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Surgical Wound-Healing and Breast Cancer Progression

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Abstract

Although surgery remains the most effective treatment for breast cancers, many studies have provided evidence that the wound-healing that follows surgical tissue damage triggers the development of metastases, facilitating the growth of pre-existing micro metastases, enhancing the cancer stem cell population, and thus affecting patient outcomes. One of the strategies that have been adopted to examine the stimulation of the metastatic potential of breast carcinoma cells by wound-healing has been the use of postsurgical drainage that is collected from patients. Perisurgical administration of anti-inflammatory agents, such as Non-steroidal Anti-Inflammatory Drugs (NSAIDs), is being investigated with regard to its ability to slow the protumoral effect of wound-healing.

Keywords: Breast cancer; Wound-healing; Surgery; Metastasis, NSAID

Introduction

Subsequent to major developments in anesthesia and antisepsis, surgery became the first line treatment for breast cancer. It was evident early on that surgical removal of breast carcinoma did not always have a benefit with regard to tumor progression. In this context, a study of breast carcinoma patients who did not receive any treatment between 1938 and 1956 reported a 5-year survival rate of nearly 70% for the small group of women who presented with localized disease [1,2].

We turn to Fisher's hypothesis to try to explain why breast cancer patients are not cured by radical mastectomy, including resection of the entire breast, the overlying skin, the underlying muscles, and most of the lymph nodes [3]. Fisher postulated that cancer spreads via the bloodstream even before its clinical detection, with the outcome being driven by tumor-host interactions [4]. Consistent with this hypothesis, adjuvant systemic therapeutic regimens have been beneficial, supporting the existence of disseminated tumor cells at the time of diagnosis, even in early breast cancers [5].

Thus, if disseminated dormant tumor cells are present at the time of surgery, as documented in many studies, radical removal of the tumor could expand these cells [6]. Wound-healing, in which several factors are released, might trigger the growth of residual cells and the development of metastases, facilitating the growth of pre-existing micro metastases, enhancing the cancer stem cell population, and thus affecting patient outcomes [7-15]. This model explains the high recurrence rate in breast carcinoma patients during the first 2 years to 3 years post surgery and the specific benefit of adjuvant therapy only in decreasing early relapse rates [16].

After the advent of high-throughput technologies and the discovery of the molecular heterogeneity of breast carcinomas, it became apparent that the acceleration of metastasis after surgical resection of primary tumors does not occur at the same rate in all breast cancers. The risk of distant recurrence in HER2-positive and Triple-Negative (TN) breast carcinomas peaks at approximately 3 years and then declines rapidly, whereas in all other breast cancer types, this risk appears to be constant, suggesting that surgery and the factors that are released during healing accelerate the events that should occur later, especially in TN and HER2 tumors, which are the most aggressive breast cancer subtypes [17].

The mechanisms of wound healing begin on physical injury at the time of surgery and proceed continuously throughout repair. Specifically, they involve: (1) inflammatory mediators and growth factors; (2) cell-cell and cell-extracellular matrix interactions; (3) epithelialization, fibroplasias, and angiogenesis; (4) wound contraction; and (5) remodeling. Because wound-healing has common features in all individuals, its greater effect in promoting relapse in TN and HER2 tumors might be due to better communication of tumor cells with healing factors.

To determine the effects of factors in them on the proliferation, migration, and invasion of tumor cell lines, postsurgical drainage samples have been collected from patients to examine

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the stimulation of proliferation and metastatic potential of breast carcinoma cells by wound-healing in *in-vitro* assays. The activity of fibroblasts, endothelial cells, and immune cells in shaping the tumor microenvironment is reflected in the composition of the wound-healing fluid. Thus, wound-healing fluids are enriched in cytokines, chemokines, and growth factors compared with normal serum, and notably, the levels of some of these soluble factors are higher in the patient's blood after surgery, supporting their action on potentially distant, disseminated, dormant individual tumor cells.

Nearly all studies have shown an increase in tumor cell proliferation, migration, and invasion on wound-healing but to varying extents, depending on the molecular characteristics of tumor cells [18]. In particular, highly aggressive breast carcinoma cells (i.e., HER2+ or TN) are affected the most by fluids *in vitro*; strengthening the hypothesis that resection of more aggressive tumors is more harmful compared with less aggressive cancers [19].

A randomized clinical trial showed that early distant relapses in node-positive patients were more frequent in those who underwent mastectomy versus quadrantectomy, raising the possibility that invasive surgery, resulting in extensive healing, accelerates the progression of disseminated cells than conservative surgical removal of the tumor. Several inflammatory mediators are enriched in the drainage of patients who undergo mastectomy, supporting that highly destructive surgeries increase inflammation [20-22].

Consistent with this hypothesis, we noted a correlation between the cellular damage that is induced by surgical resection, based on creatine phosphokinase concentrations in drainage fluid that was obtained 1 day after surgery, and the amount of EGF-like growth factors in these samples and the proliferation of HER2-positive breast carcinoma cells *in vitro* [18]. Moreover, in analyzing the randomized clinical trial that compared conservative quadrantectomy *vs.* radical mastectomy, we observed no differences in survival according to the type of surgery in HER2-negative patients, independent of node infiltration, or in HER2-positive patients without node infiltration. In patients with positive nodes and HER2-positive breast cancer, radical mastectomy significantly increased early death rates [9]. The early peak in relapse in patients with breast carcinomas that over express the HER2 oncoprotein and disseminate to the axillary lymph nodes at the time of diagnosis implicates the early proliferation of micro metastatic lesions that are induced by wound-healing growth factors that are released during surgery.

Recently, we reported that healing factors are influenced by the extent of surgical damage and the reactive stroma that is derived from the interactions between growing neoplastic cells and the surrounding microenvironment, depending on the molecular characteristics of the breast carcinoma cells [19]. IL-6, G-CSF, and MCP-1 are enriched in wound fluid from patients with invasive versus in situ breast cancer, independent of the extent of surgery. Levels of the matricellular protein Osteopontin (OPN), which supports neutrophil and mast cell recruitment to inflammatory sites and renders the metastatic site more immunosuppressive, are higher in drainage from TN tumor surgery, explaining the high recurrence rate of this breast cancer subtype [23]. Although wound-healing fluids stimulate *in vitro* proliferation of breast cancer cells of all intrinsic subtypes, the effect on proliferation is greater when the cells are treated with drainage fluid from surgery on tumors of the same intrinsic subtype, suggesting that breast tumors condition the healing factors in wound fluid by affecting the extracellular microenvironment [19,24]. Thus, in addition to the ability of breast cancer cells to interact with healing factors, tumor-induced modifications to the surgical bed might be essential in the tumor progression that is mediated by wound-healing.

Recent studies have shown that Intraoperative Radiotherapy (IORT), in which radiation is delivered to the tumor bed, reduces the risk of local recurrence by killing tumor cells directly and modifying the local microenvironment [25]. Because radiation-induced damage is mediated by factors that are secreted by irradiated cells, this bystander effect alters the composition and activity of surgical wound fluid, decreasing its ability to stimulate breast cancer cells [25]. Thus, clinical studies should determine the effects of IORT on early relapse, especially in highly aggressive breast carcinomas (i.e., HER2+ and TN).

Because surgery remains the most effective treatment for breast cancer, we must improve our understanding of the inflammatory response that occurs during local wounding and of the consequences of this response on disease progression. Recently, proinflammatory cytokines that are induced by wound healing were reported to enhance cancer stem cells that are highly resistant to current treatments and are responsible for repopulating the tumor after treatment, causing local and systemic recurrence [11].

The postsurgical administration of anti-inflammatory agents, such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), is being examined in slowing the protumoral effects of wound-healing process. NSAIDs can be prescribed post surgery to manage pain and decrease inflammation. Interest in the use of NSAIDs for breast cancer patients originated from their patent association with a lower incidence of breast cancer [26,27].

The rationale for the use of NSAIDs in improving the survival of patients who have undergone surgical excision of a breast carcinoma is based on several mechanisms, including the impairment of PTGS-2 by NSAIDs, the angiogenic activities of platelets, and Nitric Oxide (NO) production all of which affect the proliferation of blood vessels [28-31].

Exploiting the widespread use of NSAIDs as post surgery analgesics in cohorts of primary breast cancer patients, initial studies retrospectively examined the relationship between the postoperative administration of these drugs and the prognosis of the breast cancer [32]. A systematic review of the effects of postoperative NSAIDs on breast cancer outcomes noted a benefit, defined as a significant reduction in breast cancer mortality, in 5 of 9 studies [33]. This observation was confirmed by a more recent meta-analysis that demonstrated an association between aspirin use and decreased breast cancer mortality [34].

Considering that 19 million prescriptions were written for aspirin alone in 2019, primarily related to the primary prevention of or treatment after a heart attack or stroke [https://clincalc.com/DrugStats/Top300Drugs.aspx], concomitant cardiovascular disease is the clinical reason for which many breast cancer patients are treated with aspirin, representing 1 of the main limitations, with the variability in drug dosages, in retrospectively determining the true effect of these analgesics on breast cancer outcomes. Moreover, considering the link between differently reactive stroma of various breast cancer subtypes and the resulting healing factors, as discussed. The effect of NSAIDs on breast cancer prognosis should be determined in patients who are stratified by breast cancer subtype, thus, all studies agree on the need for a large-scale randomized controlled trial to establish whether

NSAIDs impact the prognosis of breast cancer and determine the ideal dose. Based on this evidence, the ADD-ASPIRIN clinical trial was begun [35].

In addition to the use of NSAIDs as adjuvant treatment, this evidence, with the good safety profile of NSAIDs, has encouraged their administration in the intraoperative setting, highlighting the benefit of a single dose of ketorolac particularly in patients with elevated Body Mass Index (BMI). Thus, the major determinant in the reduction of distant disease recurrence, particularly early events, might be the timing with which the drugs are given, instead of the dosage [36-38].

Several angiogenic factors peak on the first day post surgery during wound healing, declining significantly by day 3; this pattern corresponds to their release following platelet granulation and the initial inflammatory response [39-43]. Because tumor cells disseminate when the tumor starts to become vascular zed, proangiogenic factors that are released during wound-healing might increase the levels of Circulating Tumor Cells (CTCs) that have remained dormant until surgery and accelerate the dissemination of cancer [44]. This model supports the major benefit of NSAIDs in the perisurgical *vs.* postsurgical period.

Notably, Wang and colleagues observed increased levels of inflammatory cytokines and chemokines in drainage samples from breast cancer patients who underwent Neoadjuvant Chemotherapy (NAC), likely due to the enrichment of Reactive Oxygen Species (ROS) in the tumor microenvironment that were released on tumor cell death and necrosis [24]. Thus, particularly in NAC patients, the administration of NSAIDs in the perisurgical period should counteract the higher systemic levels of proinflammatory mediators.

Moreover, the inflammatory response that is induced by surgery might engage the STAT3 pathway in residual BC cells, which in turn could affect the acquisition of stem-like features [45]. Consistent with this model, NSAIDs lower the number of Circulating Tumor Cells (CTCs), which has recently been proposed as another mechanism by which the risk of metastasis is reduced [46].

This evidence supports the function of surgery-induced inflammation in early relapses in breast cancer and of wound-healing fluid as a carrier of protumoral signals on the systemic level. Strengthening this hypothesis, a recent study used an experimental model that consisted of murine mammary carcinoma cells that ectopically expressed green fluorescence protein and orthotopically injected them into syngeneic mice, showing that tumor resection increased the systemic inflammatory response and promoted the outgrowth of cancer cells at distant sites. Moreover, perioperative treatment of mice with NSAIDs significantly impeded the surgery-induced progression of the tumor [47].

Although surgery remains the preferred treatment for breast cancer patients, the wound-healing that follows surgery is clearly emerging as an aspect that must be considered in the postoperative setting. Tissue damage due to cancer surgery provides a favorable niche for tumor recurrence, facilitating the growth of pre-existing micro metastases, enhancing the cancer stem cell population, creating a Reactive Oxygen Species (ROS)-rich environment, and affecting patient outcomes.

Future efforts should identify treatments that extinguish the ensuing inflammation, considering 3 levels of intervention:

- Before surgery, promoting a lifestyle that systemically lowers inflammatory parameters, such as physical exercise and diet, to maintain a healthy BMI.
- During surgery, limiting resection and consequent wound-healing and administering NSAIDs perisurgically.
- Post surgery, developing new markers that track the effects of surgery-induced inflammation.

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