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Long-term consequences of the acute neural-inflammatory stress response in the cancer surgical patient: New findings and perspectives

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Introduction

Each year, as many as one in ten (10,000 procedures per 100,000 population) people living in high-income countries have surgery; 16–20% of those patients will suffer a major postoperative complication.¹ Postoperative infections occur in ~10% of patients, with an incidence ten-fold greater than that of postoperative myocardial infarction, and is likely related to altered immune function following surgery.² Surgery induces neural-inflammatory pathways that are integral to recovery from surgery and wound healing; unfortunately these pathways are also an integral component of cancer biology (Figure 1) with an alteration in immune function that may also impact cancer recurrence, increasingly recognised as a potential long-term perioperative complication that may impact cancer survival.³

Oncological surgical resection is an essential treatment modality for the management of many potentially curable solid tumors, with up to 80% of cancer patients needing anesthesia and surgery, often multiple times, for the diagnosis and/or removal of the bulk of the disease. However, of concern is that cancer surgery might in itself accelerate cancer growth and recurrence, an observation noted more than 150 years ago by Alfred Velpeau, a French anatomist and surgeon.⁴ More recently, different research teams have lent credibility to this observation, suggesting a chronologic (temporal) relationship between surgery for cancer diagnosis or treatment and cancer relapse, with a bimodal frequency of recurrence observed in patients having mastectomy for breast cancer.^{5–8} These database analyses report an early peak, with most relapses (50–80%) occurring within two years following surgery, and a late peak occurring several years later. The delayed second peak may relate to the formation of a

pre-metastatic niche in distant organs with entrapment of circulating tumor cells (CTC) that are released during surgical manipulation.^{9–11} These findings are not too surprising, as critically, neural activation and inflammation is clearly associated with the natural history of cancer¹² and biologic plausibility is found in the pathophysiological stress associated with surgery.¹³ Surgical tissue damage accompanied by the systemic release of hormones (eg. epinephrine, norepinephrine, cortisol), derived from the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis, promotes a strong inflammatory response and suppresses components of the immune system that protect against cancer^{14,15,16} These acute biological perturbations that are associated with the perioperative period may accelerate undetected micrometastatic disease to influence long-term cancer outcomes.³

Chronic stress biology and cancer

Stress biology modulates cancer outcomes through a neural-inflammatory pathway,^{17–19} with proinflammatory mediators shown to induce an immunosuppressive microenvironment in tumors.²⁰ Studies by others and us show that during periods of chronic stress, neurotransmitters (including epinephrine and norepinephrine) released by the SNS into the surrounding tissue and into the circulatory system bind cellular β -adrenergic receptors (β AR) on tumor cells, stromal cells within the tumor microenvironment, and immune cells.^{21–23} The initiation of a downstream signaling cascade leads to cAMP accumulation, protein kinase A phosphorylation, and transcription factor activation with modulation of cellular gene expression.^{24,25} As a direct consequence of this neural- β AR signaling we reported, in pre-clinical models of breast and pancreatic cancer, that long-term stress increases tumor cell dissemination from primary tumors to promote tumor cell colonization in distant organs.^{18,26,27} We demonstrated numerous effects of long-term stress on metastasis that are dependent on β AR stress signalling and on inflammation within immune cells, recruiting alternatively-activated macrophages to primary tumors.^{26,27} This tumor neural-inflammatory axis drives tumor cell dissemination via restructuring the tumor microenvironment by directly increasing tumor cell invasion and also by providing pathways for tumor cell escape. Using advanced imaging techniques in multiple pre-clinical models we found that chronic stress-induced inflammation remodels the intratumoral and draining lymphatic vessels through a VEGF-C-dependent mechanism, facilitating lymphatic mediated tumor cell dissemination.^{19,28} As such, the fundamental biologic process of inflammation, with increased endothelial permeability,^{29,30} immune cell trafficking, and increased lymphatic dilation and lymphatic flow that is intended to offset infection is ‘high-jacked’ by VEGF-expressing tumors. Breast cancers characterised by VEGF-C or VEGF-D overexpress the COX-2 enzyme or inhibit the enzyme prostaglandin dehydrogenase, with a net increase in prostaglandin levels. These prostaglandins, the common end product of inflammation (including acute surgical inflammation), mediate lymphatic dilation to facilitate dissemination of metastatic disease.²⁸ Importantly, epidemiological studies and animal studies show that β -blockers^{18,27,31–35} and anti-inflammatory agents^{28,35,36} reverse these effects. The importance of these agents as perioperative adjuncts to protect against cancer progression is gaining increasing interest.^{3,36}

Perioperative biologic perturbations and immune function

Tissue damage during surgery results in elevated inflammatory mediators, including prostaglandins, with local infiltration by inflammatory cells, including neutrophils and macrophages. It is this mechanism that is likely to play a key role in driving host susceptibility to cancer recurrence following surgery. Surgical stress profoundly impairs cell-mediated immunity and a key series of preclinical studies suggest that modulation of natural killer (NK) cell number and function impair the anti-cancer immune response and may impact cancer recurrence after surgery.^{37,38} Recognizing that the perioperative period is a window of opportunity for various interventions aimed at reducing the risk of cancer metastases – the major cause of cancer related death – we anticipate a number of studies that will target immune-stimulatory therapies, including those elevating marginating-pulmonary NK cell cytotoxicity.³⁹ It is important to note that while immunostimulants may be attractive perioperative therapies, the therapeutic effect is diminished in the context of stress, thereby placing further emphasis on adequate alleviation of the surgical stress response.^{39,40}

Similar to microbial-derived pathogen activated molecular patterns (PAMPS), tissues damaged by surgery releases alarmins (damage associated molecular patterns, DAMPS) that consist predominantly of intracellular components (e.g. mitochondrial DNA, High-Mobility-Group Box 1 protein). Both DAMPS and PAMPS activate pattern recognition receptors (e.g. membrane Toll-like receptor 9 (TLR9) and cytoplasmic NOD-like receptors) to mediate downstream phosphorylation of NF κ B and cytokine production, with consequent inflammatory and immunosuppressive effects that impact both the innate and adaptive immune systems. These changes include activation of neutrophils, impaired function of antigen presenting cells such as macrophages and dendritic cells, and TLR9-dependent immunoparesis of adaptive T-cell cytotoxicity. It is therefore not surprising that serum levels of DAMPS, such as mitochondrial DNA (mtDNA), correlate with 30-day mortality in septic patients.⁴¹ Gene expression analysis confirms that after severe tissue damage 80% of the genome in circulating leukocytes is activated, with up-regulation of genes that are characteristic of innate immunity pathways, B-cell receptor signaling and interleukin-10 signaling, and down-regulation of antigen presentation and T-cell activation.⁴²

A chronologic change in the cellular immune profile occurs in response to surgery, with neutrophils and platelets as the first-line responders. This immune signature may provide a critical link between neural-inflammation during surgery and cancer progression. Using single cell mass cytometry researchers characterized the phenotypic and functional alterations in the immune system in patients undergoing major surgery.⁴³ The cellular response and immune signature was characterised by an initial expansion of innate cell populations including neutrophils, NK cells, and CD14⁺ monocytes in the immediate postoperative period and then twenty-four hours later followed by a contraction of CD4⁺ and CD8⁺ T-cells and a six-fold expansion of neutrophil (granulocytic) and monocyte-derived cell subpopulations that are phenotypically similar to myeloid-derived suppressor cells (MDSC). Six weeks after surgery, the cell-subset frequencies were similar to pre-surgical values, indicating restoration of immune homeostasis. Importantly, MDSC subpopulations are increasingly implicated in immunosuppression and cancer biology.⁴⁴

Neutrophils, the most abundant leukocytes, play a key role in inflammation and in protecting the host against infection. These cells may also protect against cancer through direct or indirect (cell mediated and antibody mediated) cytotoxicity and enhanced adaptive immune responses by providing accessory signals for T-cell activation and facilitating T-cell recruitment and antigen presentation.⁴⁵ However, the effects of neutrophils on cancer cells seem to be dichotomous; while protecting against cancer they may also play a key role in inflammation-driven tumor growth, by secreting pro-angiogenic and proteolytic factors and recruiting other tumor promoting cells to the tumor bed. Activated neutrophils express high amounts of VEGF and MMP9, which is responsible for initiation of the angiogenic switch and support of vessel growth in tumors. Additionally, immature neutrophils, termed granulocytic myeloid-derived suppressor cells (G-MDSC), may also promote an immunosuppressive microenvironment within the tumor bed. At a systemic level, neutrophils in a pro-metastatic state secrete soluble factors, including proteases and cytokines, that activate endothelial and parenchymal cells, leading to pre-metastatic niche formation in distant organs that are prone to metastasis.⁴⁵ Neutrophils activated by platelets may also release chromatin DNA into the extracellular environment, with the formation of neutrophil extracellular traps (NET) that likely evolved to trap bacteria and parasites but may also promote adhesion of circulating tumor cells in the sinusoids of metastasis prone distant sites such as the lung and liver.¹¹

The conflicting observations that neutrophils possess a range of tumor promoting as well as tumor limiting properties may, however, relate to the fact that neutrophils are not a homogeneous population of cells and that neutrophils are highly responsive to cues in their microenvironment, which 'polarize' neutrophils to adopt an anti-tumor phenotype (N1 subpopulation, under the direction of IFN β) or a pro-tumor phenotype (N2 subpopulation, under the direction of TGF β) under certain conditions.⁴⁵ Together, these observations support the notion that neutrophil function in cancer may be dictated in a context-dependent fashion. As such, neutrophil release of tumor-promoting factors for wound-repair responses after surgery may in turn inadvertently stimulate tumor progression. Inflammatory factors, e.g. prostaglandin E2 (PGE2), are key drivers of this process. Alternatively, in cancer patients the neutrophil population may already be skewed towards the N2 phenotype, or those patients that are prone to a N2 phenotype are more likely to suffer the adverse effects of cancer surgery. This existence of neutrophil subsets may also explain why neutrophil counts or neutrophil-to-immune cell ratios (e.g. neutrophil-lymphocyte ration, NLR) often yield conflicting data in cancer outcome studies. These observations also identify the potential for therapeutically targeting cellular subpopulations, to enhance subsets with antitumor neutrophil activity while limiting those with pro-tumor properties.

Platelets, often only recognised for their hemostatic role, have a larger role as first line responders and as key inflammatory cells, with a multitude of signalling pathways that interact with the environment, inflammatory and thrombotic cascades, the endothelium and microcirculation.⁴⁶ When activated, platelets secrete numerous soluble factors that have the potential to mediate tumor progression, tumor cell survival, and angiogenesis.⁴⁷ Thrombocytosis and increased platelet activity is seen in a wide spectrum of cancers, and reported to correlate with a decrease in overall survival and poorer prognosis.⁴⁸ Within the complex tumor microenvironment platelets may promote tumor cell growth and survival

through paracrine signaling and complex interplay with tumor cells, immune cells, endothelial cells, and the extracellular matrix. Through direct cellular interactions and through secretion of bioactive proteins platelets may also facilitate tumor metastases. Platelets may aggregate with tumor cells, protecting them from host immune surveillance. Platelets may also activate neutrophils to form extracellular traps (NETs) that adhere circulating tumor cells in the sinusoids of distant organs that are prone to metastasis.¹¹ It has been shown that patients with the lowest platelet nadir after surgery were three times more likely to progress to a higher severity of post-operative kidney injury and had associated increased risk of mortality immediately after cardiac surgery.⁴⁹ While this observation is outside the setting of cancer surgery it likely points to the impact of poorly buffered inflammation with microvascular endothelial dysfunction and dysregulated biologic complexity during surgery. How this relates to cancer recurrence after cancer surgery requires further investigation. The opportunity these interactions afford to target platelets and platelet function to improve patient outcomes in the setting of cancer prevention and following cancer surgery warrants further investigation.

Myeloid cells are a major component of the tumor microenvironment. They develop an alternatively activated phenotype, which promotes tumor progression. Notably, myeloid cells including macrophages are highly sensitive to β -adrenergic stress signaling,⁵⁰ which increases their recruitment to the tumor microenvironment.²⁷ Tumor-associated macrophages participate in protumor functions including tumor growth and angiogenesis, and facilitate the metastatic cascade. Interfering with macrophage functions, e.g. through inhibition of perioperative neural-inflammatory pathways, may therefore provide an important strategy in the clinical management of cancer and metastatic disease progression after surgery.

NK cells play an important role in tumor immune surveillance by identifying and eliminating transformed cells.⁵¹ A unique population of NK cells, known as marginating-pulmonary NK cells are strategically located in the pulmonary vascular bed to recognize and eliminate abnormal circulating cells, as circulating malignant cells and infected cells are detained while passing through the lung capillaries.⁵² Tumor-derived cytokines and myeloid cells impair these NK cells and as such may play an important role in preparing the pre-metastatic niche to allow subsequent colonization by disseminated tumor cells.⁵³

From mechanisms to clinically available inflammatory biomarkers

As highlighted above, the integral role of surgical stress, acute inflammation and altered immune function on postoperative cancer recurrence renders the neural-inflammatory axis as a critical therapeutic target during the perioperative period (Figure 1). As such, the development of perioperative biomarkers to monitor at-risk patients and to assess therapeutic efficacy of anti-inflammatory strategies is warranted.

Individual inflammatory biomarkers and composite scores derived from several biomarkers have been proposed to predict oncological outcomes, both in the setting of surgical and non-surgical cancer treatments. These include C-reactive protein (CRP) level, white blood cell counts, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), the modified Glasgow prognostic score (mGPS), the Prognostic Index (PI), and the Prognostic

Nutritional Index (PNI).⁵⁴ Nevertheless, while inflammatory biomarkers and scores, including CRP, WBCs, NLR, and PNI are modified after surgery, the absence of concordance between these various biomarker scores suggests that they do not report on the same immune parameters and so are not interchangeable. As a result their use during the perioperative period to predict immune status and long term outcome should be interpreted cautiously. Indeed, NLR and CRP measures follow different kinetics after surgery suggesting that they reflect different mechanisms. Consistent with that, a multivariate analysis of a cohort of patients undergoing major abdominal surgery demonstrated moderate correlation between NLR and CRP.⁵⁵ In this study, increased NLR (but not CRP) at postoperative day 7 was an independent predictor of postoperative complications ($P<0.001$).⁵⁵ Similarly, others have reported that an elevated postoperative NLR value independently predicts immediate postoperative morbidity,⁵⁶ and 30-day and one-year mortality⁵⁷ following major abdominal surgery, and long-term recurrence after gastric cancer surgery⁵⁸. A systematic review and meta-analysis on the impact of pre-operative NLR on long-term outcomes after curative intent resection of solid tumors showed that patients with an elevated NLR >5 had significantly poorer overall and disease free survival, and may identify patients at increased risk that may benefit from anti-inflammatory strategies or more aggressive adjuvant therapy.⁵⁹

Pre-existing malnutrition is one the most important factors affecting post-surgical complications in cancer patients, and immune function can be improved through immunonutrition. The general concept of immunonutrition reflects the aim to improve immune cell function and inflammatory pathways (i.e. with a positive influence on outcome) with the oral intake of nutrients. Inflammatory and immune biomarkers would be useful in monitoring the effects of immunonutrition programs. Unfortunately, the utility of serum markers, such as albumin, transthyretin, leukocyte counts and C-reactive protein are limited and not specific to nutritional status. Similarly, composite scores are prognostic factors of outcome, but not always associated with an effect of immunonutrition.⁶⁰

Refinement of immune monitoring that aims to predict outcomes, beyond ratios such as NLR, may further improve identification of patient subpopulations that would benefit from interventions that seek to improve the surgical adaptive response (to surgery). This would help the clinician target different pathways to improve the immune defenses, e.g. by limiting SNS signaling to prevent lymphatic remodeling and metastatic dissemination in cancer patients. This would also be relevant to the acute stress and inflammation that accompanies cancer surgery. Chronic stress elevates the expression of tumor VEGF-C and shRNA VEGF-C knock-down studies confirm that tumor cell-derived VEGF-C is necessary for stress to affect lymphatic vasculature.^{17,35} As such, transcriptional profiling to reflect neural-inflammatory signaling in tumor biopsies (e.g. β -adrenoceptor, VEGF-C and COX-2) may be useful biomarkers to identify stressed individuals who may be vulnerable to the detrimental effects of chronic and acute surgical stress on cancer outcome. Given the ability of β -blockers to block SNS-induced elevation in VEGF-C levels, these data also suggest that VEGF-C may also be used as a biomarker for intervention success. Consistent with this hypothesis, a conserved transcriptional signature that includes an inflammatory component has been described in individuals who experienced chronic adverse life circumstances,⁶¹ and

may be used to identify individuals who are more likely to be responsive to therapies targeted at the tumor neural-inflammatory axis.

Perioperative modulation of the neural-inflammatory axis—An increasing number of preclinical and clinical studies suggest that perioperative factors, including anesthetic agents and anesthetic adjuncts (non-selective beta-blockers and NSAIDs), may impact long-term cancer outcome.^{3,62,63} While the steps in cancer progression that are most sensitive to surgical stress are yet to be definitively identified, the current evidence base supports a rationale to test interventions that target the neural-inflammatory pathway during cancer surgery. The goal of this intervention would be to prevent perioperative biologic disequilibrium, which in cancer patients may lead to postoperative accelerated tumor growth that is detrimental to long-term cancer outcomes.¹⁵⁵⁸

In addition, anesthetic agents *per se* have multiple other cellular effects – systemically and at the tumor site – that may impact cancer progression, either positively or negatively.⁶⁴ Anesthetic agents may inhibit neutrophil phagocytosis, induce lymphocytosis and modulate the hypothalamic-pituitary-adrenocortical, neural-immunoregulatory and cholinergic anti-inflammatory pathways. Accordingly, different anesthetic modalities may impact both short term and long term cancer outcomes.^{62,63,65,66} However, the results to date have been inconsistent, with some studies not reporting a cancer outcome benefit,^{67,68} which suggests that the most sensitive endpoints were not consistently evaluated across all studies.^{62,69}

A number of small, retrospective clinical studies suggest that when regional anesthesia, including paravertebral block, is added to general anesthesia during cancer surgery it may favourably impact cancer outcomes. Mechanisms may include improved analgesia, reduced SNS activation, modulation of the inflammatory burden, and opioid-sparing effects.^{62,67,70,71} However, the favorable effect on overall cancer survival and reduced postoperative nosocomial infections observed in those small studies were not confirmed by a *post hoc* analysis of a randomized control trial of regional analgesia⁶⁸ or by recent meta-analyses^{72,73}, and likely reflects the large heterogeneity amongst the numerous small studies included in the meta-analyses.^{72–74}

Non-steroidal anti-inflammatory drugs (NSAIDs) are ideally suited as a therapeutic intervention to target the neural-inflammatory axis. Indeed, in addition to their opiate-sparing effect, NSAIDs present a promising anticancer profile by inhibiting the pathophysiological steps of tumor proliferation and dissemination.³⁶ Therapeutic effects of chronic NSAID treatment in cancer have been described for various carcinoma types, with a great concordance between studies. While the role of NSAIDs in cancer prevention remains unclear, this is not related to a lack of data on their anticancer effect but, rather, to side effects associated with chronic administration.^{75,76} In animal models of surgery that investigated growth of disseminated cancer cells, concordant data has been published, suggesting a direct specific effect of NSAIDs on perioperative protumoral events, including survival and proliferation of circulating tumors cells and/or micrometastasis.^{77,78} Unfortunately, in human studies focusing on perioperative interventions to influence postoperative cancer outcome, methodological pitfalls including various endpoint selection and most often unreported NSAIDs use precludes any definitive conclusion.⁶⁹ Consequently,

additional studies that used patient registries of breast, prostate, lung and kidney cancer surgery, support a possible place for NSAIDs to reduce cancer recurrence risk.⁷⁹

In the future, characterising and quantifying the patient response to surgery, including changes in immune and inflammatory biomarkers, characterisation of immune cell surface markers and cytokine profiles, may identify patients at increased risk of complications due to immunocompromise, including nosocomial infection, in the immediate postoperative period and cancer recurrence in the long-term. As our understanding of the perioperative neural inflammatory and immune response increases we may be able to identify patients that may benefit from interventions that block the neural-inflammatory response, and patients that would benefit from immune stimulant strategies in order to reduce postoperative complications including cancer recurrence.

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Figure 1.

Points of pharmacological intervention (red) to block the adverse effects of surgical stress on cancer metastasis and recurrence