Harnessing cancer immunotherapy during the unexploited immediate perioperative period

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Abstract | The immediate perioperative period (days before and after surgery) is hypothesized to be crucial in determining long-term cancer outcomes: during this short period, numerous factors, including excess stress and inflammatory responses, tumour-cell shedding and pro-angiogenic and/or growth factors, might facilitate the progression of pre-existing micrometastases and the initiation of new metastases, while simultaneously jeopardizing immune control over residual malignant cells. Thus, application of anticancer immunotherapy during this critical time frame could potentially improve patient outcomes. Nevertheless, this strategy has rarely been implemented to date. In this Perspective, we discuss apparent contraindications for the perioperative use of cancer immunotherapy, suggest safe immunotherapeutic and other anti-metastatic approaches during this important time frame and specify desired characteristics of such interventions. These characteristics include a rapid onset of immune activation, avoidance of tumour-promoting effects, no or minimal increase in surgical risk, resilience to stress-related factors and minimal induction of stress responses. Pharmacological control of excess perioperative stress–inflammatory responses has been shown to be clinically feasible and could potentially be combined with immune stimulation to overcome the direct pro-metastatic effects of surgery, prevent immune suppression and enhance immunostimulatory responses. Accordingly, we believe that certain types of immunotherapy, together with interventions to abrogate stress–inflammatory responses, should be evaluated in conjunction with surgery and, for maximal effectiveness, could be initiated before administration of adjuvant therapies. Such strategies might improve the overall success of cancer treatment.

Surgical excision of the primary tumour is a cornerstone intervention in the curative-intent treatment of solid tumours. Nevertheless, disease recurrence, particularly in the form of distant metastases, remains a common concern and a key therapeutic challenge. Typically, anti-metastatic interventions, such as chemotherapy, radiotherapy or immunotherapy, are administered up to 1 month before surgery or are otherwise initiated no earlier than 1 month after surgery; the immediate perioperative period (IPP), spanning a few days before and after surgery (including the surgical period itself), is rarely exploited for such interventions given the justified and/or speculated concerns over contraindications to surgery. In this Perspective, we challenge the necessity of this dissociation and advocate for greater recognition of the clinical potential of perioperative anti-metastatic interventions, especially immunotherapies, on the basis of three foundations. First, the perioperative period provides a short window of opportunity to efficiently arrest metastatic progression with relatively minimal effort and innocuous treatments, but thereafter this goal becomes more challenging, not least because the IPP and associated factors might enable residual disease to transform into larger, proliferating, self-sustaining malignant foci with more elaborate escape mechanisms. Second, some existing immunotherapies present tolerable or circumventable contraindications to surgery and can, therefore, be used perioperatively. Third, a solid biological rationale supports the likely efficacy of various potentially synergistic anti-metastatic interventions during the IPP, including approaches to enhance immune preservation, immunometabolism and anticancer immune responses, whilst limiting stress–inflammatory responses that might directly affect malignant tissue and promote disease progression. These approaches could potentially be integrated into clinical investigations or routines.

The immediate perioperative period

For patients with cancer, the IPP encompasses a short stressful preoperative period of awaiting surgery, followed by a set of medical processes, including admission, hospitalization, preparations for surgery, anaesthesia and surgical procedures, as well as subsequent postoperative convalescence and functional recovery[1]. The duration of the IPP commonly ranges between days and a few weeks, depending on the required preparations for and magnitude of the surgery. In patients with cancer, accumulating evidence indicates that this relatively short period has a disproportionate influence on long-term metastatic outcomes[2,3]. Specifically, although surgery is usually successful in completely removing the primary tumour, most patients continue to harbour minimal residual disease (MRD) in the form of dormant or active micrometastases and/or scattered single tumour cells in the circulation and/or the lymphatic system[4,5]. In clinical trials, improvements in disease-free survival and/or overall survival (OS) have been observed with interventions restricted to the IPP, thus suggesting that perioperative factors have substantial effects on the progression of MRD[6–8]. In preclinical studies, the biological stress responses to surgery, including sympathetic, inflammatory, immunosuppressive, pro-angiogenic and/or pro-growth responses, have specifically been shown to increase the risk of cancer recurrence[2,3]. These risk factors, which are

in fact ascribed to the entire IPP (including surgery), enable or foster residual cancer cells to establish new metastatic foci or overcome obstacles in escaping dormancy, and/or to expand to form large and proliferating metastatic foci[2,3,9]. Notably, sympathetic stress responses facilitate inflammatory responses, and vice versa, creating a vicious cycle that promotes cancer progression[10]. Herein, we discuss the consequences of specific aspects of surgery and related stress–inflammatory responses on malignant tissues, as well as on anti-metastatic immune activity.

Immune suppression during the IPP

Immunosuppression throughout the perioperative period is an established phenomenon[11] that has been shown to accelerate metastatic progression in animal models[12–14]. In patients undergoing surgery, immunosuppression is a multifactorial process[15] that can begin even while awaiting surgery[16]. Potential contributors to perioperative immunosuppression include: anxiety and stress, which lead to the secretion of glucocorticoids, catecholamines and other stress hormones[2,17,18]; inflammatory responses, such as the release of prostaglandins, triggered by stress, the malignant tissue, anaesthetics, analgesics and surgical tissue damage[19,20]; hypothermia[21], which is associated with secretion of glucocorticoids and catecholamines[21], reduces the production of cytokines with anti-metastatic effects[22,23] and attenuates mitogen-induced immune responses[22]; blood loss and/or transfusion[24], which increases prostaglandin production, decreases IL-2 and antibody production and attenuates natural killer (NK) cell cytotoxicity[25]; and direct and indirect effects of anaesthetic and analgesic agents on cancer progression[26]. The immunosuppressive effects of these phenomena are mediated by alterations in the secretion of various factors by and/or the activity of several leukocyte populations, including monocytes[27,28], NK cells[14] and T cells[29] (TABLE 1). These complex immunological mechanisms are beyond the scope of this article and have been previously reviewed elsewhere[29,30].

Table 1 | **Factors with immunomodulatory effects in the IPP in preclinical models**[a]

Modulating factor	Model	Biological effects	Refs
Catecholamines	Human cells in vitro	↓ IL-12 levels ↓ NK cell cytotoxicity	190,191
	Rats	↓ NK cell cytotoxicity	192
	Mice	↓ B cell and T cell proliferation	193
Glucocorticoids	Human cells in vitro	↑ pDC apoptosis	141
	Rats	↓ IL-1β, IL-12 and TNF levels	194–196
	Mice	↑ Macrophage, DC and T cell apoptosis	194
		↓ NF-κB pathway activity	195,197
		↓ DC and monocyte differentiation and proliferation	198
Prostaglandin E_2	Human cells in vitro	↑ Regulatory T cell inhibitory capacity and numbers	199,200
	Mice	↓ IL-12 levels ↑ IL-10 levels	201
		↑ M2-phenotype macrophage differentiation	202
		↓ DC differentiation and activity	203
		↓ $CD4^+$ and $CD8^+$ T cell numbers ↓ $CD8^+$ T cell cytotoxicity	203
General anaesthetics (ketamine, thiopental, halothane and isoflurane)	Rats	↓ NK cell cytotoxicity ↓ NK cell numbers	204,205
General anaesthetics (propofol)	Rats	↓ NK cell numbers	204,205
General anaesthetics (propofol + omega-3)	Human cells in vitro	↑ Antitumour activity	206
Regional anaesthetics	Human cells in vitro Mice	↑ EGFR inhibition ↑ Antitumour activity	207–210
Opioid analgesics	Human cells in vitro	↓ Superoxide anion generation by PBMCs ↓ IFNγ and TNF production ↓ Tumour cell proliferation	211–213
	Human cells ex vivo	↓ Superoxide anion generation by PBMCs	211
	Rats	↑ SNS activity ↑ HPA axis activity	214–216
	Mice	↓ Lymphocyte proliferation ↓ IL-2 levels ↓ NK cytotoxicity	217
		↓ Macrophage phagocytic activity ↓ VEGF production	218,219
		↓ IL-1β and TNF levels	220

DC, dendritic cell; HPA, hypothalamic–pituitary–adrenal; IPP, immediate perioperative period; NK cell, natural killer cell; NF-κB, nuclear factor-κB; PBMC, peripheral blood mononuclear cell; pDC, plasmacytoid dendritic cell; SNS, sympathetic nervous system; TNF, tumour necrosis factor. [a]Partial list mostly related to mechanisms discussed in this paper.

Effects on malignant tissues

In the past two decades, various stress and inflammatory factors, and specifically catecholamines and prostaglandins, have been demonstrated to have direct effects on primary tumours and residual cancer cells, causing them to adopt pro-metastatic characteristics. Specifically, tumour cells exposed to such factors release increased amounts of pro-angiogenic factors (including VEGF), undergo epithelial-to-mesenchymal transition, acquire pro-metastatic molecular characteristics (for example, increased expression of STAT3)[31,32] and recruit and convert monocytes to tumour-promoting M2-like macrophages[33]. The tumour microenvironment is also affected by catecholamines, prostaglandins and other factors released in response to surgical stress, becoming more pro-growth and/or pro-metastatic, thus supporting the progression of MRD[2,3,34].

Window to prevent metastatic disease

Evidence from preclinical and clinical studies indicates that the multiple immunological and non-immunological pro-metastatic processes associated with the

IPP can independently and synergistically promote the progression of MRD in the perioperative context[2,35]; thus, the risk of metastatic disease is markedly increased, which suggests that the IPP is highly influential in determining long-term cancer outcomes, disproportionately to its short duration. For example, exposure of residual tumour cells or micrometastases to various growth and pro-angiogenic factors, secreted by non-malignant cells and/or the malignant cells themselves, might terminate a dormant state of the malignant foci and/or promote angiogenesis, potentially enabling the outgrowth of metastatic disease[9,36]. Concurrently, suppression of anticancer immunity might prevent cytotoxic T cells and NK cells from detecting and controlling residual disease, thereby permitting circulating tumour cells to extravasate and colonize distant organs as well as enabling micrometastases to proliferate, increase in heterogeneity (acquire additional escape mechanisms)[37], become self-sustaining[38] and, thus, eventually form immune-resilient malignant masses[39].

Owing to the likely disproportionate influence of the IPP on long-term patient outcomes, the development of interventions to optimize host immunity and physiological antitumour indices during this crucial time frame should be a research priority. To date, however, few trials exploiting this important window of opportunity have been focused on immunotherapies and/or approaches to reduce the stress–inflammatory response[8,35].

Perioperative chemotherapy

The immediate postoperative period involves wound healing processes, which are essential for a favourable surgical outcome. Thus, perturbations of this complex biological process by any intervention can result in severe surgical complications, such as anastomosis leakage that is associated with worse prognosis[40]. Some chemotherapeutic drugs and biologic agents (for example, the anti-VEGFA antibody bevacizumab)[41] can compromise immune function and/or wound healing, and therefore cannot be used safely during the perioperative period[42,43]. Indeed, in conjunction with surgery, chemotherapy can have serious adverse clinical effects, depending on the dosage, timing and mode of administration[42]. With regard to wound healing, perioperative use of alkylating agents, such as cisplatin and cyclophosphamide, has been shown to have detrimental effects (for example, decreased wound tensile strength) in animal models[44–46], but more limited or no effects on this process in clinical studies (according to the observed complication rates)[47]. Similarly, antimetabolites have been associated with inconsistent and often contradictory results in preclinical and clinical studies. For example, when administered intraperitoneally to rats at the end of surgery, methotrexate and 5-fluorouracil (5-FU) had contrasting effects on wound healing: at 14 days after surgery, methotrexate impaired the healing of colon anastomoses, which was associated with considerable weight loss, whereas 5-FU had no such effects[48]. Conversely, when different administration methods were used in clinical studies, whereby methotrexate was supplemented with folinic acid, no wound-healing complications were observed[49], whereas 5-FU used without any additional agents — a non-conventional approach — caused an increase in 'wound morbidity' for up to 10 days after surgery[50]. Antibiotics with antitumour activity, including doxorubicin and mitomycin C, also seem to have inconsistent effects: these agents hinder wound healing in some animal models, although this effect is dependent on the dosage, timing and route of administration[42].

Chemotherapy should also be considered with respect to its effects on the immune system as well as its temporal relation to surgery and other treatments. Chemotherapy-induced immune modulation has been studied extensively[51], and particular chemotherapies are known to have either immunosuppressive effects (for example, methotrexate)[52] or specific immune-enhancing antitumour effects (such as doxorubicin and gemcitabine)[53,54]. The inclusion of some types of chemotherapy in effective perioperative anti-metastatic approaches is, therefore, theoretically and practically feasible[53,55], with minimal or preventable deleterious effects on immunity or immunotherapies[55,56]. However, long periods of immunosuppression lasting up to 6 months have been reported following some types of chemotherapy[54,57,58]. Thus, such chemotherapies might theoretically increase the risk of postoperative infections and thereby jeopardize the efficacy of subsequent immunotherapy.

Overview of anticancer immunotherapy

The objective of anticancer immunotherapy is to activate or enhance various host cellular and/or humoral immune responses to the malignant tissue, with the aim of inducing regression or at least growth arrest of overt tumours and/or any occult disease, thus preventing local and distant recurrence[59]. Such goals can potentially be achieved by: directly activating immune cells, for example, using immunostimulatory cytokines[60] or Toll-like receptor (TLR) agonists[61]; deactivating inhibitory signals transmitted via various immune-checkpoint molecules, such as cytotoxic T lymphocyte protein 4 (CTLA-4) or programmed cell death 1 (PD-1) [62]; utilizing oncolytic viruses[63] or monoclonal antibodies[64] directed at the malignant tissue to induce various processes (such as immunogenic cell death, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) that enhance the capacity of the immune system to recognize and respond to tumour cells; or immune preservation and/or augmentation through blockade of various systemic immune suppressive factors (for example, using β-blockers or cyclooxygenase 2 (COX2) inhibitors) or the use of immunometabolic strategies (for example, arginine supplementation)[65] (TABLE 2). During the past decade, cancer immunotherapy has gained momentum following several successful clinical trials, in particular, of immune-checkpoint inhibitors. Across a range of solid cancers, several immune-checkpoint inhibitors have been shown to delay disease progression more effectively than standard chemotherapy[66,67], shrink operable and inoperable tumours, prolong OS and, in some patients, lead to durable complete remissions and perhaps cures[46,47,68].

Nevertheless, the current FDA-approved immunotherapies are often indicated as delayed or second-line treatments, either weeks following surgery, aiming to reduce the potential recurrence of cancers (such as melanoma)[69], or upon presentation with recurrent and/or metastatic disease (for example, breast cancer[70], oesophageal cancer[71], non-small-cell lung cancer[72] or melanoma[73]). These strategies might not harness the full potential of immunotherapy. Specifically, some types of chemotherapy exert long-lasting suppression of immune function, and therefore the use of immunotherapies following chemotherapy would be suboptimal. Moreover, delayed immunotherapy is unlikely to adequately counter the risk factors associated with cancer surgery or exploit the window of opportunity presented by the IPP.

Immediate perioperative immunotherapy

Potential risks and benefits

Routine or experimental use of immunotherapies during the IPP is rare, owing to several established and theoretical risks pertinent around the time of surgery.

Table 2 | **Examples of anticancer immunotherapeutic approaches**

Therapy	Target cells	Biological activity	Notable adverse effects	Current stage of clinical development	Refs
Immunometabolic interventions					
Pegylated arginine deiminase (arginine depletion)	Tumour cells	Arginine deprivation and induced starvation of auxotrophic tumour types, such as hepatocellular carcinoma, melanoma and prostate adenocarcinoma (in patients)	Anaphylactic reactions (rare)	Phase II–III	221–223
L-arginine (arginine supplementation)	Monocyte, NK cells and tumour cells	Increased macrophage phagocytic activity; increased NK cell cytotoxicity; and decreased tumour cell growth in some cancer types (in human cells ex vivo and in patients)	Increased insulin, growth hormone and glucagon secretion; unwanted direct growth stimulation of some cancer types	Phase III–IV	224–228
Phenylacetate (glutamine depletion)	Tumour cells	Inhibition of tumour cell proliferation and promotion of tumour cell differentiation to a non-malignant phenotype (in human cell lines in vitro)	Cachexia	Phase II–III	229–232
TLR agonists					
Poly I:C or IPH 3102 (TLR3 agonists)	DCs, NK cells and tumour cells	Increased type I interferon secretion, increased activation of NK cells, CTLs, DCs and macrophages, decreased expression of PD-1 on CTLs and decreased tumour infiltration of MDSCs (in mouse models); increased tumour cell apoptosis (in human cells in vitro)	Fever, flu-like symptoms, increased serum levels of liver enzymes and fibrin degradation products	Phase I–II	100,233–236
GLA, MPL or AGP (TLR4 agonists)	DCs, eosinophils, monocytes, neutrophils and tumour cells	Increased induced production of IFNγ, IL-12 and TNF (in human cells in vitro and in patients); decreased tumorigenesis (in mouse models)	LPS-induced increase in the growth of some cancer cell types (in human cells in vitro); LPS-induced increase in IL-6, IL-8, VEGF and TGFβ production (in murine models)	GLA: phase I; MPL: FDA-approved as an adjuvant for HPV vaccination with Cervarix	100,237–239
Imidazoquinolines, 852A or imiquimod (TLR7 agonists)	DCs, B cells and tumour cells	Increased tumour cell immunogenicity, increased proliferation of B cells and T cells, and increased expression of co-stimulatory proteins (in human cells in vitro); increased induced production of TNF, and increased type I interferon secretion (in patients)	Local administration site reaction, flu-like symptoms, fever, fatigue, nausea and myalgia	852A: phase II; Imiquimod: FDA approved	100,234,240,241
CpG ODN 7909 or MGN-1703	Plasmacytoid DCs and B cells	Increased median overall survival durations, increased CTL cytotoxicity against tumour cells, increased B cell proliferation, increased antigen-specific antibody production, increased IFNα secretion and increased expression of co-stimulatory molecules (in patients); increased resistance to apoptosis (in humans cells in vitro)	Flu-like symptoms, local injection site reaction, neutropenia, thrombocytopenia and anaemia (rare)	Phase II–III	91,100,121, 234,242,243
Cytokines					
IL-2	T cells, NK cells, B cells and ILC2s	Increased NK cell cytotoxicity and numbers, increased lymphocyte and $CD4^+$ T cell numbers, and increased induced production of IFNγ (in human cells ex vivo and in patients); increased overall survival (in patients and mouse models); increased differentiation of pathogen-specific $CD8^+$ memory T cells (in mouse models)	Transaminasaemia, nausea and vomiting, increased risk of acute renal failure, fever, increased risk of uraemic pruritus and eosinophilia	FDA-approved	8,167,168, 244–246
IFNα	Monocytes, NK cells, T cells, DCs and B cells	Decreased VEGF secretion and decreased T_{reg} cell numbers and activity (in patients); increased NK cell cytotoxicity (in human and mouse cells ex vivo); increased CTL cytotoxicity and increased antibody-dependent macrophage cytotoxicity (in mouse models)	Flu-like symptoms, leukopenia, thrombocytopenia, induction of autoimmune syndromes and depression	FDA-approved	170,171,247–250

Table 2 (cont.) | **Examples of anticancer immunotherapeutic approaches**

Therapy	Target cells	Biological activity	Notable adverse effects	Current stage of clinical development	Refs
Oncolytic viruses					
JX-594, Reolysin, Talimogene laherparepvec and Onyx-015	Tumour cells	Increased tumour cell death via direct viral effects, release of tumour antigens and promotion of antiviral and antitumour immune cell activation (NK cells, T cells and so on) (in mouse models, human cells ex vivo and in patients); increased overall survival (in mouse models)	Flu-like symptoms	Reolysin and Onyx-015: phase II–III; Talimogene laherparepvec: FDA-approved; JX-594: FDA orphan drug designation	251–254
Immune-checkpoint inhibitors					
Ipilimumab and tremelimumab (anti-CTLA4 antibodies)	T cells	Increased abundance of $CD4^+ICOS^+$ T cells in periphery and tumour tissue, and increased CTL cytotoxicity against tumour cells (in human cells ex vivo and in patients); increased overall survival (in patients and mouse models); increased and prolonged tumour-specific CTL response and reversed antigen tolerance by CTLs (in mouse models)	Increased risk of autoimmune manifestations, diarrhoea, pruritis and hepatotoxicity	Ipilimumab: FDA-approved; Tremelimumab: FDA orphan drug designation; phase II–III	87,255–257
Pembrolizumab, atezolizumab and nivolumab (anti-PD-1 or anti-PD-L1 antibodies)	T cells, NK cells and B cells	Decreased induction of CTL apoptosis by tumour cells, increased CTL cytotoxicity against tumour cells and increased overall survival (in human cells ex vivo and/or in patients)	Myocarditis, myositis, myasthenia gravis and pneumonitis	FDA-approved	258–261
PF-04518600 (anti-OX40 antibodies)	T cells	Increased antitumour activity of T cells and B cells, and increased infiltration of T cells into the tumour microenvironment (in patients); increased CTL survival and cytotoxicity (in mouse and primate models); attenuation of T_{reg} cell-induced inhibition of CTL (in mouse models)	Splenomegaly and lymphadenopathy (in primates)	Phase II	262–268

AGP, aminoakyl glucoaminide 4-phosphate; CTL, cytotoxic T cell; CTLA-4, cytotoxic T lymphocyte protein 4; DC, dendritic cell; GLA, glucopyranosyl lipid adjuvant; HPV, human papillomavirus; ICOS, inducible T cell co-stimulatory; IFN, interferon; ILC2, group 2 innate lymphoid cell; LPS, lipopolysaccharide; MDSC, myeloid-derived suppressor cell; MPL, monophosphoryl lipid A; NK cell, natural killer cell; ODN, oligodeoxynucleotide; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; polyI:C, polyinosinic–polycytidylic acid; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{reg} cell, regulatory T cell.

In addition to potential deleterious effects on wound healing, such concerns include the induction of fever, weakness, headaches, changes in blood pressure and low white blood cell counts[74–76]. As well as increasing the risk of post-surgical complications[77], these physiological perturbations cannot be distinguished from signs of infection and might result in surgery being delayed, thereby potentially negating the effects of perioperative immunotherapy or even resulting in loss of disease control. Indeed, we examined the latest 300 clinical trials registered by the US National Cancer Institute (NCI) and ClinicalTrials.gov (from 1 January 2016 to date), searching for the keywords 'immune therapy' and 'immunotherapy', and found only 10 trials that included the IPP as a target window for therapeutic intervention; most of these 10 trials involved immune preservation or nutritional approaches. Moreover, the exclusion criteria in most of the 300 trials required a minimum period of 3–4 weeks between any type of surgery and either the initiation of postoperative immunotherapy or the termination of preoperative immunotherapy[78,79].

We suggest, however, that the use of immunotherapy as a routine treatment, especially during the crucial IPP, could hold various advantages. To reiterate, the short perioperative period seems to be non-proportionally influential in determining long-term cancer outcomes, and thus any treatment that is successfully applied during this time frame is likely to be more effective than application of the same treatment at other periods in the cancer care continuum. In addition, removal of the primary tumour often results in decreased production of tumour-secreted and/or tumour-associated immunosuppressive factors[2,11] (for example, IL-10 and TGFβ secreted by tumour-associated macrophages[80] or prostaglandins produced by tumour cells[81]), and thus immunotherapy might have increased effectiveness in enhancing immune capacity to eradicate MRD when applied during the IPP. Such early activation or reinvigoration of the anticancer immune response, prior to adaptation of various new escape mechanisms by the residual disease following tumour excision, might minimize the potential for transformation of MRD into proliferating metastatic foci[82]. Indeed, circulating tumour cells could potentially be more efficaciously controlled by immune cells activated through immunotherapy during the IPP, preventing their extravasation and metastatic colonization of distant organs.

Theoretically, simultaneous use of several antitumour treatment modalities has advantages over serial treatment because each sequential intervention, in turn, can select for more elaborate escape mechanisms, resulting in tumour cells that are highly resistant to therapy[83]. Thus, applying immune-enhancing approaches perioperatively[84,85] — simultaneously with

removal of the primary source of circulating tumour cells, elimination of primary tumour-associated immunosuppressive effects and support for metastatic foci[86], and attenuation of excess stress–inflammatory responses — would be advantageous over the serial use of such approaches.

Desired characteristics

The use of immunotherapy during the IPP might present challenges, for example, relating to an increased risk of adverse events or enhancement of pro-metastatic processes. To enable a safe and efficacious use of immunotherapy during this time frame, approaches that induce a rapid immunological response, lack tumour-promoting effects, present minimal contraindications to surgery, are resilient to perioperative stress and have a limited capacity to induce stress responses should be pursued.

Rapid immunological response. Whereas some immunotherapeutic approaches, such as those involving IL-12 or the antagonistic anti-CTLA-4 antibody ipilimumab, are based on repeated dosing and require weeks or months to generate the desired responses[87,88], others induce rapid activation of immune responses and/or modification of immunological indices[89]. Interventions of the latter type should be prioritized in the development of effective perioperative immunotherapy, given the limited duration of the IPP. For example, 7 days of an immune-enhancing nutritional diet (including arginine, omega-3 fatty acids and RNA supplements), beginning at 6 h post surgery, have been associated with a reduction in postoperative infectious complications as well as the incidence of anastomotic leak in patients with gastric cancer[90]. In patients with non-Hodgkin lymphoma, increases in the number of and cytotoxicity activity of circulating NK cells were observed several hours following treatment with the TLR9 agonist CpG 7907, reaching peak levels after 48 h (REF.[91]). Moreover, treatment of patients with ovarian cancer using ACA125, a monoclonal anti-idiotypic antibody mimicking an epitope of ovarian carcinoma antigen 125 (CA125), yielded markedly increased intracellular levels of the T helper 1 cell-type cytokines IFNγ and IL-2 within 72 h (REF.[92]). Moreover, preclinical studies have demonstrated the anti-metastatic effects of TLR agonists (including CpG class C (CpG-C) or polyinosinic–polycytidylic acid (polyI:C) oligodeoxynucleotides, glucopyranosyl lipid adjuvant (GLA), resiquimod and an influenza vaccine) and cytokines (such as IL-12) or stimulation of interferon gene expression using STING-RR (2′3′-c-di-AM(PS)2 (Rp,Rp))[93–98]. These interventions were effective when administered during the IPP (typically <24 h before tumour excision)[93–98].

Avoidance of tumour-promoting effects. Unfortunately, some types of immunotherapy might have tumour-promoting effects, for example, by increasing recruitment of specific immunosuppressive subsets of lymphocyte to the tumour microenvironment[99] or by increasing the proliferation of tumour cells[100,101]. In addition, in vitro treatment with the TLR4 agonist lipopolysaccharide (LPS) for 24 h engendered human lung cancer cells with resistance to apoptosis induced by tumour necrosis factor (TNF) or TNF-related apoptosis-inducing ligand (TRAIL)[102]; the viability of tumour cells from patients with ovarian cancer (as determined in cell proliferation assays) was increased 24–48 h following similar treatment[103]. Correspondingly, expression of MYD88, a key adapter protein of the TLR4 signalling pathway, in excised ovarian tumour tissue was associated with inferior recurrence-free survival after surgery and six cycles of adjuvant paclitaxel and carboplatin (median 23 months versus 42 months in patients with tumours lacking expression of MYD88; $P=0.03$)[103]. The immunostimulatory cytokine granulocyte–macrophage colony-stimulating factor (GM-CSF) has been shown to promote the in vitro proliferation of several human cancer cell lines, including osteogenic sarcoma, breast carcinoma and colon adenocarcinoma cells[104,105]. Moreover, increased endogenous levels of GM-CSF have been correlated with a poor prognosis in patients with a range of cancer types, with studies verifying the presence of GM-CSF receptors on the various malignant tissues[80,101,106].

During the IPP, the use of agents that selectively activate immunity or prevent immunosuppression is instrumental in order to avoid potential beneficial effects on malignant tissues. Alternatively, the time point of intervention could be chosen to maximize immune activation and minimize the potential tumour-promoting effects. Specifically, administration of immunotherapy 1 day before surgery might suffice to activate anti-metastatic immune responses without providing marked benefits to any residual disease. Specifically, cell-mediated immunity might be more effectively activated before commencement of the immunosuppressive effects of surgery; removal of the primary tumour 1 day later will negate any direct benefits of the immunotherapy on the tumour cells and/or prevent them from evolving resistance mechanisms in response to prolonged selective pressure, as well as ensuring the lowest malignant burden (without support for the now-excised primary tumour), while immune stimulation continues for several additional days. Indeed, we and other researchers have found that immunostimulatory treatment with CpG-C, GLA or low-dose polyI:C 12–24 h prior to primary tumour resection is effective in arresting the metastatic process and increasing long-term survival in various preclinical models[93,94,107–109].

Minimal contraindications to surgery. Prior to surgery, surgeons and anaesthesiologists conduct an overall medical evaluation of the patient to identify likely risk factors for perioperative morbidity and mortality[110], foreseeing potential surgical or recovery complications. Among the various factors examined, some can lead to temporary postponement of surgery, including fever, cardiovascular morbidity, abnormal plasma glucose levels, irregular cell counts and aberrant liver function[111–115]; however, for certain surgical risk factors, postponement might not be necessary when the underlying cause is known (for example, fever following immunotherapy)[8].

An excessive inflammatory response, which might result from immune activation, can also constitute a surgical risk factor and can lead to systemic inflammatory response syndrome and multi-organ failure[116,117]. Thus, an optimal perioperative immunotherapy treatment should have minimal deleterious effects on indicators of surgical risk. For example, preclinical studies have revealed that TLR9 stimulation of polarized intestinal epithelial cells resulted in distinct zonal responses with balanced inflammatory effects: basolateral activation led to a classic pro-inflammatory response, whereas apical surface activation resulted in tolerance to subsequent TLR activation and an anti-inflammatory response[118].

Unfortunately, most effective immunotherapies can directly and indirectly lead to reactions resembling infection, a phenomenon known as sterile inflammation[119]. Nevertheless, promising immune responses or long-term cancer outcomes have been observed following such

reactions. For example, 8 weeks of treatment with IL-2 and IFNα, together with 5-FU, has been associated with prolonged survival in patients with metastatic renal cell carcinoma (compared with tamoxifen), despite malaise and fever occurring in >70% of patients during treatment[120]. In patients with non-Hodgkin lymphoma, administration of the TLR9 agonist CpG at least 4 weeks after surgery resulted in an increased abundance and activity of NK cells simultaneously with hypotension and fever[91]. Moreover, the addition of CpG to chemotherapy for advanced-stage non-small-cell lung carcinoma resulted in a twofold increase in the median OS duration, even though patients receiving the TLR agonist had injection-site reactions and an increased incidence of fatigue[121]. Furthermore, clinical trials of various anti-CTLA-4 or anti-PD-1 antibodies have revealed prolonged OS in spite of immune-related adverse events (irAEs) in ~60–70% of patients, most commonly fatigue, decreased appetite, nausea and diarrhoea[122,123].

We suggest that some degree of fever and other transient irAEs, which might occur immediately following initiation of immunotherapy in some patients, should not constitute absolute contraindications to oncological surgeries. The known source of these perturbations and/or the minimal associated risks of unfavourable surgical outcomes should be considered in decisions regarding whether an operation could be conducted or temporarily delayed without compromising the potential benefits of immune stimulation.

Resilience to perioperative stress. The perioperative period is highly stressful for patients, entailing psychological stress relating to anxieties over the disease process and the ensuing therapies as well as physiological stress responses to surgery[124]. Various hormonal and metabolic changes occur during this period: catecholamine and glucocorticoid levels rise following activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, and prostaglandins, pro-inflammatory and anti-inflammatory factors are secreted in response to stress and surgical tissue damage[2,3,35] (FIG. 1). These and additional factors can dysregulate immune function and hamper leukocyte trafficking, proliferation, cytokine secretion and cell cytotoxicity, often resulting in marked systemic immunosuppression[10,18].

Such reactions are counterproductive to the main goal of anticancer immunotherapy, which is to activate and enhance various host cellular immune responses to the malignant cells. Indeed, we and others have shown in preclinical studies that different forms of stress can reduce and even abolish the efficacy of various immunostimulatory agents[125,126]; however, this impairment is probably dependent on several factors, including the magnitude and duration of stress and the doses and time of administration of the immunotherapeutic agents. Notably, the effects of surgical and psychological stress on immune and immunotherapy responses can be successfully attenuated in preclinical models through simple and safe pharmacological treatments (such as inhibition of β-adrenergic and glucocorticoid receptors or COX2 inhibition)[107], and could probably be addressed similarly in most patients with cancer[35].

To enable productive activation of the immune system within this stressful setting and time frame, we suggest that psychological stress should be reduced when feasible; that immunotherapies that are less susceptible to stress responses should be used[127,128]; and that the immunotherapeutic schedule should be based on patients' initial immune responses to immunotherapy. In addition, pharmacological interventions that lessen the deleterious effects of perioperative stress and the related inflammatory responses on immune activation, and have demonstrated clinical feasibly and benefits when used perioperatively[35,129], might supplement immunotherapy[109].

Minimal induction of stress responses. Several FDA-approved immunotherapies involve systemic administration of high doses of individual cytokines (for example, IL-2 or IFNα)[130]. Such treatments have been reported to activate the HPA axis and/or the sympathetic nervous system, resulting in increased circulating levels of catecholamines and glucocorticoids in both animals models[131,132] and patients with cancer[133,134], perhaps as a natural immune inhibitory feedback loop aimed at limiting the cytokine response to pathogens[135]. Such stress responses might lead to temporary or prolonged suppression of some aspects of immunity, including the anti-metastatic activities of cytotoxic T cells and NK cells[18], for example, and thereby facilitate cancer progression. Additionally, stress hormones can have direct pro-metastatic effects on the tumour cells and/or their microenvironment[10,136].

In preclinical models, different doses of human recombinant IFNα have been associated with inconsistent induction of stress response; high doses result in increased corticosterone levels (reflecting activation of the HPA axis), whereas low doses lead to inhibition of the HPA axis[137,138]. Clinical studies have provided evidence of activation of the HPA axis as early as 3 h following administration of IFNγ or IFNβ1b (REFS[139,140]). In addition, IFNβ1b therapy decreases circulating numbers of NK cells, T helper cells, cytotoxic T cells and B cells[139]. These effect would be expected to be detrimental to anticancer immunity and, ultimately, patient outcomes.

By contrast, CpG-C does not cause elevations of glucocorticoid levels and is associated with marked activation of NK cells in preclinical models[12,125]. Additionally, in vitro studies in human plasmacytoid dendritic cells have shown that stimulation with CpG increases resistance of these cells to glucocorticoid-induced apoptosis[141]. Indeed, the use of ligands such as CpG-C, which induce physiological (host-dependent) activation of the immune system through the well-orchestrated and controlled secretion of multiple cytokines[61], has limited deleterious effects on immunity, in contrast to the non-physiological, systemic, high-dose administration of a single or a few cytokines.

Overall, we hypothesize that an optimal immunotherapy regimen should induce low levels of cytokine secretion and/or cytokine-mediated cell activation, or should be restricted to the site of disease through local administration. These approaches might help to avoid unwanted and potentially deleterious stress responses (for example, activation of the HPA axis or sympathetic nervous system).

One could suggest that addressing all of the desired characteristics of perioperative immunotherapy described herein might present challenges or even be impossible; however, several novel or clinically approved agents seem well suited to this strategy. For example, the TLR9 agonist CpG-C and the TLR4 agonist GLA have been associated with few or no irAEs in clinical trials[142–144] and, in both preclinical and clinical studies, improve various immune indices within the proposed time frame. In preclinical models of cancer, these TLR ligands suppress metastasis[95] and/or increase long-term survival[93]. Nevertheless, the effect of these immunotherapies on surgical risk and the wound-healing process should be ascertained prior to their clinical use in the IPP.

Exploiting existing immune therapies

Anti-metastatic perioperative therapies can be divided into three major categories: those with direct immunological mechanisms of action, such as IL-2 or TLR9 agonists; those with biological effects that indirectly preserve or enhance immunity (including COX2 inhibitors or β-adrenergic receptor antagonists); and those that counteract postoperative metastatic disease via non-immunological mechanisms (for example, oncolytic viruses).

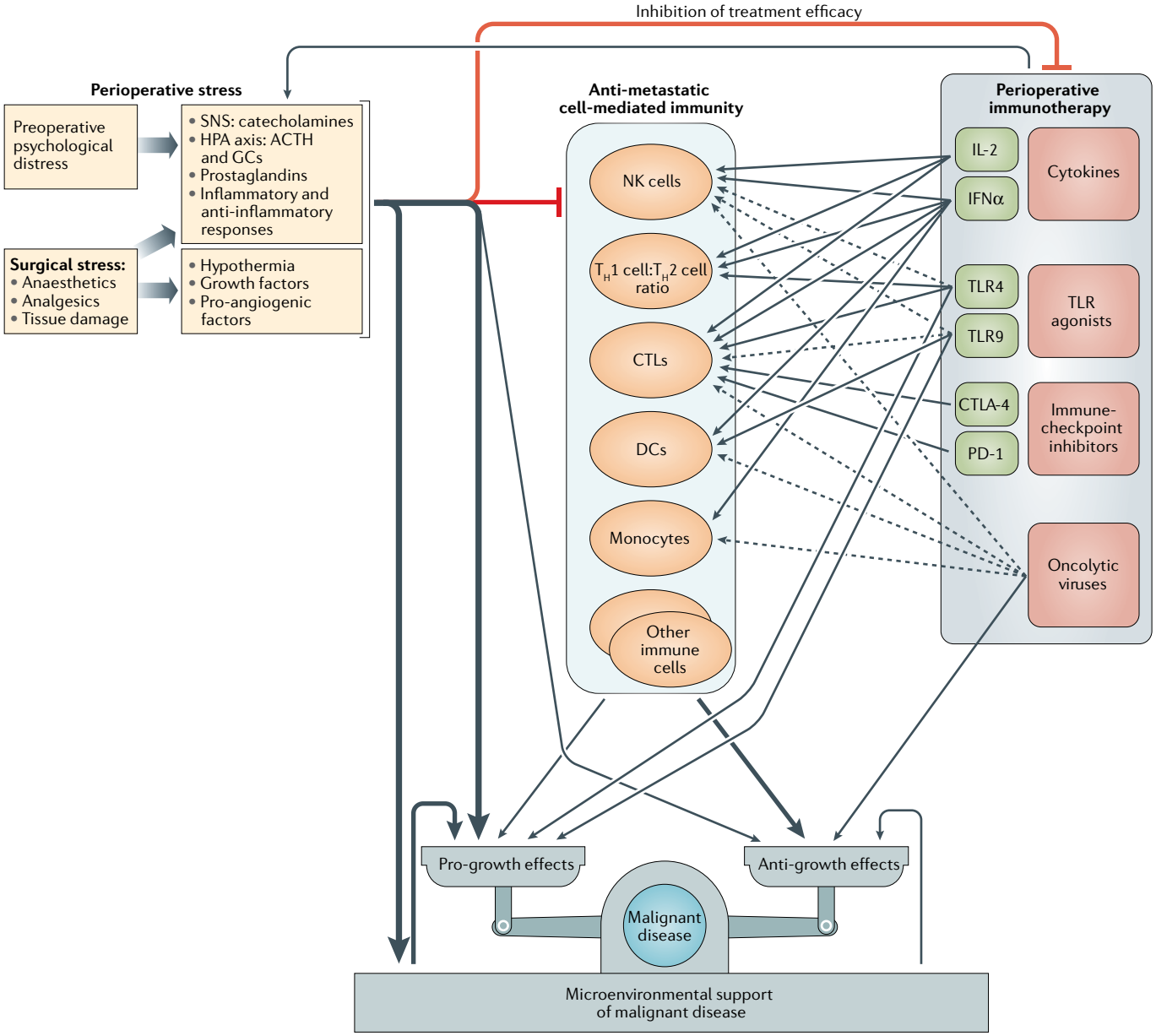

Fig. 1 | **Interactions between perioperative physiological responses to surgery, the immune system and immunotherapy, and the associated effects on cancer growth.** Numerous pathways that are activated perioperatively promote and/or inhibit cancer progression, including residual disease, tipping the scale towards worse or better long-term outcomes, respectively. Specifically, anti-metastatic immune responses can be enhanced by various immunotherapies. During the perioperative period, however, stress–inflammatory responses can suppress anti-metastatic immunity and might also dampen the efficacy of immunotherapy. In addition, perioperative physiological responses, including stress–inflammatory responses, might enhance the growth of cancer cells via direct effects on the malignant tissue and/or its microenvironment. Moreover, certain immunotherapies might enhance the progression of cancer through their direct effect on malignant tissue, as well as by enhancing perioperative stress–inflammatory responses and pro-angiogenic responses. Not shown in the figure are additional interventions, such as perioperative β-adrenergic blockade and cyclooxygenase 2 (COX2) inhibition, which could potentially attenuate the deleterious effects of stress–inflammatory responses on immunity and on the malignant tissue; these interventions might, therefore, act synergistically with perioperative immunotherapy. Of note, certain factors, whether an immune-stimulating agent or a physiological hormonal response, can have both enhancing and suppressive effects on tumour progression (not shown in the figure). For example, IL-2 is known to both increase anti-metastatic cytotoxicity activity of cytotoxic T cells (CTLs) and also enhance the immunosuppressive activity of regulatory T cells. In the figure, red lines indicate inhibitory effects; full black arrows, direct effects; and dashed black arrows, indirect and potential direct effects. ACTH, adrenocorticotropic hormone; CTLA-4, cytotoxic T lymphocyte protein 4; DC, dendritic cell; GCs, glucocorticoids; HPA, hypothalamic–pituitary–adrenal; IFNα, interferon-α; NK cell, natural killer cell; PD-1, programmed cell death 1; SNS, sympathetic nervous system; T_H1 cell, T helper 1 cell; T_H2 cell, T helper 2 cell; TLR, Toll-like receptor.

After thoroughly examining the current literature and clinical trial databases, we identified only a few studies focused on application of immunomodulatory approaches during the IPP, whereas our search revealed numerous studies evaluating immunological interventions initiated a month before or after surgery. Although success in any approach during the IPP indicates the importance of this period, immunotherapies seem most promising thus far and, in our opinion, could be improved substantially if integrated with other complementary perioperative approaches detailed in the following sections of this manuscript.

Immunonutrition

In contrast to the paucity of information on perioperative pharmacological immunotherapy, evidence for the beneficial effects of perioperative immunonutrition is accumulating[145]. Immunonutrition interventions are predicated on the use of nutrient-rich dietary supplements, containing essential amino acids, fatty acids, various vitamins and other elements, for several days immediately prior to surgery[145,146]. For example, a specific immunonutrition regimen (Impact; Nestlé Health Science, Switzerland)[147] has been shown to increase the abundance of tumour-infiltrating lymphocytes in patients with colorectal cancer[148], to improve various systemic immunological indices preoperatively and postoperatively in patients with head and neck cancer[149,150], and to reduce the incidence of postoperative infectious complications and anastomotic leak in patients with gastric cancer[90]. This intervention has also been reported to reduce the duration of postoperative hospitalization[145,151].

Exercise

Physical fitness, as determined through cardiopulmonary exercise testing, is an important predictor of complications following lung cancer resection[152,153] or non-cardiopulmonary surgeries[154,155]. Patients with colorectal cancer with lower preoperative fitness scores have a higher degree of postoperative morbidity[156], as well as worse cancer-specific and OS outcomes[157], than patients with a 'supra-threshold' fitness score. Correspondingly, increasing the physical activity of patients after a diagnosis of colorectal cancer has been associated with prolongation of survival[158–160]. Moderate physical exercise is known to enhance cell-mediated immunity[161,162] and to reduce stress responses and inflammation[163]. Thus, the aforementioned benefits of exercise in patients with cancer might be mediated through several immunological, as well as non-immunological, mechanisms.

Cytokine treatment

Cytokines are pivotal components of an effective antitumour immune response[164]. Several cytokines have been administered in preclinical models to activate antitumour immunity, and have subsequently been applied clinically as monotherapy or in conjunction with other therapies.

IL-2. IL-2 is a crucial factor in the generation and regulation of immune responses[165], and directly affects various leukocytes, including all subtypes of T cells, and can exert either anti-metastatic or pro-metastatic effects in a dose-dependent manner[166]. Over the past three decades, treatment with recombinant IL-2 has gained increased momentum, but rarely in the IPP. Nevertheless, findings indicate that preoperative treatment with low-dose IL-2 for 3 days, ending 36 h prior to surgery, increased postoperative lymphocyte counts and significantly improved 5-year disease-free survival and OS of patients with pancreatic cancer ($P < 0.05$)[6] and reduced the frequency of disease progression in patients with colorectal cancer ($P < 0.03$)[8], compared with placebo. Similar results have been reported with preoperative high-dose IL-2 (REFS[167,168]) or administration of IL-2 immediately after surgery[169]. With regard to irAEs and in accordance with our earlier assertions, although fever occurred in almost all patients treated with IL-2, no interference with the surgical treatment or increase in short-term or long-term surgical complications was reported[8,167,168].

Type I interferons. IFNα has been found to induce activation of most types of cytotoxic immune cells, enhance phagocytic activity and promote the differentiation and maturation of dendritic cells. Recombinant IFNα was the first cytokine-based therapy approved by the FDA, in 1986, for patients with hairy cell leukaemia. Clinical studies of this agent in the IPP have revealed reduced postoperative suppression of NK cell cytotoxicity[170] and decreased circulating levels of VEGF and numbers of regulatory T cells[171]. Adjuvant therapy with this agent combined with continuous arterial infusion of 5-FU, starting 2–3 weeks after surgery, resulted in 1-year OS of 100% in 15 patients with hepatocellular carcinoma invading the major branches of the portal vein, compared with 30% in 15 patients who underwent surgery alone[172]. However, treatment of patients with colorectal cancer with IFNα-2b in the week before tumour resection has been reported to increase the proportion of tumour cells arrested in the G0–G1 phase of the cell cycle, which could potentially reduce the sensitivity of these cells to 5-FU[173]. In addition, a single dose of IFNα administered immediately following transurethral resection of superficial bladder cancer did not improve OS compared with surgery alone[174].

Other cytokines. The immediate perioperative use of other cytokines in a clinical setting is less common and oncological outcomes have not been reported; however, immunological effects have been studied and seem somewhat heterogeneous. Perioperative administration of granulocyte colony-stimulating factor (G-CSF) increased serum levels of IL-1 receptor antagonist (IL-1RA) and TNF receptor, increased TNF secretion and HLA-DR expression by monocytes, decreased lymphocyte anergy and reduced the incidence and severity of infectious complications in patients undergoing elective surgeries compared with those observed in patients treated with placebo[175]. In patients undergoing resection of primary colorectal cancer, low-dose treatment with GM-CSF from 3 days before until 4 days after surgery attenuated postoperative suppression of cell-mediated immunity (phytohaemagglutinin skin test reactivity), increased neutrophil and monocyte counts and enhanced monocyte expression of HLA-DR (relative to placebo); however, GM-CSF was also associated with increased plasma levels of IL-6 and a higher incidence of fever[176]. Patients undergoing major surgery and treated with preoperative IFNγ (on days 7, 5 and 3 before surgery) had increased IL-2 and decreased IL-4 levels in postoperative mitogen-stimulated white blood cell culture supernatants compared with those treated with placebo[177].

Anti-stress–inflammatory approaches

Hormonal manipulation. More than two decades ago, high levels of oestrogen concurrently with low levels of progesterone were hypothesized to constitute a risk factor for metastatic progression in patients with operable breast cancer[178]. Notably, in rodents and in humans, this hormonal pattern is associated with higher expression levels of β-adrenergic receptors in lymphocytes[179], and with higher stress-induced and surgery-induced suppression of NK cytotoxicity[180,181]. Moreover, in preclinical

studies, this hormonal pattern has been associated with increased susceptibility to cancer metastasis in the context of stress hormones or surgery[182,183]. A pivotal randomized controlled trial conducted in almost 1,000 patients with operable breast cancer revealed that a single dose of synthetic progesterone (hydroxyprogesterone) administered 5–14 days before surgery, which disrupts this potentially disadvantageous hormonal pattern for 2–4 weeks, reduced the recurrence rate relative to that observed with placebo. This advantage was evident in patients with tumour-positive lymph nodes, but not in those with lymph node-negative disease (who have a lower risk of metastatic progression), irrespective of tumour hormone receptor status[7].

COX2 inhibition and β-adrenergic receptor blockade. We have developed a novel immediate perioperative approach targeting the excess perioperative release of catecholamines and prostaglandins, which have been shown to suppress anti-metastatic immune responses and enhance metastasis in preclinical studies[2,3,10,11,184]. Correspondingly, the results of our preclinical studies indicate that blocking these responses in the context of surgery improves several indices of anti-metastatic immunity, reduces metastasis and improves OS in several in vivo models[93,94]. We have also tested this approach in two clinical trials, one in patients with breast cancer[27,129] and the other in patients with colorectal cancer[165]; patients received 11–20 days of treatment with the β-adrenergic receptor antagonist propranolol and the COX2 inhibitor etodolac (or placebo in the control group), initiated 5 days prior to tumour excision. Molecular analysis of excised tumour specimens revealed statistically significant reductions in markers of epithelial-to-mesenchymal transition and in the activity of several pro-metastatic and/or inflammatory transcription factors, including GATA-binding factor 1 (GATA1, also known as erythroid transcription factor), GATA2, early growth response protein 3 (EGR3) and signal transducer and activator of transcription 3 (STAT3), with the experimental treatment versus placebo ($P < 0.05$ for all comparisons)[27,165]. Additionally, propranolol and etodolac shifted the tumour-infiltrating leukocyte milieu towards a pattern typically associated with a favourable anticancer immunological response[35,185] and reduced expression of the proliferation marker Ki67 in breast cancer specimens[129]. Moreover, this perioperative treatment also reduced systemic pro-metastatic and pro-inflammatory indices (including plasma levels of IL-6 and C-reactive protein) and improved anti-metastatic immune indices (such as NK cell expression of CD11a)[35].

Importantly, perioperative treatment with propranolol and etodolac was well tolerated, with adverse event and complication rates comparable with those of placebo; potential treatment-related adverse events (such as bradycardia) were rare and easily reversible through treatment discontinuation[35,185]. Hazut et al.[186] and Benjamin et al.[187] assessed the effect of this drug combination on wound healing, anastomosis strength and abdominal wall wounds in rats, and reported no deleterious effect. This evidence of a favourable safety profile, which has not yet been demonstrated for the perioperative use of agents with direct immunostimulatory activity, make the propranolol and etodolac regimen attractive for testing in large-cohort clinical trials, with the aim of improving long-term cancer outcomes.

Conclusions

We believe that the use of immunomodulatory interventions during the crucial IPP, in conjunction with surgery, could potentially improve cancer survival, warranting further research to define the benefits and risks associated with this strategy. Existing immunotherapies, as well as novel approaches, will need to be tailored to this medical setting. Currently, immunotherapy typically involves systemic administration of high doses of cytokines or immune-checkpoint inhibitors[60,130], which often cause irAEs that might constitute contraindications to surgery. However, the perioperative use of immunostimulatory agents (for example, TLR agonists) and/or monoclonal antibodies directed at the tumour and MRD might cause tolerable sterile inflammation and the release of multiple cytokines at levels within physiological ranges, which might better orchestrate immune responses towards MRD, consequently improving long-term cancer outcomes. Harnessing the immune system during the IPP, when any residual disease is at its lowest level, still mostly clinically insignificant and potentially more amenable to immune control, could offer important therapeutic advances.

The use of immunotherapy before initiating chemotherapy and/or radiotherapy could potentially circumvent the long-lasting immunosuppressive effects of these cytotoxic treatments[54,57,58,188], enabling better immune activation towards residual tumour cells prior to therapy-induced evolutionary selection of highly resistant clones. Interestingly, immunotherapies are not contraindicated in the setting of chemotherapy or radiotherapy, and thus the latter standard adjuvant therapies could be initiated a few weeks following surgery, subsequent to or concurrent with immunotherapy, after the major advantages of immunotherapies have already been harnessed in the IPP. In the future, if indeed successful, perioperative immunotherapies could potentially spare the need for postoperative standard adjuvant treatments and the related adverse effects.

As elaborated above, the IPP is associated with various psychological and physiological stress–inflammatory responses, which might reduce the effectiveness of a given immunotherapy. In preclinical studies, we have shown that perioperative blockade of adrenergic and prostaglandin responses can improve the efficacy of immunostimulatory therapies[107,109]. In clinical trials, this strategy robustly improved perioperative immunological indices and reduced the levels of biomarkers of metastatic progression[35,129]. Accordingly, and as has already proven effective in preclinical models[93,107,189], we suggest that adding pharmacological inhibitors of stress–inflammatory signalling to perioperative immunotherapy might further improve patient outcomes. Such an integrated approach might maximize the effectiveness of immunotherapy and negate the possible adverse effects of stress and surgery on the metastatic capacity of residual cancer cells.

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