SURGICAL PROCEDURE AS AN INDUCER OF TUMOR ANGIOGENESIS

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Surgical resection remains the main treatment modality for the vast majority of patients with locally confined solid tumors. However, many patients develop local recurrence and remote metastasis from residual tumor cells years after «curative» resection [1]. Though there are numerous reasons (e.g. further mutations, weakened host defenses) potentially responsible for the relapse of disease, the early local and systemic effects (including physiological and pathological reasons) of the surgical procedure may have a long-term effect on the progression of cancer. In particular, the healing process following surgery necessitates extensive angiogenesis which can be a clinical challenge due to its tumor-promoting effects. An improved knowledge regarding the molecular mechanisms for angiogenesis has facilitated the development of anti-angiogenesis therapy in cancer patients. However, since these therapies might interfere with the physiological angiogenic response, special attention should be paid to its adverse effects and safety issues in perioperative use have to be taken into account. In the current review, we mainly focus on recent advances regarding mechanisms of tumor angiogenesis; potential causes of postoperative angiogenic response; influence of postoperative angiogenic response on residual tumor biology as well as the use of anti-angiogenesis therapy in the perioperative setting.

Mechanisms of tumor angiogenesis. Our understanding of the molecular basis for tumor angiogenesis has advanced dramatically over the years. The current model suggests that tumor angiogenesis is rather a complex and dynamic process mediated by a number of key pro- and antiangiogenic molecules. Specifically, it mainly involves sprouting of endothelial cells from existing vessels; incorporation of bone marrow (BM) derived endothelial progenitors as well as hematopoietic cells (e.g. Tie-2 expressing monocytes/macrophages) into growing vascular bed [2]. In particular, vascular endothelial growth factors (VEGFs) and angiopoietin-2 (Ang-2) are two important cytokines mediating these events [3]. Locally, in response to various stimuli (e.g. hypoxia, changes in metabolism, inflammation), cancer cells as well as «normal» cells (e.g. immune cells, fibroblasts) secrete VEGFs and Ang-2 in order to either fulfill nutritional needs of cancers cells or to repair tissue injury (following surgical wounding) by promoting angiogenesis. Upon binding to their receptor VEGFR, mainly located on endothelial cells, VEGFs initiate a cascade of signal transduction in endothelial cells sustaining cell proliferation, migration (sprouting) and survival. Of note, the survival of newly sprouting endothelial cells relies heavily on the activity of the VEGF/VEGFR axis [4, 5]. Collaboratively, the interaction between Ang-2 and Tie-2 receptors on endothelial cells leads to vessel destabilization which allows for the vessel remodeling effect of VEGFs. Therefore, a coupled effect of VEGFs, Ang-2 and other factors essentially coordinates the angiogenesis process [3]. In addition, the «spillover» of these pro-angiogenic factors into the circulation also switches the BM microenvironment from a quiescent state to a highly pro-angiogenic one. As a result, mobilized BM-derived endothelial (e.g. CD34* VEGFR2*) and hematopoietic (e.g. Tie-2 expressing) progenitor cells are recruited to the tumor or wounded site, and further participate in the angiogenesis process [6–8]. It is speculated that the recruitment of Tie-2 expressing monocytes/macrophages is mediated via Ang-2/Tie-2 interaction [8]. Though the exact identity of

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Abbreviations used: Ang-2 — angiopoietin-2; BM — bone marrow; VEGF — vascular endothelial growth factor.
these BM-derived cells (properly a mixed population) requires further characterization, the significant contribution of these cells on tumor and physiological angiogenesis (e.g. wound healing, organ regeneration) has been demonstrated by many studies. To conclude, the angiogenesis process constitutes a regional and systematic response involving a series of coordinated signal transduction events.

**The pro-angiogenic response after surgery.**

Due to its essential role in angiogenesis, VEGF has been used as a surrogate marker to assess the postoperative angiogenic response in a variety of surgical settings. However, there are many inconsistencies regarding the length and extent of this response between different reports deriving from discrepancies in the studied samples (e.g. wound fluid, plasma or serum), in tumor biology (benign or malignant), and in employed surgical techniques (open or minimally-invasive) [9–15]. Nevertheless, the angiogenic response, as reflected by significantly increased free VEGF levels (compared to preoperative samples), can occur as early as day 1 postoperatively and can remain persistently elevated for up to 4 weeks. In general, VEGF levels in wound fluids are more reliable to represent the local angiogenic response than circulating VEGF (plasma and serum) [11]. In contrast, plasma VEGF levels are more precise in reflecting the systemic angiogenic response than serum levels because serum measurements of VEGF are usually complicated by released VEGF from platelets upon serum preparation [10]. Moreover, case-control studies have demonstrated that such surgery-associated angiogenesis seems to be more pronounced in patients with malignant tumors than in those with benign counterparts [12, 13]. In addition, the extent of surgical resection also affects the postoperative angiogenesis response since it has been shown that extended surgery is associated with a stronger angiogenesis response [15]. In line with this, many studies have provided evidence that minimally invasive surgery is superior to open surgery in avoiding the postoperative angiogenic response presumably due to reduced surgical trauma [12, 16]. However, conflicting results have been reported on VEGF levels in wound fluid after colon cancer resection: VEGF was significantly higher in minimally invasive group compared to open surgery [9]. Therefore, it remains unknown whether the extent of the postoperative angiogenic response is mainly determined by the extent of the surgical wound, or whether it mainly depends on the tumor biology itself.

Though the postoperative angiogenesis response is well-established after major surgery, the exact reasons and source of angiogenic factors remain unclear. It is proposed that surgery-induced hypoxia, metabolic changes and inflammation are three major causes for the production of triggering angiogenic factors in cancer cells as well as in normal cells (e.g. immune cells, fibroblasts). Recent genome-wide genetic characterization efforts have revealed that nearly all cancer cells carry genetic alterations in cell growth pathways (e.g. Ras-ERK, PI3K-AKT) leading to persistent and uncontrolled cell growth signaling [17, 18]. These oncogenic growth signals converge at hypoxia-inducible factor (HIF) with hypoxia signals in residual cancer cells upon surgery to induce expression of downstream angiogenic factors such as VEGF-A and Ang-2 [3]. These findings imply that cancer cells are actually more tolerant to hypoxia than normal and benign tumor cells, thereby constituting a significant source of angiogenic factors. Except for the extent of resection, this may partially explain why cancer patients generally experience more pronounced postoperative angiogenic responses than patients with benign tumors. There is a body of evidence proving that surgical procedures lead to tissue hypoxia which results in an unfavorable prognosis in cancer patients. For instance, prolonged vascular clamping during hepatic surgery to reduce perioperative blood loss induces tissue hypoxia which might affects disease-related prognosis of cancer patient in the long-run [19–21]. Furthermore, hemorrhage - an inevitable surgical event- often leads to anemia, therefore reducing oxygen delivery to organs (hypoxia). Besides, anemia-induced bone marrow mobilization might unintentionally aid in amplifying the systemic angiogenic response (as illustrated earlier). It has been shown that low haemoglobin levels were associated with reduced survival of cancer patients [20, 22, 23]. Furthermore, recent progress has identified a HIF-independent angiogenesis pathway which is mainly mediated by the metabolic sensor peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1alpha) in ischemic skeletal muscle. This finding has further strengthened the emerging link between angiogenesis and metabolism [24–26]. Given the systemic effect of surgery on metabolism in general, it is hypothesized that this alternative angiogenesis pathway may also be involved in the postoperative angiogenic response in cancer patients, at least in a subgroup of patients (e.g. diabetic). Finally, surgery-related inflammation is another crucial contributor of the angiogenic response after surgical tumor resection. The infiltrating macrophages, immature dendritic cells and carcinoma-activated fibroblast (CAFs) [27, 28] are recruited to the surgical site and release numerous angiogenic factors to promote angiogenesis and wound healing. Moreover, there is experimental evidence showing that postoperative intra-abdominal infection actually increases angiogenesis and tumor recurrence after surgical removal of colon cancer in mice [29]. Taken together, the exact causes of the postoperative angiogenic response can greatly differ; therefore any decisions toward anti-angiogenesis therapies should be made on an individualized basis depending on the perioperative settings (see below).

**The influence of surgery-related angiogenesis on cancer biology.**

Following surgical resection, many patients develop local recurrence and remote metastasis from residual tumor cells years after «curative» resection. This might be due to a fact that many of these «curative» resections actually leave behind residual cancer cells [30] either as primary micro-
invaded cancer cells or hidden in a dormant state as remote micro-metastasis. Extensive postoperative angiogenesis may help these residual cancer cells to develop into the clinically detectable disease by promoting initial metastasis, survival, chemoresistance and the switch to an angiogenic phenotype [31]. Many of these deleterious effects lie in the pleiotropic functions of VEGF on both endothelial and cancer cells. Firstly, by interaction with integrin and cell-cell adhesion molecules on endothelial cells (VE-cadherin), VEGF increases vascular permeability, which further leads to leaking of serum/plasma proteins and circulating cells to the extracellular space. These deposited extra proteins/cells eventually increase the interstitial pressure of surrounding cancer cells which will hinder the delivery efficiency of chemotherapeutic drugs [32]. Furthermore, VEGF is able to directly promote cell motility of cancer cells via activation of Src family kinases [33]. Therefore, together with VEGF-mediated disruption of the vascular barrier as well as surgery-associated vessel injury, it may potentiate extravasation of tumor cells [32]. Recent studies in genetically engineered mice have suggested that myeloid cell-derived VEGF is predominantly responsible for this vessel permeability effect [34]. Loss of myeloid-cell VEGF induces vascular normalization in tumor vessels and increases the susceptibility of the tumors to chemotherapeutic cytotoxicity. In addition, VEGF has been shown to enhance tumor cells survival by activating PI3K-AKT pathways [35] further underscoring its role as a context-dependent tumor protector or promoter. Given these the pleiotropic effects of VEGF on tumor biology, it is reasonable to speculate that the postoperative angiogenic response is crucial for residual cancer cells to transiently expand and to construct an initial tumor-supportive niche, especially considering that in reality it occurs within the time-frame in which usually no conventional adjuvant therapy is applied.

The use of antiangiogenesis therapy and surgery. Given the key importance of the VEGF/VEGFR axis in angiogenesis, it is conceived that blocking this pathway would eliminate tumor vasculature and potentially cure cancer. Indeed, three clinically applied anti-angiogenesis drugs (bevacizumab, sunitinib and sorafenib) have significantly prolonged survival of cancer patients in many clinical settings [36–38]. All three agents inhibit VEGF signaling by blocking VEGF ligand or VEGF receptor function. However, recent studies in mice presented intriguing evidence that although VEGF-targeted therapy inhibited growth of the primary tumor, it reduced overall survival of mice by promoting tumor metastasis [39, 40]. Therefore, it requires further investigation to exploit such anti-angiogenesis drugs in order to offer an enduring therapeutic effect [41]. In addition, since these drugs might also interfere with physiological angiogenesis necessary for wound healing, organ regeneration, and surgical recovery, special attention should be drawn upon the adverse effect of perioperative usage, as recently reviewed by Bose and coauthors [42]. Generally, «surgery in patients receiving VEGF-targeted therapies seems to be safe when appropriate interval of time is allowed between surgical procedures and treatment» [42].

OUTLOOK

Given the fact that cancer patients are exposed to high levels of proangiogenic factors in a time period when no conventional adjuvant therapy is usually applied, it is proposed that anti-angiogenic therapies should be initiated in the early postoperative period before the start of conventional chemotherapy. However, safety issues and «gains and losses» in terms of long-term survival require further investigation.

REFERENCE


