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The effects of surgery-induced immunosuppression and angiogenesis on tumour growth

Tsuyoshi Kadosawa *, Ai Watabe

Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Surgical removal of primary tumours can help in the treatment of cancer but carries the risk of triggering the proliferation of dormant micrometastases. Many experimental and clinical studies have demonstrated that anti-angiogenic mechanisms and immune surveillance are essential to inhibit metastatic tumour cells from growing. As surgical stress often induces a reduction in anti-angiogenic factors in parallel with increases in angiogenic factors and suppression of immune surveillance during the post-operative period, new strategies for peri-operative immunostimulation and chemotherapy are required. This review summarises the factors and proposed mechanisms underlying the effects of surgery on immunosuppression and angiogenesis.

Introduction

Surgical resection is usually the first choice of treatment for the management of localised malignant tumours, and offers the best chance of a cure. However, many patients die of recurrence or metastasis even after complete resection. In human medicine, clinical investigations and experimental tumour model studies suggest that surgical resection may accelerate the development of metastases by promoting increases in the proliferation of residual tumour cells. Several mechanisms for this phenomenon have been proposed (Fig. 1), including dissemination of tumour cells during surgery (Yamaguchi et al., 2000), blood loss and transfusion (Atzil et al., 2008), anaesthetic and analgesic drugs (Melamed et al., 2003), decreased levels of anti-angiogenic factors, local and systemic increase in pro-angiogenic and growth factors (Hofer et al., 1999), and suppression of cell-mediated immunity (Shakhar and Ben-Eliyahu, 2003). In this article, the mechanisms of immunosuppression and angiogenesis after surgical removal of tumours that are more frequently reported are reviewed.

Growth of distant tumours

Experimental studies

A century ago, Ehrlich and Apolant (1905) performed experiments using double inoculations of rat sarcomas and observed the retarded growth of the tumour subsequently inoculated compared with the primary tumour (Ehrlich and Apolant, 1905). They also recognised the effects of the primary tumour on tumour growth at distant sites. Subsequently, Marie and Clunet (1910) found that implanted tumours that rarely produced spontaneous metastases frequently generated metastases when the primary implant tumour was incompletely excised (Marie and Clunet, 1910). They demonstrated that surgical resection might enhance metastatic development.

Hadfield (1954) advocated the concept of the dormant cancer cell in 1954; it was characterised by prolonged survival in tissues, showing no evidence of multiplication during this time while retaining its former and vigorous capacity to multiply. The concept was supported by the Fisher brothers' experiments on the effect of partial hepatectomy or sham hepatectomy, and their observations of the development of hepatic metastases (Fisher and Fisher, 1959).

Further findings, such as the relationship between tumours at different sites, surgery-related effects and tumour dormancy, have been reported. Gershon et al. (1968) suggested that tumour-bearing animals might be refractory to re-inoculation with a number of identical tumour cells that were 100,000 times higher than the number required to produce primary tumours, while removal of the tumour may rapidly result in the appearance of metastatic deposits. Furthermore, Yuhas and Pazmino (1974) reported that tumour growth at subcutaneous injection sites was depressed in mice that had artificially induced metastases.

Clinical investigations

Surgeons practicing human and veterinary medicine have long suspected that surgery facilitates the metastatic process, but it is

* Corresponding author. Tel.: +81 11 388 4889.
E-mail address: kado@rakuno.ac.jp.

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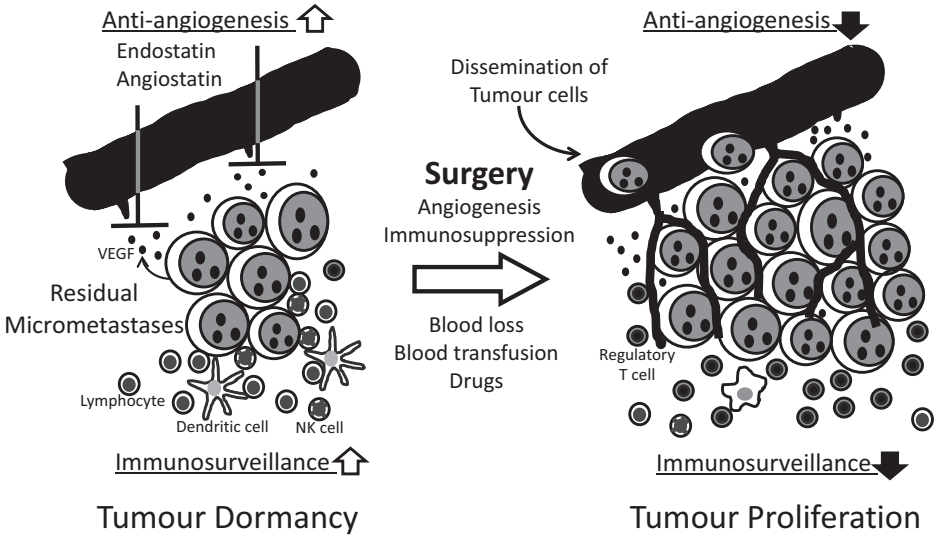

Fig. 1. A schematic overview of the proposed mechanisms for surgery-inducing tumour growth. The dissemination of tumour cells during surgery, blood loss and transfusion, anaesthetic and analgesic drugs, decreased levels of anti-angiogenic factors (angiostatin and endostatin), local and systemic increase in pro-angiogenic and growth factors (e.g. VEGF), and the suppression of cell-mediated immunity (decrease of cytotoxic T lymphocyte and natural killer cells, increase of regulatory T cells) have been proposed.

difficult to demonstrate this phenomenon. A randomised study following 111 humans with prostatic adenocarcinoma for 23 years showed no survival benefit of radical prostatectomy (Iversen et al., 1995). Similar results were observed in canine prostate cancer (Cornell et al., 2000). A prospective cohort study of 1173 patients with breast cancer examining the death-specific hazard rate, showed an early first peak 3–4 years after mastectomy compared with 4–5 years in untreated patients (Demicheli et al., 2001). This finding indicates that the natural history of breast cancer may be adversely altered by tumour removal. Moreover, veterinary surgeons often encounter cats that develop pulmonary metastases soon after the removal of mammary carcinomas >3 cm in size (MacEwen et al., 1984).

The degree of surgical stress has been shown to influence outcome. Open resection of colorectal cancer was associated with shorter disease-free intervals (DFIs) and time-to-recurrence (TTR) compared with laparoscopic resection (Lacy et al., 2002). In a study of total cystectomy for canine bladder transitional carcinoma (Kadosawa et al., 2012), where surgery was limited to cases without lymph node involvement, distant metastasis was assessed by diagnostic imaging, and about half of the cases had ureteral dilations in the long-term course of the disease; metastatic progress occurred in approximately one-third of cases within 6 months of surgery.

Proposed mechanisms

Immunosuppression

The immune system plays an important role in host protection against pathogens such as viruses, bacteria and parasites, and also against tumour cells. Burnet (1967) coined the term 'immune surveillance' to describe the ability of the immune system, especially cell-mediated immunity, to recognise and destroy transformed cells.

Tumour immunity has been supported by many clinical and experimental studies. Pre-existing immune–tumour interactions and lymphocytic responses against excised autologous tumour tissue in vitro were reported to predict long-term survival rates better than tumour stage and grade (Uchida et al., 1990; McCoy et al., 2000). There is an increased frequency of certain malignancies and a dramatic increase in metastatic progression in immunocompromised patients, including those receiving immunosuppressive drugs (Penn, 1993; Detry et al., 2000) and those that carry anti-lymphocyte antibodies (Decaens et al., 2006). The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor blocker, ipilimumab, which enhances T-cell-mediated anti-tumour immunity, was shown to increase the survival time of patients with metastatic or unresectable melanoma (Postow et al., 2011).

From a long-term perspective, surgical resection of the primary tumour is immunologically beneficial as it will restore anti-tumour immune responses by abolishing tumour-dependent immunosuppression (Pollock and Roth, 1989). However, from a short-term perspective, surgical stress often induces dysfunction in immune surveillance and outgrowth of disseminated tumour cells into overt metastases.

Stress hormones, especially catecholamines, opioids and glucocorticoids, have been shown in animal models to causally promote metastatic progression through immunological and non-immunological mechanisms (Shavit et al., 2004; Benish et al., 2008; Goldfarb et al., 2009; Inbar et al., 2011). In clinical studies, surgery and the associated neuroendocrine and paracrine responses were shown to increase the secretion of immune suppressing hormones, to decrease the numbers and activity of natural killer (NK), Th1 and cytotoxic T lymphocyte (CTL) cells, and to reduce interleukin-12 (IL-12) and interferon-γ (IFN-γ) expression (Greenfeld et al., 2007; Bartal et al., 2010).

Post-operative changes in lymphocyte counts and transformation responses usually returned to normal values within a week, whereas depression of specific cellular immunity to tumour-associated antigens in vitro and delayed cutaneous hypersensitivity reactions in vivo persisted for about 1 week and gradually returned to normal by 3 weeks (Lee, 1977). In dogs undergoing ovariohysterectomy, T lymphocyte function, based on blastogenesis to phytohaemagglutinin in vitro, was depressed for 24 h after surgery (Medleau et al., 1983). Regulatory T cells (Tregs), a subset of T cells with immunosuppressive function, were significantly increased on day 6 after surgery (Saito et al., 2013). Similar results were observed in dogs (Watabe et al., 2012), where the relative percentage of Tregs increased on day 2 and decreased until 2 weeks after surgery.