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What Pain Tells Us About Cancer

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Abstract

Cancer pain sends a message. It is frightening to the patient. It heralds progression or recurrence to the oncologist. It is a biologic readout of the cancer-nerve interaction for the scientist. Nerves have been considered bystanders within the cancer microenvironment. However, emerging information suggests that nerves are recruited and participate in the carcinogenic process. These newly formed fibers respond to mediators secreted by constituents of the cancer microenvironment. In this manner these nerves serve as bellwethers and sensors embedded within the cancer. When we rigorously assess patients' cancer pain we gain insight into the action of cancer. An enhanced understanding of cancer pain offers biologic questions which if answered might not only provide relief from cancer pain but might also improve survival.

Introduction

The sensory nervous system enables each of us to acquire information about our external environment. However, this same system monitors the body's internal environment and can alert us to pathologic processes including cancer. Activation of the sensory nervous system in the region of a cancer often results in the sensation of pain. Pain can herald the development of cancer and can provide information regarding cancer activity including metastasis. The character, duration and timing of a cancer patient's pain is useful to physicians who treat cancer and to scientists who study the disease.

While cancer pain can be excruiating for patients and difficult to alleviate, this symptom is often the sole reason that patients seek treatment. Accordingly, cancer pain can lead to earlier diagnosis and improved outcome associated with early diagnosis and treatment. Pain is commonly viewed as an incidental consequence of cancer proliferation, tissue destruction and invasion. Now, however, we understand that the nervous system is integral to carcinogenesis; pain is an indicator of specific processes and physiological consequences related to the mechanisms that propel malignancy. Many cancers are highly innervated; some directly infiltrate and preferentially proliferate within nerves as well [1]. The molecular mechanisms driving dense innervation and perineural involvement are complex and only partially revealed in recent research. In this manuscript I will review emerging

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perspectives on cancer pain and summarize our current understanding of the relationship between pain and carcinogenesis.

Pain is a Bellwether for Cancer

For some histological types of cancer, well-localized pain at the primary site is a common presenting symptom. For example, in patients with head and neck squamous cell carcinoma pain is the most common symptom. In a recent study of 812 organ transplant recipients who developed cancer as a result of immunosuppression, pain was the most common patient-reported harbinger of squamous cell carcinoma invasion [2]. Benign or precancerous lesions are generally not painful but pain can signal a transformative process. Sensory afferent activation might herald carcinogenesis because it can occur early in the transformative process [10]. In a recently published preclinical model of pancreatic cancer, sensory afferent involvement was observed prior to the transformation to cancer [22]. For patients with head and neck squamous cell carcinoma, pain most commonly occurs at the primary site. However, head and neck cancer pain can be referred. A classic description of ear pain referred from head and neck cancer was described over a century ago by Wilfred Trotter [23].

Pain is notable even for cancers which are typically not thought to be painful at the primary site. Breast adenocarcinoma is often characterized as painful only after it metastasizes to bone [24]. When the rate of cancer pain in the breast is rigorously evaluated, however, the prevalence of pain in the breast is surprisingly high. Pain as measured by the Breast Symptoms Questionnaire and the Pain Qualities Assessment Scale was reported by 28.2% of the 398 breast cancer patients in a recent study [15]. Moreover, a review of older literature reveals that investigators previously documented pain in 13 to 45% of breast cancer patients across five studies [5]. The intensity and character of breast cancer pain is different than head and neck cancer pain in part because it does not appear to be function-related. The exact causes of differences in pain phenotype between head and neck squamous cell carcinoma and breast adenocarcinoma pain are unclear; however, the density or molecular features of the peripheral nervous system at the two primary sites or the disparate function associated with a specific anatomic site might greatly affect the severity of pain. Meticulous inquiry into the cancer and host factors contributing to cancer pain might provide a vantage point to understand carcinogenesis and the cancer-nerve interaction.

Pain Reveals Essential Steps in Carcinogenesis

Stimulation of peripheral afferent nociceptors contributes to cancer pain; however, the molecular mediators and the direct interaction by which malignant or resident cells modulate nociceptors is not precisely known. Investigation of the basic elements of the intercellular pathways has yielded a better understanding of this process [18]. It is generally accepted that cancers secrete algogenic mediators that subsequently sensitize or activate neurons in the cancer microenvironment. These algogens include proteases, endothelin-1 (ET-1), ATP, protons, neurotrophic factors, bradykinin and tumor necrosis factor [18]. Secreted products from cancer alone activate primary afferent neurons. Small-to-medium trigeminal neurons (approximately 40%) respond to oral squamous cell carcinoma supernatant when measured

with calcium imaging [25] or whole cell patch clamp recordings [29]. *In vivo* behavioral studies demonstrate that inoculated squamous cell carcinoma supernatant in a naïve mouse leads to mechanical allodynia [9].

Many of the algogenic mediators secreted by cancer have overlapping functions with cancer-related processes (Table 1). For example, proteases activate protease activated receptor-2 on primary afferent nociceptor and proteases including collagenases and matrix metalloproteinases (MMPs) are critical for cancer invasion [9]. ET-1 activates the endothelin A receptor on primary afferent nocicetpors but also has vasoactive properties in the cancer microenvironment and contributes to angiogenesis [27]. Bradykinin also induces angiogenesis through the kinin B1 receptor [6–7]. Nerve growth factor (NGF) activates primary afferent nociceptors and leads to pain and also leads to neurogenesis and angiogenesis in the cancer microenvironment [13,26]. Activation of the primary afferent nociceptors by these algogens might contribute to carcinogenesis.

Neurons exhibit plasticity in response to secreted products of cancer cells. There is robust neurogenesis of sensory and sympathetic nerve fibers within the cancer microenvironment [12]. In addition, neurotrophins can originate from the cancer itself or from cancer-associated fibroblasts. Antagonism of NGF can lead to a reversal in cancer pain and cancer growth [19]. This effect has now been demonstrated in a model of head and neck squamous cell carcinoma and in a bone cancer model [14,28]. Moreover, spinal cord neurochemical changes secondary to cancer have been well documented in preclinical cancer models [18]. *In vitro* approaches demonstrate that neuronal plasticity is observed when cancer cells (oral squamous cell carcinoma) are co-cultured with trigeminal neurons. Co-cultured trigeminal neurons that respond to ATP with a sustained current, as measured by whole cell patch recordings, exhibit an enhanced and prolonged response to ATP when no longer in co-culture. Trigeminal neurons that respond with a transient current do not show a change. Anti-NGF treatment modulates P2X2 expression and blocks the effects seen in neurons responding with a sustained current [29]. These findings reveal interesting features of the cancer-neuron interaction: not all neurons respond to cancer cell supernatant, and neurons that do respond to supernatant demonstrate plasticity in response to cancer co-culture. This form of plasticity is also likely to occur in patients. However, such plasticity does not commonly lead to persistent pain because resection of the cancer almost always alleviates pain from head and neck squamous cell carcinoma in patients [8].

Pain Phenotype Variability Reflects Cancer Genomic Heterogeneity

There can be great variability in the cancer pain phenotype. Many histological types of cancer such as melanoma (even in the head and neck) are typically not painful at the primary site or at metastatic sites. For oral squamous cell carcinoma, pain is the most common presenting symptom; pain is also the most common symptom when the cancer recurs. Even the same histological types of cancer located in similar anatomic sites may present with different pain phenotypes as a result of other factors, such as etiology (or, more likely, unknown factors). Human papilloma virus (HPV) is an etiologic agent contributing to over half of oropharyngeal cancers. Oropharyngeal cancer that is HPV positive typically does not present with pain; however, HPV negative oropharyngeal cancer is generally painful [16].

The point should be made that oral (as compared to oropharyngeal) squamous cell carcinomas are rarely infected with HPV (less than 5%) and tend to be associated with higher levels of pain.

Genomic analysis demonstrates that malignant cells often possess thousands of mutations. Oral cancers demonstrate vast genomic heterogeneity which is reflected in the widely disparate pain phenotypes observed in histologically similar tumors located in the same anatomic region [4,21]. Some patients with oral squamous cell carcinoma (a notoriously painful cancer) never experience pain from their disease. Adenoid cystic carcinoma is a rare salivary gland malignancy that affects major and minor salivary glands, including those in the oral cavity. Perineural invasion is a common pathologic feature in this disease. The pain associated with adenoid cystic carcinoma is typically vague and dull compared to the intense and well-localized pain of oral squamous cell carcinoma [3]. The genomic alterations which have been documented in these two distinct oral cancers are different, as are their clinical behavior and response to surgical and radiation treatment [17,20].

The Emerging Role of the Nervous System in Carcinogenesis

The nervous system responds to cancer and the processes of carcinogenesis. Emgerging data corroborate interplay between the nervous system and carcinogenesis. For example, sympathetic and parasympathetic nervous system activation is required for prostate carcinogenesis [11]. To confirm these results and to ascertain whether sympathetic signals locally delivered in the tumor microenvironment were requisite for carcinogenesis, the above authors surgically cut the nerves that carry selectively sympathetic fibers (hypogastric nerves) into the prostate gland prior to orthotopic injection of tumor cells. Tumors failed to grow under these conditions.

Similar results were found when the vagal nerve was severed to block development of gastric cancer [30]. Zhao et al. demonstrated that the vagal nerve (which conveys signals to the stomach through muscarinic receptors) contributes to the growth of gastric tumors; vagotomy (surgical interruption of the vagal nerve) prevents gastric cancer in mice and reduces recurrence of gastric tumors in patients. Moreover, the same result can be achieved in mice treated with drugs that inhibit vagal nerve signaling (Botox or anticholinergic drugs). This treatment method raises the prospect of a safer treatment for gastric cancer that also avoids irreversible side effects.

Summary

The complex interplay between pain and carcinogenesis in several different histological types of cancer is now readily apparent in the scientific literature. Many obstacles stymie our efforts to alleviate pain in cancer patients. In the near future we must develop more sophisticated clinical instruments to distinguish cancer pain phenotypes, employ molecular techniques to investigate the relavent pathways and create better preclinical cancer models to recapitulate the patient condition. We must also train investigators with backgrounds in cancer biology and neuroscience to formulate and address the biologic questions most relevant to understanding and treating cancer pain. Answers to these critical questions might

allow us to modulate the responsible pathways. A nuanced understanding of this system might also improve our ability to curb carcinogenesis.

References

1. Bapat AA, Hostetter G, Von Hoff DD, Han H. Perineural invasion and associated pain in pancreatic cancer. Nat Rev Cancer. 2011; 11:695–707. [PubMed: 21941281]
2. Bouwes Bavinck JN, Harwood CA, Genders RE, Wisgerhof HC, Plasmeijer EI, Mitchell L, Olasz EB, Mosel DD, Pokorney MS, Serra AL, Feldmeyer L, Baumann Conzett K, Piaserico S, Belloni Fortina A, Jahn K, Geusau A, Gerritsen MJ, Seckin D, Gulec AT, Cetkovska P, Ricar J, Imko-Walczuk B, Proby CM, Hofbauer GF. Pain identifies squamous cell carcinoma in organ transplant recipients: the SCOPE-ITSCC PAIN study. Am J Transplant. 2014; 14:668–676. [PubMed: 24730051]
3. Closmann JJ, Schmidt BL. Adenoid cystic carcinoma manifesting as maxillary jaw pain refractory to conventional treatment: a case report. Gen Dent. 2006; 54:195–197. [PubMed: 16776413]
4. Connelly ST, Schmidt BL. Evaluation of pain in patients with oral squamous cell carcinoma. J Pain. 2004; 5:505–510. [PubMed: 15556829]
5. Corry DC. Pain in carcinoma of the breast. Lancet. 1952; 1:274–276. [PubMed: 14889840]
6. Hu DE, Fan TP. [Leu8]des-Arg9-bradykinin inhibits the angiogenic effect of bradykinin and interleukin-1 in rats. Br J of Pharmacol. 1993; 109:14–17. [PubMed: 7684297]
7. Ishihara K, Kamata M, Hayashi I, Yamashina S, Majima M. Roles of bradykinin in vascular permeability and angiogenesis in solid tumor. Int Immunopharmacol. 2002; 2:499–509. [PubMed: 11962729]
8. Kolokythas A, Connelly ST, Schmidt BL. Validation of the University of California San Francisco Oral Cancer Pain Questionnaire. J Pain. 2007; 8:950–953. [PubMed: 17686656]
9. Lam DK, Dang D, Zhang J, Dolan JC, Schmidt BL. Novel animal models of acute and chronic cancer pain: a pivotal role for PAR2. J Neurosci. 2012; 32:14178–14183. [PubMed: 23055487]
10. Lam DK, Schmidt BL. Orofacial pain onset predicts transition to head and neck cancer. Pain. 2011; 152:1206–1209. [PubMed: 21388740]
11. Magnon C, Hall SJ, Lin J, Xue X, Gerber L, Freedland SJ, Frenette PS. Autonomic nerve development contributes to prostate cancer progression. Science. 2013; 341:1236361. [PubMed: 23846904]
12. Mantyh WG, Jimenez-Andrade JM, Stake JI, Bloom AP, Kaczmarska MJ, Taylor RN, Freeman KT, Ghilardi JR, Kuskowski MA, Mantyh PW. Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. Neuroscience. 2010; 171:588–598. [PubMed: 20851743]
13. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. Nat Rev Rheumatol. 2012; 8:390–398. [PubMed: 22641138]
14. McCaffrey G, Thompson ML, Majuta L, Fealk MN, Chartier S, Longo G, Mantyh P. NGF blockade at early times during bone cancer development attenuates bone destruction and increases limb use. Cancer Research. 2014
15. McCann B, Miaskowski C, Koetters T, Baggott C, West C, Levine JD, Elboim C, Abrams G, Hamolsky D, Dunn L, Rugo H, Dodd M, Paul SM, Neuhaus J, Cooper B, Schmidt B, Langford D, Cataldo J, Aouizerat BE. Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. J Pain. 2012; 13:425–437. [PubMed: 22515947]
16. McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg. 2014; 140:441–447. [PubMed: 24652023]
17. Rao PH, Roberts D, Zhao YJ, Bell D, Harris CP, Weber RS, El-Naggar AK. Deletion of 1p32-p36 is the most frequent genetic change and poor prognostic marker in adenoid cystic carcinoma of the salivary glands. Clin Cancer Res. 2008; 14:5181–5187. [PubMed: 18698036]

18. Schmidt BL. The neurobiology of cancer pain. The Neuroscientist. 2014; 20:546–562. [PubMed: 24664352]
19. Sevcik MA, Ghilardi JR, Peters CM, Lindsay TH, Halvorson KG, Jonas BM, Kubota K, Kuskowski MA, Boustany L, Shelton DL, Mantyh PW. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. Pain. 2005; 115:128–141. [PubMed: 15836976]
20. Shao C, Sun W, Tan M, Glazer CA, Bhan S, Zhong X, Fakhry C, Sharma R, Westra WH, Hoque MO, Moskaluk CA, Sidransky D, Califano JA, Ha PK. Integrated, genome-wide screening for hypomethylated oncogenes in salivary gland adenoid cystic carcinoma. Clin Cancer Res. 2011; 17:4320–4330. [PubMed: 21551254]
21. Snijders AM, Schmidt BL, Fridlyand J, Dekker N, Pinkel D, Jordan RC, Albertson DG. Rare amplicons implicate frequent deregulation of cell fate specification pathways in oral squamous cell carcinoma. Oncogene. 2005; 24:4232–4242. [PubMed: 15824737]
22. Stopczynski RE, Normolle DP, Hartman DJ, Ying H, DeBerry JJ, Bielefeldt K, Rhim AD, DePinho RA, Albers KM, Davis BM. Neuroplastic changes occur early in the development of pancreatic ductal adenocarcinoma. Cancer Res. 2014; 74:1718–1727. [PubMed: 24448244]
23. Trotter W. On Certain Clinically Obscure Malignant Tumours of the Naso-Pharyngeal Wall. Brit Med J. 1911; 2:1057–1059. [PubMed: 20765847]
24. Truscott BM. Carcinoma of the breast; an analysis of the symptoms, factors affecting prognosis, results of treatment and recurrences in 1211 cases treated at the Middlesex Hospital. Brit J Cancer. 1947; 1:129–145. [PubMed: 20266450]
25. Viet CT, Dang D, Ye Y, Ono K, Campbell RR, Schmidt BL. Demethylating drugs as novel analgesics for cancer pain. Clin Cancer Res. 2014; 20:4882–4893. [PubMed: 24963050]
26. Walsh DA, McWilliams DF, Turley MJ, Dixon MR, Franses RE, Mapp PI, Wilson D. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. Rheumatology (Oxford). 2010; 49:1852–1861. [PubMed: 20581375]
27. Wu MH, Lo JF, Kuo CH, Lin JA, Lin YM, Chen LM, Tsai FJ, Tsai CH, Huang CY, Tang CH. Endothelin-1 promotes MMP-13 production and migration in human chondrosarcoma cells through FAK/PI3K/Akt/mTOR pathways. J Cell Physiol. 2012; 227:3016–3026. [PubMed: 21959927]
28. Ye Y, Dang D, Zhang J, Viet CT, Lam DK, Dolan JC, Gibbs JL, Schmidt BL. Nerve growth factor links oral cancer progression, pain, and cachexia. Mole Cancer Ther. 2011; 10:1667–1676.
29. Ye Y, Ono K, Bernabe DG, Viet CT, Pickering V, Dolan JC, Hardt M, Ford AP, Schmidt BL. Adenosine triphosphate drives head and neck cancer pain through P2X2/3 heterotrimers. Acta Neuropathol Commun. 2014; 2:62. [PubMed: 24903857]
30. Zhao CM, Hayakawa Y, Kodama Y, Muthupalani S, Westphalen CB, Andersen GT, Flatberg A, Johannessen H, Friedman RA, Renz BW, Sandvik AK, Beisvag V, Tomita H, Hara A, Quante M, Li Z, Gershon MD, Kaneko K, Fox JG, Wang TC, Chen D. Denervation suppresses gastric tumorigenesis. Sci Transl Med. 2014; 6:250ra115.

Table 1

Processes and mediators involved in carcinogenesis that likely lead to cancer pain

Carcinogenesis process	**Algogenic mediators involved with carcinogenesis**
Cancer proliferation	ATP, protons
Tissue invasion and metastasis	proteases
Perineural invasion	proteases
Angiogenesis	ET-1, bradykinin, neurotrophins
Neurogenesis within cancer microenvironment	neurotrophins