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Review

Effects of surgery on the cancer stem cell niche

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Abstract

Recent identification of a cancer stem cell (CSC) phenotype in solid tumors has greatly enhanced the understanding of the mechanisms responsible for cancer cell metastasis. In keeping with Pagets 'seed and soil' theory, CSCs display dependence upon stromal derived factors found within the niche in which they reside. Inflammatory mediators act as a 'fertilizer' within this niche when interacting with CSCs at the tumor–stromal interface and can potentiate the metastatic ability of CSCs. Interestingly, the same components of the pro-inflammatory milieu experienced by cancer patients perioperatively are known to promote the metastagenic potential of CSCs. On the basis of this observation we discuss how surgery-induced inflammation potentiates colon CSC involvement in the metastatic process. We hypothesize that the high rates of recurrence and metastasis associated with tumor resection are potentiated by the effects of surgery-induced inflammation on CSCs. Finally we discuss potential therapeutic strategies for use in the perioperative window to protect cancer patients from the oncological effects of the pro-inflammatory milieu.

Keywords: Cancer stem cell; Cancer; Metastasis

Introduction

Cancer stem cells (CSCs) represent a small, yet highly influential cancer cell phenotype.[1] The term CSC arises due to their behavioral similarities to non cancer stem cells. Appreciation of the presence of a CSC nuance in recent times has contributed immensely to the understanding of the step by step dynamics required for metastasis. It is now evident that CSCs act as essential governors of successful cancer cell metastasis.[2] Although the metastatic process is notoriously inefficient, CSCs enhance metastatic efficiency through their inherent stem cell traits, including a clonogenic and self-renewal capacity, which are deficient in the non-stem cell population.[2] CSCs were first described in hematological malignancies but their role in solid tumors including breast, lung, and colon cancer is now becoming evident.[3–5]

Surgical resection constitutes the mainstay of treatment for solid tumors including breast and colon cancer. There is a well-established mechanistic link between surgery-induced inflammation and potentiation of the risk of tumor recurrence and metastasis, particularly in colon cancer. The foundations of this link are built upon a large amount of experimental and clinical data which have highlighted the role of the accompanying surge of inflammatory mediators including VEGF, IL-6 and reactive oxygen species in subsequent disease recurrence and development of metastasis.[6–9]

The tumor microenvironment in which CSCs reside is referred to as the stem cell niche.[10] The CSC niche itself can be found within primary tumors, sites of metastatic spread such as lymph nodes or in the portal and systemic circulation. Within this niche, CSCs interact with local stromal factors and inflammatory mediators, consisting of transformed myofibroblasts, recruited myeloid cells, other cell types and extracellular components such as growth factors and cytokines. These combine to dictate CSC behavior.

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Emerging evidence demonstrates how the metastagenic properties of CSCs are potentiated in response to a milieu of pro-inflammatory mediators including TNF-α, IL-6 and reactive oxygen species, all of which are elevated in the perioperative window.[11–18] It is also evident that both stem and non-stem cell cancer cells are present in circulation and are referred to as circulating tumor cells (CTCs) and circulating cancer stem cells (CCSCs) respectively. This also represents another niche in which the components of systemic inflammation and CSCs can potentially interact.

In this article we explore how inflammatory mediators generated during the perioperative window can mitigate the behavior of CSCs. Additionally, we delineate how CSCs facilitate metastasis and hypothesize that surgery-induced inflammation promotes tumor recurrence and metastatic potentiating effect from residual and disseminated cancer stem cells. Finally, we highlight possible therapeutic opportunities which may be of benefit in the already underutilized perioperative window.

Oncological effects of surgery

A mechanistic link between surgery and the potentiation of tumor growth dates back over a century.[19] Our understandings of the molecular mechanisms responsible have evolved with time, yet there has not been any progress made in terms of targeting this phenomenon. The rates of recurrence and metastasis for colorectal cancer remain unacceptably high with approximately 20–30 per cent of node positive patients recurring within 5 years, 70 per cent of these recurring within the first 2 years post operatively.[20] The recurrence rate is even higher for patients undergoing resection of hepatic metastasis, with up to 50 per cent of patients recurring within 5 years.[21] Postoperative complications such as anastomotic leakage also have a negative impact on survival.[22]

The perioperative window represents a unique period for cancer patients undergoing resection of the primary tumor. The inflammatory cascade initiated by surgical trauma consists of elevated levels of pro-inflammatory cytokines including TNF-α and IL-6 and oxidative stress as part of the acute phase response.[23,24] Recent evidence also clearly demonstrates that the levels of growth factors such as VEGF and EGF are elevated postoperatively in cancer patients.[25–27] All of these mediators are known to potentiate the metastatic ability of CSCs upon interaction (Fig. 1).[28–30]

Postoperatively, there are 2 important sites of interaction where CSCs are exposed to the perioperative pro-inflammatory milieu. The first is in the form of minimal residual disease which can be found locally following curative resectional surgery. The second is in the form of circulating tumor cells (CTCs) which have been disseminated. Although CTCs can be detected prior to surgery, an increase in the quantity of CTCs is witnessed in the perioperative window thus increasing the risk of haematogenous spread of the cancer.[31] The interaction of inflammatory mediators and CSCs in each of these 'niches' promises to shine new light and renew focus on the unassailable link between inflammation and tumor recurrence and metastasis.

'Seed and soil' theory – CSC niche

In order to understand the manipulative effects of surgery on CSCs, it is first important to grasp the concept of the CSC niche which plays a vital role in the day to day maintenance of CSCs. Paget's 'seed and soil' theory complements very well the idea that CSCs are dependent on the support of their niche for survival. This support is provided in the form of stromal factors active at the tumor–stromal interface.[32] These stromal factors also influence the metastatic behavior of CSCs and are key determinants of the success of a metastasizing CSC. It is helpful to look at the process of the development of metastases in distinct cancer models.

The metastatic success of CSCs is determined by their microenvironment.[33] Malanchi et al. recently demonstrated using an in vivo breast cancer model that successful lung metastasis is dependent upon a stromal factor known as periostin which is released locally by fibroblasts within the tumor microenvironment. Without periostin, metastasizing breast cancer stem cells are unable to develop into a metastatic deposit.[2] In the absence of periostin CSCs also lose their inherent stem cell traits or 'stemness' such as sphere formation. In pancreatic cancer paracrine Nodal/Activin signaling within the CSC niche promotes the CSC phenotype. In vitro these embryonic morphogens facilitate sphere formation and potentiate the invasiveness of pancreatic cancer stem cells.[34]

Another important niche factor necessary for successful metastasis is the presence of vasculature. In a squamous cell carcinoma and brain cancer model, CSCs were found to reside in a perivascular niche.[35] VEGF secreted locally by the endothelial cells was shown to regulate the growth of CSCs.[36] VEGF exerts its influence in a paracrine manner and acts as a promoter of CSC stemness and can stimulate self-renewal in skin cancer. Deletion of neuropilin-1 (Nrp-1) which is a VEGF co-factor resulted in inhibition of VEGF's ability to promote stemness and self-renewal in vivo.[36] CSCs have been shown to proliferate successfully under hypoxic conditions which may mirror very well the actual conditions within solid tumors. HIF-1α and HIF-2α have displayed regulatory roles in CSCs and inhibition of each prevents CSC proliferation and self-renewal.[37–39]

Stromal factors do not appear to be niche specific. Periostin for example is responsible primarily for bone development and was expressed in primary breast tissue, metastatic lymph nodes and lung tissue. Whether or not stromal factors are cancer type specific however is unknown. If this was the case this may help explain the target organ tropism