxic stress, partly by inducing secretion of VEGF and other angiogenic factors (Tavare et al., 2012). Opiate administration, and endogenously secreted opioids in response to nociception, were shown to facilitate tumor proliferation, promote tumor angiogenesis, and enhance tumor blood supply through nitric-oxide (NO) release (Gach et al., 2011; Gupta et al., 2002). Opiates were also shown to suppress NK and phagocytic activity, the production of antibodies, and the release of pro-CMI cytokines (Vallejo et al., 2004). Notably, at much lower doses, opiates are known to have central beneficial effects, reducing anxiety and pain, and were shown to actually attenuate postoperative stress responses and improve resistance to metastasis (Page et al., 2001). Therefore, pain alleviation and stress management, which are not based on systemic high-dose opiate administration, may be advantageous. Accordingly, some studies point at centrally-mediated mechanisms underlying beneficial effects of RA. Specifically, in two studies employing animal models of experimental metastasis, mice or rats were subjected to laparotomy under GA. Adding a spinal block resulted in a diminished deleterious effect on the IFN-γ/IL-4 ratio (reflecting the Th1/Th2 balance), on NK activity, and on the numbers of experimental liver or lung metastases (Bar-Yosef et al., 2001; Wada et al., 2007).

Human prospective and retrospective studies concur with the above causative findings. For example, several experimental studies in humans have recently shown that the GA approach as a whole can directly affect the malignant tissue and promote its growth. In two studies, breast cancer patients were randomly assigned to undergo either GA or RA. Only the GA approach (which includes opiate administration) was shown to directly increase serum levels of VEGF (Looney et al., 2010), MMP-3, and MMP-9 (Deegan et al., 2010). In another study, sera taken from patients who were randomly allocated to undergo GA, rather than RA, promoted the *in vitro* proliferation of a breast cancer cell line (Deegan et al., 2009). Other studies have reported that the use of RA had resulted in a reduced perioperative stress response, and spared postoperative immunity (reviewed in (Kurosawa and Kato, 2008)). For example, in patients undergoing hysterectomy, GA, but not RA, had resulted in a 3-day long lymphopenia and reduced NK activity, accompanied by an increased glucocorticoid and sympathetic responses (Tonnesen and Wahlgreen, 1988). Most exciting, two retrospective studies in cancer patients reported a marked improvement in survival when regional anesthesia was added to GA. Breast and prostate cancer patients that during surgery also received paravertebral or epidural analgesia (respectively), had shown a more than twofold higher long-term recurrence-free survival (3–5 years postoperatively) (Biki et al., 2008; Exadaktylos et al., 2006). These findings most likely reflect a cumulative effect of many potential mediating mechanisms, immunological and non-immunological, and their significance stems from the important clinical outcome of recurrence rates.

However, despite the extensive evidence suggesting that the anesthetic/analgesic approach can influence long term cancer recurrence, so far no randomized clinical trial has shown a causative effect on measures of survival. Thus, RCTs, including ongoing studies (e.g., (Sessler et al., 2008)) are required to provide direct evidence that the anesthetic/analgesic approach can affect long-term cancer prognosis.

5. Conclusions

The premise that immunosuppression during the perioperative period can increase long-term cancer recurrence rates is based on

empirical findings in animal studies, and on indirect evidence and argumentations based on findings from human studies. Prominent among these are (i) the recent identification of new leukocyte populations that exhibit uniquely potent cytolytic activity against autologous tumor cells that were traditionally considered "immune-resistant", (ii) the accumulation of evidence in cancer patients indicating *in vivo* immune control over the progression of cancer metastasis, (iii) the notion that the short perioperative period is markedly influential in determining long-term cancer recurrence, given the many risk factors that occur simultaneously and act synergistically during this period, including suppression of anti-metastatic CMI, (iv) the evidence that variations in surgical procedures, including anesthetic approaches and blood transfusion, affect tumor metastasis in animal models and apparently in cancer patients, through immunological and non-immunological mechanisms, and (v) the recent identification of neuroendocrine, paracrine, and cytokine mediators of the immunosuppressive and metastasis promoting effects of stress and surgery, of which we believe that catecholamines and prostaglandins are key players. Given that both catecholamines and prostaglandins are abundant during the perioperative period, are involved both in immunosuppression and in direct facilitation of malignant tissue progression, and can be pharmacologically controlled during the perioperative period, we believe that their simultaneous blockade presents an unexplored opportunity to limit long-term cancer recurrence employing a short and safe perioperative intervention during this critical timeframe.

Conflict of Interest

The authors of this manuscript have nothing to declare.

Acknowledgments

This work was supported by the National Cancer Institute at the National Institute of Health (CA125456 to S.B.E.), a grant from the Israeli Science Foundation (to S.B.E.), and a grant from the Israel-USA bi-national Science Foundation (2005331 to S.B.E.).

References

Abramovitch, R., Marikovsky, M., Meir, G., Neeman, M., 1999. Stimulation of tumour growth by wound-derived growth factors. Br. J. Cancer 79 (9–10), 1392–1398.

Amato, A., Pescatori, M., 2006. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst. Rev. (1), CD005033.

Antoni, M.H., Lutgendorf, S.K., Cole, S.W., Dhabhar, F.S., Sephton, S.E., McDonald, P.G., Stefanek, M., Sood, A.K., 2006. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat. Rev. Cancer 6 (3), 240–248.

Ashwell, J.D., Lu, F.W., Vacchio, M.S., 2000. Glucocorticoids in T cell development and function*. Annu. Rev. Immunol. 18, 309–345.

Atzil, S., Arad, M., Glasner, A., Abiri, N., Avraham, R., Greenfeld, K., Rosenne, E., Beilin, B., Ben-Eliyahu, S., 2008. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. Anesthesiology 109 (6), 989–997.

Bar-Yosef, S., Melamed, R., Page, G.G., Shakhar, G., Shakhar, K., Ben-Eliyahu, S., 2001. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology 94 (6), 1066–1073.

Barlozzari, T., Leonhardt, J., Wiltrout, R.H., Herberman, R.B., Reynolds, C.W., 1985. Direct evidence for the role of LGL in the inhibition of experimental tumor metastases. J. Immunol. 134 (4), 2783–2789.

Barlozzari, T., Reynolds, C.W., Herberman, R.B., 1983. *In vivo* role of natural killer cells: involvement of large granular lymphocytes in the clearance of tumor cells in anti-asialo GM1-treated rats. J. Immunol. 131 (2), 1024–1027.

Bartal, I., Melamed, R., Greenfeld, K., Atzil, S., Glasner, A., Domankevich, V., Naor, R., Beilin, B., Yardeni, I.Z., Ben-Eliyahu, S., 2010. Immune perturbations in patients along the perioperative period: alterations in cell surface markers and leukocyte subtypes before and after surgery. Brain Behav. Immun. 24 (3), 376–386.

Ben-Eliyahu, S., 2003. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. Brain Behav. Immun. 17 (Suppl 1), 27–36.

Ben-Eliyahu, S., Rosenne, E., Sorski, L., Levi, B., 2010. Second Thoughts on the Role of Glucocorticoids in the *in vivo* Suppression of NK Activity Following Stress. PNIRS, Dublin, Ireland.

Ben-Eliyahu, S., Shakhar, G., Page, G.G., Stefanski, V., Shakhar, K., 2000. Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. Neuroimmunomodulation 8 (3), 154–164.

Ben-Eliyahu, S., Shakhar, G., Rosenne, E., Levinson, Y., Beilin, B., 1999. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. Anesthesiology 91 (3), 732–740.

Benish, M., Bartal, I., Goldfarb, Y., Levi, B., Avraham, R., Raz, A., Ben-Eliyahu, S., 2008. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann. Surg. Oncol. 15 (7), 2042–2052.

Bernabe, D.G., Tamae, A.C., Biasoli, E.R., Oliveira, S.H., 2011. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain Behav. Immun. 25 (3), 574–583.

Bernstein, L., Hamilton, A.S., 1993. The epidemiology of AIDS-related malignancies. Curr. Opin. Oncol. 5 (5), 822–830.

Berzins, S.P., Smyth, M.J., Baxter, A.G., 2011. Presumed guilty: natural killer T cell defects and human disease. Nat. Rev. Immunol. 11 (2), 131–142.

Biki, B., Mascha, E., Moriarty, D.C., Fitzpatrick, J.M., Sessler, D.I., Buggy, D.J., 2008. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence. a retrospective analysis. Anesthesiology 109 (2), 180–187.

Bodner, G., Ho, A., Kreek, M.J., 1998. Effect of endogenous cortisol levels on natural killer cell activity in healthy humans. Brain Behav. Immun. 12 (4), 285–296.

Brecht, K., Weigert, A., Hu, J., Popp, R., Fisslthaler, B., Korff, T., Fleming, I., Geisslinger, G., Brune, B., 2011. Macrophages programmed by apoptotic cells promote angiogenesis via prostaglandin E2. FASEB J. 25 (7), 2408–2417.

Burnet, F.M., 1967. Immunological aspects of malignant disease. Lancet 1 (7501), 1171–1174.

Cao, Y., Pearman, A.T., Zimmerman, G.A., McIntyre, T.M., Prescott, S.M., 2000. Intracellular unesterified arachidonic acid signals apoptosis. Proc. Natl. Acad. Sci. USA 97 (21), 11280–11285.

Cole, S.W., Sood, A.K., 2012. Molecular pathways: beta-adrenergic signaling in cancer. Clin. Cancer Res. 18 (5), 1201–1206.

Condeelis, J., Pollard, J.W., 2006. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 124 (2), 263–266.

Cox, W.I., Holbrook, N.J., Friedman, H., 1983. Mechanism of glucocorticoid action on murine natural killer cell activity. J. Natl. Cancer Inst. 71 (5), 973–981.

de Oliveira Jr., G.S., Ahmad, S., Schink, J.C., Singh, D.K., Fitzgerald, P.C., McCarthy, R.J., 2011. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. Reg. Anesth. Pain Med. 36 (3), 271–277.

Decaens, T., Roudot-Thoraval, F., Bresson-Hadni, S., Meyer, C., Gugenheim, J., Durand, F., Bernard, P.H., Boillot, O., Compagnon, P., Calmus, Y., Hardwigsen, J., Ducerf, C., Pageaux, G.P., Dharancy, S., Chazouilleres, O., Cherqui, D., Duvoux, C., 2006. Role of immunosuppression and tumor differentiation in predicting recurrence after liver transplantation for hepatocellular carcinoma: a multicenter study of 412 patients. World J. Gastroenterol. 12 (45), 7319–7325.

Deegan, C.A., Murray, D., Doran, P., Ecimovic, P., Moriarty, D.C., Buggy, D.J., 2009. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function *in vitro*. Br. J. Anaesth. 103 (5), 685–690.

Deegan, C.A., Murray, D., Doran, P., Moriarty, D.C., Sessler, D.I., Mascha, E., Kavanagh, B.P., Buggy, D.J., 2010. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg. Anesth. Pain Med. 35 (6), 490–495.

Demicheli, R., Valagussa, P., Bonadonna, G., 2001. Does surgery modify growth kinetics of breast cancer micrometastases? Br. J. Cancer 85 (4), 490–492.

Detry, O., Honore, P., Meurisse, M., Jacquet, N., 2000. Cancer in transplant recipients. Transplant Proc. 32 (1), 127.

Ebert, L.M., Meuter, S., Moser, B., 2006. Homing and function of human skin gammadelta T cells and NK cells: relevance for tumor surveillance. J. Immunol. 176 (7), 4331–4336.

Elenkov, I.J., Chrousos, G.P., 2002. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann. NY Acad. Sci. 966, 290–303.

Eschwege, P., Dumas, F., Blanchet, P., Le Maire, V., Benoit, G., Jardin, A., Lacour, B., Loric, S., 1995. Haematogenous dissemination of prostatic epithelial cells during radical prostatectomy. Lancet 346 (8989), 1528–1530.

Exadaktylos, A.K., Buggy, D.J., Moriarty, D.C., Mascha, E., Sessler, D.I., 2006. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 105 (4), 660–664.

Faist, E., Schinkel, C., Zimmer, S., 1996. Update on the mechanisms of immune suppression of injury and immune modulation. World J. Surg. 20 (4), 454–459.

Gach, K., Szemraj, J., Wyrebska, A., Janecka, A., 2011. The influence of opioids on matrix metalloproteinase-2 and -9 secretion and mRNA levels in MCF-7 breast cancer cell line. Mol. Biol. Rep. 38 (2), 1231–1236.

Giguere, V., Labrie, F., 1983. Additive effects of epinephrine and corticotropin-releasing factor (CRF) on adrenocorticotropin release in rat anterior pituitary cells. Biochem. Biophys. Res. Commun. 110 (2), 456–462.

Glasner, A., Avraham, R., Rosenne, E., Benish, M., Zmora, O., Shemer, S., Meiboom, H., Ben-Eliyahu, S., 2010. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor. J. Immunol. 184 (5), 2449–2457.

Glass, C.K., Ogawa, S., 2006. Combinatorial roles of nuclear receptors in inflammation and immunity. Na. Rev. Immunol. 6 (1), 44–55.

Goldfarb, Y., Benish, M., Rosenne, E., Melamed, R., Levi, B., Glasner, A., Ben-Eliyahu, S., 2009. CpG-C oligodeoxynucleotides limit the deleterious effects of beta-

adrenoceptor stimulation on NK cytotoxicity and metastatic dissemination. J. Immunother. 32 (3), 280–291.
Goldfarb, Y., Sorski, L., Benish, M., Levi, B., Melamed, R., Ben-Eliyahu, S., 2011. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Ann. Surg. 253 (4), 798–810.
Goswami, S., Sahai, E., Wyckoff, J.B., Cammer, M., Cox, D., Pixley, F.J., Stanley, E.R., Segall, J.E., Condeelis, J.S., 2005. Macrophages promote the invasion of breast carcinoma cells via a colony-stimulating factor-1/epidermal growth factor paracrine loop. Cancer Res. 65 (12), 5278–5283.
Greenfeld, K., Avraham, R., Benish, M., Goldfarb, Y., Rosenne, E., Shapira, Y., Rudich, T., Ben-Eliyahu, S., 2007. Immune suppression while awaiting surgery and following it: dissociations between plasma cytokine levels, their induced production, and NK cell cytotoxicity. Brain Behav. Immun. 21 (4), 503–513.
Gupta, A., Bjornsson, A., Fredriksson, M., Hallbook, O., Eintrei, C., 2011. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. Br. J. Anaesth. 107 (2), 164–170.
Gupta, K., Kshirsagar, S., Chang, L., Schwartz, R., Law, P.Y., Yee, D., Hebbel, R.P., 2002. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 62 (15), 4491–4498.
Hata, K., Zhang, X.R., Iwatsuki, S., Van Thiel, D.H., Herberman, R.B., Whiteside, T.L., 1990. Isolation, phenotyping, and functional analysis of lymphocytes from human liver. Clin. Immunol. Immunopathol. 56 (3), 401–419.
Hegde, S., Fox, L., Wang, X., Gumperz, J.E., 2010. Autoreactive natural killer T cells: promoting immune protection and immune tolerance through varied interactions with myeloid antigen-presenting cells. Immunology 130 (4), 471–483.
Hellstrand, K., Hermodsson, S., 1989. An immunopharmacological analysis of adrenaline-induced suppression of human natural killer cell cytotoxicity. Int. Arch. Allergy Immunol. 89 (4), 334–341.
Henley, D.E., Lightman, S.L., 2011. New insights into corticosteroid-binding globulin and glucocorticoid delivery. Neuroscience 180, 1–8.
Howe, L.R., 2007. Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. Breast Cancer Res. 9 (4), 210.
Inbar, S., Neeman, E., Avraham, R., Benish, M., Rosenne, E., Ben-Eliyahu, S., 2011. Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity. PLoS One 6 (4), e19246.
Jones, M.K., Wang, H., Peskar, B.M., Levin, E., Itani, R.M., Sarfeh, I.J., Tarnawski, A.S., 1999. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. Nat. Med. 5 (12), 1418–1423.
Kalinski, P., 2012. Regulation of immune responses by prostaglandin E2. J. Immunol. 188 (1), 21–28.
Kim, R., Emi, M., Tanabe, K., Arihiro, K., 2006. Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res. 66 (11), 5527–5536.
Kinsey, D.L., 1961. Effects of surgery upon cancer metastasis. JAMA 178, 734–735.
Kirman, I., Cekic, V., Poltaratskaia, N., Asi, Z., Bessler, M., Huang, E.H., Forde, K.A., Whelan, R.L., 2002. Plasma from patients undergoing major open surgery stimulates in vitro tumor growth: lower insulin-like growth factor binding protein 3 levels may, in part, account for this change. Surgery 132 (2), 186–192.
Kirman, I., Jain, S., Cekic, V., Belizon, A., Balik, E., Sylla, P., Arnell, T., Forde, K.A., Whelan, R.L., 2006. Altered plasma matrix metalloproteinase-9/tissue inhibitor of matrix [corrected] metalloproteinase-1 concentration during the early postoperative period in patients with colorectal cancer. Surg. Endosc. 20 (3), 482–486.
Koren, H.S., Leung, K.H., 1982. Modulation of human NK cells by interferon and prostaglandin E2. Mol. Immunol. 19 (10), 1341–1346.
Kurosawa, S., Kato, M., 2008. Anesthetics, immune cells, and immune responses. J. Anesth. 22 (3), 263–277.
Landmann, R., 1992. Beta-adrenergic receptors in human leukocyte subpopulations. Eur. J. Clin. Invest. 1, 30–36.
Larmonier, N., Fraszczak, J., Lakomy, D., Bonnotte, B., Katsanis, E., 2010. Killer dendritic cells and their potential for cancer immunotherapy. Cancer Immunol. Immunother. 59 (1), 1–11.
Lee, J.W., Shahzad, M.M., Lin, Y.G., Armaiz-Pena, G., Mangala, L.S., Han, H.D., Kim, H.S., Nam, E.J., Jennings, N.B., Halder, J., Nick, A.M., Stone, R.L., Lu, C., Lutgendorf, S.K., Cole, S.W., Lokshin, A.E., Sood, A.K., 2009. Surgical stress promotes tumor growth in ovarian carcinoma. Clin. Cancer Res. 15 (8), 2695–2702.
Levi, B., Benish, M., Goldfarb, Y., Sorski, L., Melamed, R., Rosenne, E., Ben-Eliyahu, S., 2011. Continuous stress disrupts immunostimulatory effects of IL-12. Brain Behav. Immun. 25 (4), 727–735.
Li, Q., Liang, Z., Nakadai, A., Kawada, T., 2005. Effect of electric foot shock and psychological stress on activities of murine splenic natural killer and lymphokine-activated killer cells, cytotoxic T lymphocytes, natural killer receptors and mRNA transcripts for granzymes and perforin. Stress 8 (2), 107–116.
Liao, X., Che, X., Zhao, W., Zhang, D., Bi, T., Wang, G., 2010. The beta-adrenoceptor antagonist, propranolol, induces human gastric cancer cell apoptosis and cell cycle arrest via inhibiting nuclear factor kappaB signaling. Oncol. Rep. 24 (6), 1669–1676.
Lin, L., Liu, C., Tan, H., Ouyang, H., Zhang, Y., Zeng, W., 2011. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br. J. Anaesth. 106 (6), 814–822.
Looney, M., Doran, P., Buggy, D.J., 2010. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor beta in women undergoing anesthesia and surgery for breast cancer. Anesthesiology 113 (5), 1118–1125.
Luo, D., Vanderkerken, K., Chen, M.C., Vermijlen, D., Asosingh, K., Willems, E., Triantis, V., Eizirik, D.L., Kuppen, P.J., Wisse, E., 2001. Rat hepatic natural killer cells (pit cells) express mRNA and protein similar to in vitro interleukin-2 activated spleen natural killer cells. Cell. Immunol. 210 (1), 41–48.
Luo, D.Z., Vermijlen, D., Ahishali, B., Triantis, V., Plakoutsi, G., Braet, F., Vanderkerken, K., Wisse, E., 2000. On the cell biology of pit cells, the liver-specific NK cells. World J. Gastroenterol. 6 (1), 1–11.
Lutgendorf, S.K., Cole, S., Costanzo, E., Bradley, S., Coffin, J., Jabbari, S., Rainwater, K., Ritchie, J.M., Yang, M., Sood, A.K., 2003. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. Clin. Cancer Res. 9 (12), 4514–4521.
Macleod, A.S., Havran, W.L., 2011. Functions of skin-resident gammadelta T cells. Cell. Mol. Life Sci. 68 (14), 2399–2408.
Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpe, S., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10 (4), 313–318.
Martinet, L., Poupot, R., Fournie, J.J., 2009. Pitfalls on the roadmap to gammadelta T cell-based cancer immunotherapies. Immunol. Lett. 124 (1), 1–8.
Masera, R., Gatti, G., Sartori, M.L., Carignola, R., Salvadori, A., Magro, E., Angeli, A., 1989. Involvement of Ca2+-dependent pathways in the inhibition of human natural killer (NK) cell activity by cortisol. Immunopharmacology 18 (1), 11–22.
Masur, K., Niggemann, B., Zanker, K.S., Entschladen, F., 2001. Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. Cancer Res. 61 (7), 2866–2869.
McCoy, J.L., Rucker, R., Petros, J.A., 2000. Cell-mediated immunity to tumor-associated antigens is a better predictor of survival in early stage breast cancer than stage, grade or lymph node status. Breast Cancer Res. Treat. 60 (3), 227–234.
Melamed, R., Bar-Yosef, S., Shakhar, G., Shakhar, K., Ben-Eliyahu, S., 2003. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. Anesth. Analg. 97 (5), 1331–1339.
Melamed, R., Benish, M., Rosenne, E., Goldfarb, Y., Levi, B., Ben-Eliyahu, S., 2010a. The marginating immune compartments in rats' lungs and liver: characteristics of continuous inflammation and unique activation potential. Paper presented at the PNIRS, Dublin, Ireland.
Melamed, R., Rosenne, E., Benish, M., Goldfarb, Y., Levi, B., Ben-Eliyahu, S., 2010b. The marginating-pulmonary immune compartment in rats: characteristics of continuous inflammation and activated NK cells. J. Immunother. 33 (1), 16–29.
Melamed, R., Rosenne, E., Shakhar, K., Schwartz, Y., Abudarham, N., Ben-Eliyahu, S., 2005. Marginating pulmonary-NK activity and resistance to experimental tumor metastasis: suppression by surgery and the prophylactic use of a beta-adrenergic antagonist and a prostaglandin synthesis inhibitor. Brain Behav. Immun. 19 (2), 114–126.
Melchi, C.F., Mele, A., Baliva, G., Scio, M., Fucci, M., Pasquini, P., Corona, R., 1995. Prognostic value of anesthesia type for patients treated for cutaneous melanoma. Dermatol. Surg. 21 (9), 786–788.
Metelitsa, L.S., Naidenko, O.V., Kant, A., Wu, H.W., Loza, M.J., Perussia, B., Kronenberg, M., Seeger, R.C., 2001. Human NKT cells mediate antitumor cytotoxicity directly by recognizing target cell CD1d with bound ligand or indirectly by producing IL-2 to activate NK cells. J. Immunol. 167 (6), 3114–3122.
Metelitsa, L.S., Weinberg, K.I., Emanuel, P.D., Seeger, R.C., 2003. Expression of CD1d by myelomonocytic leukemias provides a target for cytotoxic NKT cells. Leukemia 17 (6), 1068–1077.
Motohashi, S., Nakayama, T., 2009. Invariant natural killer T cell-based immunotherapy for cancer. Immunotherapy 1 (1), 73–82.
Myles, P.S., Peyton, P., Silbert, B., Hunt, J., Rigg, J.R., Sessler, D.I., 2011. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ 342, d1491.
O'Reilly, M.S., Boehm, T., Shing, Y., Fukai, N., Vasios, G., Lane, W.S., Flynn, E., Birkhead, J.R., Olsen, B.R., Folkman, J., 1997. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell 88 (2), 277–285.
O'Reilly, M.S., Holmgren, L., Shing, Y., Chen, C., Rosenthal, R.A., Moses, M., Lane, W.S., Cao, Y., Sage, E.H., Folkman, J., 1994. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 79 (2), 315–328.
Oehling, A.G., Akdis, C.A., Schapowal, A., Blaser, K., Schmitz, M., Simon, H.U., 1997. Suppression of the immune system by oral glucocorticoid therapy in bronchial asthma. Allergy 52 (2), 144–154.
Page, G.G., Blakely, W.P., Ben-Eliyahu, S., 2001. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 90 (1–2), 191–199.
Page, G.G., McDonald, J.S., Ben-Eliyahu, S., 1998. Pre-operative versus postoperative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery. Br. J. Anaesth. 81 (2), 216–223.
Palermo-Neto, J., de Oliveira Massoco, C., Robespierre de Souza, W., 2003. Effects of physical and psychological stressors on behavior, macrophage activity, and Ehrlich tumor growth. Brain Behav. Immun. 17 (1), 43–54.
Pascual, M., Alonso, S., Pares, D., Courtier, R., Gil, M.J., Grande, L., Pera, M., 2011. Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer. Br. J. Surg. 98 (1), 50–59.

Penn, I., 1993. The effect of immunosuppression on pre-existing cancers. Transplantation 55 (4), 742–747.
Postow, M., Callahan, M.K., Wolchok, J.D., 2011. Beyond cancer vaccines: a reason for future optimism with immunomodulatory therapy. Cancer J. 17 (5), 372–378.
Prigione, I., Benvenuto, F., Bocca, P., Battistini, L., Uccelli, A., Pistoia, V., 2009. Reciprocal interactions between human mesenchymal stem cells and gammadelta T cells or invariant natural killer T cells. Stem Cells 27 (3), 693–702.
Reader, J., Holt, D., Fulton, A., 2011. Prostaglandin E(2) EP receptors as therapeutic targets in breast cancer. Cancer Metastasis Rev. 30 (3–4), 449–463.
Rettori, V., Fernandez-Solari, J., Mohn, C., Zorrilla Zubilete, M.A., de la Cal, C., Prestifilippo, J.P., De Laurentiis, A., 2009. Nitric oxide at the crossroad of immunoneuroendocrine interactions. Ann. NY Acad. Sci. 1153, 35–47.
Roche-Nagle, G., Connolly, E.M., Eng, M., Bouchier-Hayes, D.J., Harmey, J.H., 2004. Antimetastatic activity of a cyclooxygenase-2 inhibitor. Br. J. Cancer 91 (2), 359–365.
Rosenberg, S.A., Lotze, M.T., 1986. Cancer immunotherapy using interleukin-2 and interleukin-2-activated lymphocytes. Annu. Rev. Immunol. 4, 681–709.
Rosenne, E., Shakhar, G., Melamed, R., Schwartz, Y., Erdreich-Epstein, A., Ben-Eliyahu, S., 2007. Inducing a mode of NK-resistance to suppression by stress and surgery: a potential approach based on low dose of poly I-C to reduce postoperative cancer metastasis. Brain Behav. Immun. 21 (4), 395–408.
Schlagenhauff, B., Ellwanger, U., Breuninger, H., Stroebel, W., Rassner, G., Garbe, C., 2000. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. Melanoma Res. 10 (2), 165–169.
Schuller, H.M., Tithof, P.K., Williams, M., Plummer 3rd., H., 1999. The tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a beta-adrenergic agonist and stimulates DNA synthesis in lung adenocarcinoma via beta-adrenergic receptor-mediated release of arachidonic acid. Cancer Res. 59 (18), 4510–4515.
Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol. Bull. 130 (4), 601–630.
Seino, K., Motohashi, S., Fujisawa, T., Nakayama, T., Taniguchi, M., 2006. Natural killer T cell-mediated antitumor immune responses and their clinical applications. Cancer Sci. 97 (9), 807–812.
Seok, J.H., Kim, L.S., Hong, N., Hong, H.J., Kim, S.J., Kang, H.J., Jon, D.I., 2010. Psychological and neuroendocrinological characteristics associated with depressive symptoms in breast cancer patients at the initial cancer diagnosis. Gen. Hosp. Psychiatry 32 (5), 503–508.
Serafini, P., Borrello, I., Bronte, V., 2006. Myeloid suppressor cells in cancer: recruitment, phenotype, properties, and mechanisms of immune suppression. Semin. Cancer Biol. 16 (1), 53–65.
Sessler, D.I., Ben-Eliyahu, S., Mascha, E.J., Parat, M.O., Buggy, D.J., 2008. Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp. Clin. Trials 29 (4), 517–526.
Shaashua, L., Sominsky, L., Page, G.,Ben-Eliyahu, S., 2011. Stress and surgery reduce baseline plasma IL-12 levels in rats: mediation by prostaglandins and corticosterone, but not catecholamines. Paper presented at the PNIRS, Chicago, Illinois.
Shahzad, M.M., Arevalo, J.M., Armaiz-Pena, G.N., Lu, C., Stone, R.L., Moreno-Smith, M., Nishimura, M., Lee, J.W., Jennings, N.B., Bottsford-Miller, J., Vivas-Mejia, P., Lutgendorf, S.K., Lopez-Berestein, G., Bar-Eli, M., Cole, S.W., Sood, A.K., 2010. Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. J. Biol. Chem. 285 (46), 35462–35470.
Shakhar, G., Abudarham, N., Melamed, R., Schwartz, Y., Rosenne, E., Ben-Eliyahu, S., 2007. Amelioration of operation-induced suppression of marginating pulmonary NK activity using poly IC: a potential approach to reduce postoperative metastasis. Ann. Surg. Oncol. 14 (2), 841–852.
Shakhar, G., Ben-Eliyahu, S., 1998. *In vivo* beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. J. Immunol. 160 (7), 3251–3258.
Shakhar, G., Ben-Eliyahu, S., 2003. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann. Surg. Oncol. 10 (8), 972–992.
Shakhar, G., Blumenfeld, B., 2003. Glucocorticoid involvement in suppression of NK activity following surgery in rats. J. Neuroimmunol. 138 (1–2), 83–91.
Shavit, Y., Ben-Eliyahu, S., Zeidel, A., Beilin, B., 2004. Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study. Neuroimmunomodulation 11 (4), 255–260.
Sica, A., Schioppa, T., Mantovani, A., Allavena, P., 2006. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: potential targets of anti-cancer therapy. Eur. J. Cancer 42 (6), 717–727.
Sinicrope, F.A., Gill, S., 2004. Role of cyclooxygenase-2 in colorectal cancer. Cancer Metastasis Rev. 23 (1–2), 63–75.
Smyth, M.J., Godfrey, D.I., Trapani, J.A., 2001. A fresh look at tumor immunosurveillance and immunotherapy. Nat. Immunol. 2 (4), 293–299.
Sood, A.K., Armaiz-Pena, G.N., Halder, J., Nick, A.M., Stone, R.L., Hu, W., Carroll, A.R., Spannuth, W.A., Deavers, M.T., Allen, J.K., Han, L.Y., Kamat, A.A., Shahzad, M.M., McIntyre, B.W., Diaz-Montero, C.M., Jennings, N.B., Lin, Y.G., Merritt, W.M., DeGeest, K., Vivas-Mejia, P.E., Lopez-Berestein, G., Schaller, M.D., Cole, S.W., Lutgendorf, S.K., 2010. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. J. Clin. Invest. 120 (5), 1515–1523.
Sood, A.K., Bhatty, R., Kamat, A.A., Landen, C.N., Han, L., Thaker, P.H., Li, Y., Gershenson, D.M., Lutgendorf, S., Cole, S.W., 2006. Stress hormone-mediated invasion of ovarian cancer cells. Clin. Cancer Res. 12 (2), 369–375.
Soumaoro, L.T., Uetake, H., Higuchi, T., Takagi, Y., Enomoto, M., Sugihara, K., 2004. Cyclooxygenase-2 expression: a significant prognostic indicator for patients with colorectal cancer. Clin. Cancer Res. 10 (24), 8465–8471.
Stefanski, V., 2001. Social stress in laboratory rats: behavior, immune function, and tumor metastasis. Physiol. Behav. 73 (3), 385–391.
Svendsen, M.N., Werther, K., Nielsen, H.J., Kristjansen, P.E., 2002. VEGF and tumour angiogenesis. Impact of surgery, wound healing, inflammation and blood transfusion. Scand. J. Gastroenterol. 37 (4), 373–379.
Tavare, A.N., Perry, N.J., Benzonana, L.L., Takata, M., Ma, D., 2012. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents*. Int. J. Cancer 130 (6), 1237–1250.
Thaker, P.H., Han, L.Y., Kamat, A.A., Arevalo, J.M., Takahashi, R., Lu, C., Jennings, N.B., Armaiz-Pena, G., Bankson, J.A., Ravoori, M., Merritt, W.M., Lin, Y.G., Mangala, L.S., Kim, T.J., Coleman, R.L., Landen, C.N., Li, Y., Felix, E., Sanguino, A.M., Newman, R.A., Lloyd, M., Gershenson, D.M., Kundra, V., Lopez-Berestein, G., Lutgendorf, S.K., Cole, S.W., Sood, A.K., 2006. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat. Med. 12 (8), 939–944.
Thornton, L.M., Andersen, B.L., Blakely, W.P., 2010. The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Health Psychol. 29 (3), 333–337.
Tonnesen, E., Wahlgreen, C., 1988. Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. Br. J. Anaesth. 60 (5), 500–507.
Torgersen, K.M., Vaage, J.T., Levy, F.O., Hansson, V., Rolstad, B., Tasken, K., 1997. Selective activation of cAMP-dependent protein kinase type I inhibits rat natural killer cell cytotoxicity. J. Biol. Chem. 272 (9), 5495–5500.
Tseng, R.J., Padgett, D.A., Dhabhar, F.S., Engler, H., Sheridan, J.F., 2005. Stress-induced modulation of NK activity during influenza viral infection: role of glucocorticoids and opioids. Brain Behav. Immun. 19 (2), 153–164.
Uchida, A., Kariya, Y., Okamoto, N., Sugie, K., Fujimoto, T., Yagita, M., 1990. Prediction of postoperative clinical course by autologous tumor-killing activity in lung cancer patients. J. Natl. Cancer Inst. 82 (21), 1697–1701.
Uotila, P., 1996. The role of cyclic AMP and oxygen intermediates in the inhibition of cellular immunity in cancer. Cancer Immunol. Immunother. 43 (1), 1–9.
Vallejo, R., de Leon-Casasola, O., Benyamin, R., 2004. Opioid therapy and immunosuppression: a review. Am. J. Ther. 11 (5), 354–365.
van der Bij, G.J., Oosterling, S.J., Beelen, R.H., Meijer, S., Coffey, J.C., van Egmond, M., 2009. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. Ann. Surg. 249 (5), 727–734.
Vanderkerken, K., Bouwens, L., De Neve, W., Van den Berg, K., Baekeland, M., Delens, N., Wisse, E., 1993. Origin and differentiation of hepatic natural killer cells (pit cells). Hepatology 18 (4), 919–925.
Viswanathan, K., Dhabhar, F.S., 2005. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. Proc. Natl. Acad. Sci. USA 102 (16), 5808–5813.
Wada, H., Seki, S., Takahashi, T., Kawarabayashi, N., Higuchi, H., Habu, Y., Sugahara, S., Kazama, T., 2007. Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anesthesiology 106 (3), 499–506.
Wei, D., Wang, L., He, Y., Xiong, H.Q., Abbruzzese, J.L., Xie, K., 2004. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res. 64 (6), 2030–2038.
Weitz, J., Herfarth, C., 2001. Surgical strategies and minimal residual disease detection. Semin. Surg. Oncol. 20 (4), 329–333.
Whalen, M.M., Bankhurst, A.D., 1990. Effects of beta-adrenergic receptor activation, cholera toxin and forskolin on human natural killer cell function. Biochem. J. 272 (2), 327–331.
Wisse, E., van't Noordende, J.M., van der Meulen, J., Daems, W.T., 1976. The pit cell: description of a new type of cell occurring in rat liver sinusoids and peripheral blood. Cell Tissue Res. 173 (4), 423–435.
Wong, H.P., Ho, J.W., Koo, M.W., Yu, L., Wu, W.K., Lam, E.K., Tai, E.K., Ko, J.K., Shin, V.Y., Chu, K.M., Cho, C.H., 2011. Effects of adrenaline in human colon adenocarcinoma HT-29 cells. Life Sci. 88 (25–26), 1108–1112.
Yakar, I., Melamed, R., Shakhar, G., Shakhar, K., Rosenne, E., Abudarham, N., Page, G.G., Ben-Eliyahu, S., 2003. Prostaglandin e(2) suppresses NK activity *in vivo* and promotes postoperative tumor metastasis in rats. Ann. Surg. Oncol. 10 (4), 469–479.
Yamaguchi, K., Takagi, Y., Aoki, S., Futamura, M., Saji, S., 2000. Significant detection of circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. Ann. Surg. 232 (1), 58–65.
Yang, E.V., Kim, S.J., Donovan, E.L., Chen, M., Gross, A.C., Webster Marketon, J.I., Barsky, S.H., Glaser, R., 2009. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav. Immun. 23 (2), 267–275.
Yucel, Y., Barlan, M., Lenhardt, R., Kurz, A., Sessler, D.I., 2005. Perioperative hypothermia does not enhance the risk of cancer dissemination. Am. J. Surg. 189 (6), 651–655.
Zha, S., Yegnasubramanian, V., Nelson, W.G., Isaacs, W.B., De Marzo, A.M., 2004. Cyclooxygenases in cancer: progress and perspective. Cancer Lett. 215 (1), 1–20.
Zhang, D., Ma, Q., Shen, S., Hu, H., 2009. Inhibition of pancreatic cancer cell proliferation by propranolol occurs through apoptosis induction: the study of beta-adrenoceptor antagonist's anticancer effect in pancreatic cancer cell. Pancreas 38 (1), 94–100.