

# A framework for the role of acute inflammation in tumor progression

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**Abstract** Breast cancer remains the second leading cancer-related death in women in the United States. Despite improvements in early detection, prevention, and treatment, the mortality rate in breast cancer remains high secondary to the potential for cancer recurrence and the development of metastasis. To minimize breast cancer-related morbidity and mortality, understanding the factors leading to an increased risk of metastasis and developing clinical interventions that reduce this risk is essential. While the association between chronic inflammation and cancer progression is well documented in the literature, the role of acute inflammation and its impact on tumor proliferation and metastasis is less well understood. Here, we will review recently published preclinical studies in mouse models indicating that acute inflammation caused by clinical interventions plays an important role in the risk of peripheral metastases. In addition, we will address the potential impact that these findings may have on the clinical management of breast cancer.

**Keywords** Breast cancer · Biopsy · Acute inflammation

## Chronic inflammation and cancer

In 1983 two Australian scientists postulated that gastric cancer may be the result of an inflammatory process caused by chronic *Helicobacter pylori* (*H. pylori*) infection in the stomach [1]. Subsequent studies confirmed this correlation and demonstrated that *H. pylori* infection was associated with a significantly increased risk of gastric cancer [2]. It was at this point of history that viral causes of cancer were also being discovered; for example, the correlation between human papilloma virus (HPV) and cervical cancer [3, 4]. More recently, the mechanism of HPV potentially contributing to the development of oropharyngeal squamous cell cancer has been observed in studies [5, 6]. These findings marked a paradigm shift in the concept of carcinogenesis and opened new pathways for the treatment and prevention of certain cancers. Likewise, chronic ulcerative colitis and Crohn's disease are well-recognized risk factors for the development of colorectal cancer [7, 8]. Interestingly, even colorectal cancers not associated with inflammatory bowel disease demonstrate an inflammatory response with an increased expression of pro-inflammatory cytokines [9].

Prior studies utilizing mouse models have informed our understanding of the correlation between chronic inflammation and cancer development. These studies expand our understanding of which components of the immune system promote tumor progression relative to those that facilitate efficient elimination of the tumor cells. Immune cells that have been shown to promote tumorigenesis are macrophages, several subtypes of CD4<sup>+</sup> cells, and neutrophils.

Macrophages, which are well known for playing a critical role in regulating tissue homeostasis in normal tissues, can cause a maladaptive response in the tumor microenvironment that leads to promotion of tumor growth and

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invasion into adjacent tissues [10, 11]. Also, several subtypes of CD4<sup>+</sup> T cells have been recognized to contribute to tumorigenesis via multiple pathways [12]. Neutrophils, a key component of the acute inflammatory response, have also been shown to contribute to tumor progression and metastasis [13, 14]. At the other end of the spectrum, immunosurveillance and response to tumor-specific antigens via cytotoxic CD8<sup>+</sup> T cells is an important mechanism of cancer suppression and regression [15].

The role of the immune system in cancer progression is complex, depending on both the tissue and tumor type involved, and remains somewhat controversial [16]. However, the association between chronic inflammation and tumorigenesis has become more evident.

### **The concept of acute inflammation and risk of cancer progression**

Given the demonstration of chronic inflammation promoting the development and progression of cancer through factors produced within immune cells (e.g. cytokines, growth factors, reactive oxygen species), one can hypothesize that an acute inflammatory response within the tumor may drive cancer progression through a similar mechanism. The presence of acute inflammatory cells in the tumor could play a detrimental role by supporting tumor cell proliferation and, more importantly, metastasis.

In contrast to chronic inflammation, very little is known about the physiological consequences of an acute inflammatory response within tumors. Acute inflammation is clearly triggered by standard diagnostic and therapeutic interventional procedures in cancer treatment [17]. Mechanical trauma induces tissue damage, which results in wound healing, creating an acute local inflammatory state and the recruitment of inflammatory cells (primarily cells from the innate immune system), as well as the production of cytokines, chemokines, and growth factors which may stimulate tumor progression and/or metastasis [18].

Core needle biopsies are standard procedures in breast cancer diagnosis [19]. Although only a small section of the tumor is removed, it is enough to trigger an acute inflammatory reaction as part of the normal wound healing response. This biopsy-mediated acute inflammatory response is theorized to have a proliferative effect on residual tumor cells. This may be relevant given that the period of time between the biopsy and subsequent surgery or the initiation of other cancer treatment can vary from 10 days to 5 weeks, providing time for tumor cell stimulation promoted by the immune response. Likewise, in the case of positive margins following a partial mastectomy, residual tumor cells may be exposed to an inflammatory microenvironment favoring tumor cell progression. Surgical excision of tumors promotes a

strong acute inflammatory response at the site of excision. Some have speculated that in cases where re-excision is required for suspected residual tumor, the presence of inflammatory cells during the period between surgeries could provide an opportunity for proliferation or even migration (i.e. metastasis) of residual cancer cells [20, 21].

While studies investigating the potential risk of biopsies and local excision have focused on tumor displacement, no studies have previously addressed the impact of the acute inflammatory response on local and distal tumor recurrence. This may be due to the fact that the concept of acute inflammation being a factor that can promote tumor progression is relatively new. However, with our current knowledge of the link between inflammation and cancer, identifying the potential impact of the acute inflammatory response on tumor cells may offer new insights into our understanding and clinical management of cancer.

### **Evidences from mouse models supporting the role of acute inflammation in breast cancer metastasis**

Very few studies have approached how acute inflammation can promote tumor growth or metastases using animal models. In a rat Lewis-lung model, a sharp spike in angiogenesis stimulators and growth factors to aid in wound healing were shown to lead to an environment fertile for tumor proliferation and metastasis [22]. However, no association with specific inflammatory or immune cells was made. Bouchard et al. studied the affect of radiation-induced inflammation as a possible predictor on cancer cell migration and development of lung metastasis using BALB/c mouse model. Their results showed that pre-irradiation of the mammary gland increased the quantity of circulating cancer cells 2.0-fold, but more importantly, also showed a 2.4-fold increase in the number of lung metastasis associated with the induction of interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) [23].

To address whether acute inflammation may have an effect on tumor progression or metastasis, we established a mouse model for mammary biopsies where the immune response is physiologically developed (e.g. not in a xenograft model). We used MMTV-PyMT transgenic mice [24] as a mammary tumor mouse model for breast cancer and performed a live surgical punch biopsy as the trigger of acute inflammation. Our study demonstrated that the biopsy triggers an accumulation of inflammatory cells in the tumors within the area of the biopsy. While the biopsy had no strong effect on primary tumor growth, there was an increased ratio of proliferating cells in the tumor area adjacent to the biopsy relative to distal areas of the tumor. The most revealing finding from these studies was the prominent increase (3–5-fold) in the number of newly generated lung metastasis in the

mice that underwent biopsy compared with control mice. This effect was associated with the recruitment of inflammatory cells and elevated levels of certain cytokines such as IL-6 in the lung. Anti-inflammatory treatment prior to and after the biopsy reduced the development of metastases triggered by the biopsy. In addition, inhibiting IL-6 production mitigated the number of metastases upon biopsy [25].

Based on early mouse models, we have evidence to support the concept that acute inflammation resulting from ‘wounding’ of primary tumors can increase the rate of metastases. Importantly, the increased development of metastasis promoted by the biopsy could be minimized by administration of anti-inflammatory medication (ibuprofen) at the time of the procedure [25]. These studies in mouse models present a foundation upon which future clinical studies can elucidate the clinical significance that acute inflammation may have on the management of patients with breast cancer. Indeed, recent findings from a retrospective study of 327 consecutive breast cancer patients demonstrated that Non-Steroidal Anti-Inflammatory Drug (NSAID) analgesic used in surgery resulted in improved 5-year disease-free survival, and a reduction of early relapse events [26]. These findings may ultimately have implications on the timing of breast cancer therapy, impact of positive margins, and role of anti-inflammatory therapy in patients undergoing invasive procedures for breast cancer treatment.

## Future considerations

In summary, there is emerging evidence that invasive procedures may have an impact on breast cancer progression, including recurrence and metastasis. The significance and impact of these preliminary findings warrant further studies in human breast cancer. Investigating the potential correlation between the acute immune response and tumor progression may further our understanding of carcinogenesis and open channels to novel, immune-based therapeutic strategies to reduce the development of metastasis.

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