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Perspective

Cancer Research

Connecting (T)issues: How Research in Fascia Biology Can Impact Integrative Oncology

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Abstract

Complementary and integrative treatments, such as massage, acupuncture, and yoga, are used by increasing numbers of cancer patients to manage symptoms and improve their quality of life. In addition, such treatments may have other important and currently overlooked benefits by reducing tissue stiffness and improving mobility. Recent advances in cancer biology are underscoring the importance of connective tissue in the local tumor environment. Inflammation and fibrosis are well-recognized contributors to cancer, and connective tissue stiffness is emerging as a driving factor in tumor growth. Physical-based therapies have been shown to reduce connective tissue inflammation and fibrosis and thus may have direct beneficial effects on cancer spreading and metastasis. Meanwhile, there is currently little knowledge on potential risks of applying mechanical forces in the vicinity of tumors. Thus, both basic and clinical research are needed to understand the full impact of integrative oncology on cancer biology as well as whole person health. *Cancer Res; 76(21); 6159–62. ©2016 AACR.*

Introduction

With early diagnosis and advanced treatment of cancer, an increasing number of patients survive long term, but many suffer consequences of their anticancer treatments. It is estimated that 14.5 million cancer survivors currently live in the United States, and at least 40% of them use complementary or integrative approaches to manage symptoms and improve their well-being during and after conventional cancer treatment (1). Emerging research suggests that body-based therapies like yoga, acupuncture, and massage may improve symptoms and quality of life in cancer patients (2). To date, clinical research in integrative medicine has mostly focused on patient-reported outcomes, such as pain, fatigue, insomnia, and psychologic distress (2, 3). Much less is known about physical components of these outcomes, such as stiffness, range of motion, balance, coordination, and strength, which affect the well-being and functional independence. Furthermore, even less is known about whether these treatments can influence the disease process of cancer itself. Thus, there is a need for research to better understand the physical impact of these therapies and the underlying mechanisms by which many patients realize a benefit from these approaches. In this article, we propose that recent advances in connective tissue biology are providing clues to potential mechanisms by which physical-based treatments may directly reduce cancer growth, spreading, and metastasis, in addition to improving symptoms and quality of life. We also underscore the need for evaluating the safety of these approaches along with potential benefits.

Importance of Connective Tissue in Cancer Biology

The connective tissue network is an integrated, whole-body system that is amenable to physical manipulation by modalities, including massage, acupuncture, acupressure, yoga, and similar mind–body exercises (4, 5). Fasciae are composed of an extracellular connective tissue matrix that forms structures surrounding every organ of the body, integrates the musculoskeletal system, and houses the blood and lymphatic vasculature. The lymphatic vessels then deliver local chemical information from the tissues they drain to the immune system via lymph nodes (6). The normal mobility of fascial tissues is due in part to gliding movement between adjacent fascial layers (7). Stiffness and lack of mobility of fascia has implications beyond a patient being unable to move adequately; it is also a feature of the underlying structure of the connective tissue, which can affect the behavior of all cells interacting with the connective tissue matrix (8, 9).

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Pathologic processes involving chronic inflammation and tissue fibrosis result in stiff connective tissue; this is likely a bidirectional feedback, as emerging evidence points to tissue stiffness itself being a contributor to the fibrotic process (10, 11). In addition, there is evidence that these factors are important in cancer biology as well (11–17). Although the importance of connective tissue or stroma in cancer was first hypothesized over a century ago (18), cancer research has predominantly focused on the neoplastic transformation of the cancer cells themselves. However, the last decades have seen a growing interest in the factors within the "soil" that may influence cancer growth, such as angiogenesis (19) and inflammation (20–22). Indeed there is increasing evidence that inflammation and metabolic abnormalities within the cancer microenvironment are not simply a passive reaction to cancer cells, but can also drive neoplastic transformation (23, 24). This knowledge is beginning to be translated into clinical applications in the development of personalized chemotherapeutic regimens based on *in vitro* testing incorporating elements of the patient's tumor microenvironment (25). This new understanding is also shaping primary prevention strategies that promote a cancer-resistant extracellular environment, such as aspirin for colon cancer and metformin for breast cancer (26, 27). Although these strategies so far have mostly targeted the biochemical aspects of the extracellular "milieu," such as locally released cytokines and growth factors (23), there is also a growing interest in biophysical factors within connective tissue, including extracellular matrix stiffness, alignment, and porosity, that may influence cancer growth (28–30). It has long been recognized that wound healing, fibrosis, and cancer share many common features, including epithelial-to-mesenchymal transition (EMT), myofibroblast transformation, and collagen deposition (11, 31). In particular, the possible link between extracellular matrix stiffness and cancer has generated substantial interest for several decades in both primary tumors and the tumor metastatic niche (18, 30, 32). Although there are challenges in directly measuring tissue stiffness *in situ*, imaging methods, such as elastography and atomic force microscopy, show that malignant tumors are on average stiffer compared with benign lesions (33) and have a heterogeneous stiffness profile with soft and stiff areas corresponding to cancer cells and fibrotic stroma, respectively (34). In human biopsies, increased local stiffness (17) and perpendicular collagen alignment at the periphery of malignant tumors (16) have been associated with increased invasiveness. In animal models and *in vitro* experiments, increased collagen deposition, alignment, and cross-linking were shown to promote tumor progression (15, 35, 36). However, the question of whether extracellular matrix stiffness can, by itself, promote cancer growth is not fully answered. Although experiments in 3-dimensional gels suggest that matrix stiffness can independently promote malignant transformation (37), tumor cells have been shown to migrate both toward and away from areas of increased stiffness (30). A current model is that, in primary tumors, a desmoplastic response of the developing tumor stroma driven by both neoplastic cells and cancer-associated fibroblasts results in release of growth factors, such as TGFβ, that promote EMT, which itself feeds forward to both enhance matrix deposition and stiffness as well as tumor invasion (38). On the other hand, efforts to suppress tumor-associated stroma have generally been unsuccessful and have even resulted in increased tumor invasiveness in some models (12, 39–41). Although clearly many questions remain on the role played by connective tissue stiffness in cancer biology, it is a concern that conventional cancer treatments, including surgery and radiotherapy, can themselves contribute to fibrosis and matrix stiffening (42, 43). Furthermore, a broader consideration of the connective tissue system throughout the host has been largely overlooked. At the patient level, loss of mobility and activity can lead to additional tissue stiffness and impact quality of life, and the possibility that increased stiffness of the connective tissue network as a whole could, in addition, impact cancer growth and metastasis is mostly unexplored.

Potential Effects of Physical-Based Treatments on Cancer

Recent advances in understanding the effect of mechanical forces on tissues provide clues that may now be useful to understand the biology of physical-based therapies in relation to cancer and perhaps eventually develop physical treatments that may enhance natural healing responses. Although epidemiologic studies have documented a positive association between physical activity and survival in many cancer types (44–46), the mechanisms underlying this association remain to be elucidated. Investigations of physiologic responses to exercise that may inhibit cancer growth have focused on energy metabolism (47, 48), inflammation (49), and immune surveillance (50, 51). Meanwhile, the possibility that mechanical forces produced within tissues during exercise could directly impact tumor growth or recurrence has received little attention. Noticing the paucity of metastases to muscle, Weiss (52) found rapid destruction of injected tumor cells by contracting muscles. Animal models have shown that gentle stretching can reduced chronic inflammation and collagen deposition within local connective tissue (53–55) and that manual manipulation of lymphatics can modify lymphatic flow, which plays a pivotal role in the interaction between connective tissue and tumors (13, 56). Although separating mechanical versus biochemical effects is difficult *in vivo*, experiments *ex vivo* are suggesting that stretching of connective tissues may have local anti-inflammatory effects independent of vascular, neural, or other systemic factors (53). This raises the question of whether the growth, spreading, and/or dissemination of a malignant lesion could be inhibited by mechanical forces applied actively or passively (e.g., during stretching exercises, yoga, massage, or acupuncture). On the other hand, it has long been a concern that applying mechanical pressure or shear force to a tumor might dislodge malignant cells and encourage their migration into lymphatics or blood vessels (57–59). More recently, the presence of labeled epithelial cells in sentinel axillary nodes in patients with breast cancer was found to be increased in patients who underwent breast massage prior to the procedure (60). Although this was interpreted as a form of "benign mechanical transport," similar to that occurring with needle biopsies, rather than true micrometastases (61), there is a remaining debate on the long-term risks associated with such findings (62, 63). There is also controversy over the role and safety of manual therapies and acupuncture in the management of lymphedema postcancer treatment (64, 65). Although some studies have concluded that such treatment is safe even in areas with residual tumor (66–68), to date, no randomized prospective study has examined this issue. Meanwhile, there is virtually no basic research on physical manipulation of the connective tissue matrix surrounding tumors to influence the behavior of the tumor as it interacts with its surrounding matrix, or at distant sites to influence the receptivity of

the matrix to metastatic seeding. This constitutes an important gap in knowledge and is an opportunity to both advance our understanding of mechanobiology and improve patient care through determining the potential benefits versus risks of body-based therapies in cancer patients. An intriguing possibility is that these outcomes may be related to long-term relapse and survival. Although the safety of applying direct mechanical forces in the vicinity of tumors should be a prime concern, the possibility that active or passive mechanical forces applied away from the tumor itself may promote a healthy connective tissue environment that is inhospitable to cancer should be considered and systematically investigated. As we connect the fields, we hope to emerge with a better understanding of the interplay between integrative medicine, matrix biology, and oncology.

Summary and Conclusions

Increasing evidence indicates that the physical and mechanical environment can regulate cell behavior and tumor progression at a cellular level. It is likewise clear that many patients benefit from physical manipulation of connective tissue, but it is not clear what happens at the cellular and molecular level when these manipulations occur. Thus, a large disconnect exists between the cell and connective tissue biology and integrative medicine approaches. Advancing this field will require a coordinated effort combining epidemiology with cancer cellular and extracellular matrix biology.

As such, considerations of physical sciences in oncology should be expanded to include the whole host and possible ways that integrative medicine might be deployed, to determine whether we can safely impact tumor progression and the underlying biology with active and passive physical manipulation. Conversely, body-based therapy research should be expanded to consider the underlying matrix, cell, and molecular mechanisms so that we understand what tissue-level effects derive from physical manipulations of the host.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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