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

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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

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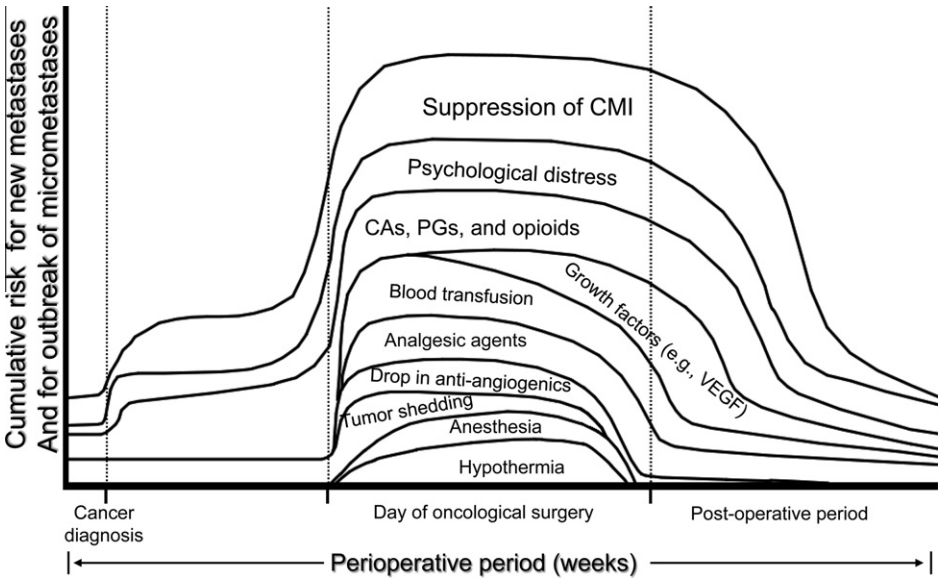

Fig. 1. A schematic representation of the cumulative kinetics of several perioperative risk factors for the initiation of new metastases and the outbreak of preexisting micrometastases in cancer patients (reviewed in Section 1). Each risk factor is represented by a horizontal layer, whose height at different 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