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The Neurobiology of Cancer Pain

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Abstract

Oral cancers are often severely painful and clinically difficult to manage. Few researchers investigate the neurobiological factors responsible for cancer pain; however, the study of oral cancer pain might inform us about the fundamental biology of cancer. The purpose of this paper is to summarize 1) clinical challenges inherent in oral cancer pain management, 2) oral cancer pain mechanisms and mediators, and 3) the convergence of the investigation of carcinogenesis and pain.

The Clinical Problem of Cancer Pain

Worldwide, an enormous number of patients suffer with painful malignancies. Pain treatment in these patients remains a daunting clinical challenge. Even in more developed countries patients do not escape pain from cancer. Opioids are initially effective in reducing or alleviating pain from some types of cancer; however, within a few weeks, tolerance to these drugs generally develops. Larger doses of opioids are prescribed. Side effects from opioids are debilitating and worsen as larger doses are administered. In addition, as our scientific knowledge about cancer has improved, we have extended the lives of cancer patients. Ironically this success has also extended the duration for which some of these patients suffer with pain.

We do not understand many of the biological mechanisms responsible for cancer pain; depending on the type and anatomic location of cancer, different mechanisms might be responsible. For example, the cause of metastatic bone cancer pain is different than the cause of pain from a squamous cell carcinoma in the tongue. In the case of metastatic bone cancer pain we have a robust understanding of the mechanism and good clinical outcomes when treating pain in these patients with a non-opioid therapy. In the case of oral squamous cell carcinoma, little scientific knowledge about the etiology of pain is available. We are equally feckless in our clinical approach to obtund oral cancer pain and we seek a targeted, data-driven approach to manage oral cancer pain. This approach might still include exogenous opioids.

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Oral Cancer Pain

Most oral cancers are squamous cell carcinoma. Oral squamous cell carcinoma is often excruciatingly painful. Operative treatment nearly always relieves oral cancer pain. Moreover, operative treatment is not appropriate for all oral cancers, some patients are too ill to undergo surgery or have recurrent or inoperable tumors. We believe that oral cancers produce (or induce surrounding cells to produce) and secrete mediators. These putative mediators then sensitize or activate primary afferent nociceptors. Other hypotheses to explain cancer pain have been posited including tissue destruction or nerve compression. Clinical findings and preclinical experiments do not support this hypothesis. For example, ameloblastomas can be destructive but pain is atypical. Cancer pain could also be caused by inflammation. Preclinical studies, however, demonstrate that cancer pain is distinguishable from inflammatory pain. Moreover, non-steroidal anti-inflammatory drugs (NSAIDS) are ineffective for cancer pain [1].

Few studies document and quantify pain in patients with oral cancer. Several quality-of-life questionnaires have been employed. Questionnaires from the University of Washington and the European Organization for the Research and Treatment of Cancer (EORTC) have been used but these questionnaires are not specific for oral cancer (only for head and neck cancer). Moreover, these questionnaires do not distinguish functional from spontaneous pain. This distinction is important for cancers of the oral cavity (as opposed to nasopharyngeal, oropharyngeal, hypopharyngeal, laryngeal) because the oral cavity is extensively and continually manipulated as part of the musculoskeletal apparatus utilized for everyday oral functions, e.g. talking, swallowing, eating and drinking. A validated oral cancer pain questionnaire, the *UCSF Oral Cancer Pain Questionnaire* was devised to measure pain in patients with oral cancer. This questionnaire discriminates between spontaneous from functional pain [2, 3]. Using adjectives from the *McGill Pain Questionnaire*, the UCSF questionnaire has been used to show that oral cancer patients experience more functional than spontaneous pain [2, 3].

Tumor size does not generally correlate with pain severity. Patients report greater pain severity at the primary site for oral cancers that have metastasized to the cervical lymphatics. Premalignant oral lesions including dysplasia are rarely painful [4]. The transformation of a premalignant lesion into a cancer is often heralded by pain. Excision of the oral cancer relieves pain in most if not all patients. This finding supports the hypothesis that oral cancer pain stems from mediators within the cancer microenvironment [3].

Oral squamous cell carcinoma exhibits high genomic heterogeneity and manifests in the disparate oral cancer phenotypes. Oral cancer (pain) is not predictable; some lesions are painful, some are painless. Similar findings have been demonstrated in preclinical models generated with disparate histologic cancer types such as sarcoma and adenocarcinoma. Different histologic cancer types inoculated into the same anatomic site in a series of rodents generate distinct pain phenotypes as well as distinct neurochemical reorganization of the spinal cord [5].

Cancer Pain Mechanisms from Preclinical Models

We hypothesize that cancers produce and secrete pain-inducing mediators that activate or sensitize primary afferent nociceptors. Cancers can also induce plasticity in the peripheral and central nervous system. Carcinogenesis also involves the recruitment of neurons, lymphocytes, endothelial cells and fibroblasts. Cancer-evoked responses in rodent models mirror some symptoms observed in patients, however, preclinical cancer models are inherently artificial. Accordingly, laboratory findings (mostly rodent studies) are not always relevant to conditions observed in patients. The most important variables that influence the pain phenotype in these preclinical models include the proliferative, invasive, and metastatic potential of the cell line; anatomic site; the behavioral assay employed (and whether it is reflexive or operant); genetics of the animal; and the duration of tumor development.

Pain assays employed to characterize pain in the cancer models are often not relevant to pain observed in patients. For example, heat hyperalgesia is commonly found in bone cancer models that employ nonorthotopic hindlimb models that test hyperalgesia in the paw. Bone cancer patients with femur involvement, however, rarely complain of heat hyperalgesia in the foot. Many models also employ surgical manipulation, e.g. bone cancer models and post-surgical pain might confound results. Moreover, in most published studies, the model is generated with only one cancer cell line. Due to the genotypic heterogeneity of cancers, especially oral cancers, the applicability of the results are limited.

Mediators that contribute to cancer pain

Key mediators that contribute to cancer pain include endothelin, adenosine triphosphate, neurotrophins, and proteases. Some non-opioid drugs have been found to alleviate nociception in preclinical cancer pain models. Researchers often administer antagonists to reveal the contribution of putative pain mediators. A few of these drugs have also been shown to reduce tumor proliferation.

Oral squamous cell carcinoma produces very high levels of endothelin-1 (ET-1) [6–8]. Oral administration of the ETAR antagonists YM598 and atrasentan have been shown to inhibit ET-1 induced nociception. Nociceptive effects of ET-1 are peripherally mediated in the cancer microenvironment [7]. BQ-123 antagonizes ETAR directly within the cancer microenvironment and produces antinociception at levels similar to acutely administered, high dose, systemic morphine [8]. ATP release by endothelium has been reported to be sensitized by ET-1 [9]. ATP generates pain by activating $P2X_{2/3}$ receptors on nociceptors. In a fibrosarcoma model, tumors were shown to cause $P2X_3$ receptor upregulation [10]. An antagonist of the $P2X_3$ receptor, A317491, attenuated cancer pain.

Oral squamous cell carcinoma also produces several neurotrophic factors including nerve growth factor (NGF) and neuturin [11]. NGF has been shown to play a role in cancer pain. The cancer itself or constituent cells might produce NGF [12, 13]. Sequestration of NGF with an antibody alleviates pain in preclinical cancer models [12, 14]. Cancer-induced changes in the spinal cord are reversed in similar experiments [15]. Anti-NGF reduces

cancer pain, cancer progression and cachexia in a mouse model of squamous cell carcinoma [12].

Through protein catabolism, proteases can cause destruction of tissue. Proteases have also been shown to modify signaling pathways that regulate cytokines [16]. Protease modulation of cytokine activity can subsequently increase protease activity in a positive feedback cycle. Some cancers can produce (or induce surrounding cells to produce) proteases that facilitate expansion and invasion of a cancer through tissue destruction. Cancer associated proteases have been documented in cancer cell culture, rodent models, and in patients [17]. Proteases have also been shown to cause nociception (pain) in rodent cancer models. The role of protease activated receptor-2 (PAR2) in producing cancer pain was demonstrated with a pharmacologic and genetic approach. In rodent models, a serine protease inhibitor significantly reduced cancer pain in the animals. An oral cancer model in a global PAR2 knockout mouse generates significantly less pain and oral dysfunction than in control animals [18].

Perineural Invasion

Cancer cells and adjacent sensory nerves interact to generate pain. Cain and others [19] published a classic paper that demonstrated the effect of fibrosarcoma cells on sensory nerves. The fibrosarcoma cells were inoculated in and immediately adjacent to the calcaneus of a mouse. C fibers adjacent to the tumor were spontaneously active, showed greater sensitivity to heat, and exhibited mechanical hypersensitivity. During early cancer growth, epidermal nerve fibers branch and sprout. However, within 16 to 24 days post-implantation, the number of epidermal nerve fibers decreases [19].

Coculture of neurons and cancer cells offers an effective *in vitro* method to investigate neuronal plasticity following exposure to cancer-associated mediators. With this method, release of CC chemokine ligand 2 has been demonstrated. This change causes an increase in voltage-gated Ca^{2+} channels that ultimately leads to neuronal hypersensitivity [20]. Experiments undertaken with a similar coculture system demonstrate the release of proteases from oral squamous cell carcinoma and subsequent upregulation of PAR2 in neurons [4].

In the very first scientific account of perineural invasion, a clinical case of squamous cell carcinoma of the lower lip was described; pain from the cancer was noted [21]. Not all cancers lead to perineural invasion but head and neck cancer and pancreatic cancer have been shown to consistently produce high rates of perineural invasion. There is also clear evidence that neuronal interaction with cancer helps facilitate carcinogenesis [22]. Integrins including α6 integrin adhesion receptor, modulate the molecular interaction between cancer and peripheral nerves. A bone cancer model, generated with inoculate that expresses mutated α6 integrin, demonstrates less tumor cell migration, less pain and fewer bone fractures. This study leaves open the possibility that pain from some histological types of cancer could be reduced or alleviated by activating the α6 integrin receptor. This may be accomplished by inhibiting urokinase-type plasminogen activator [23].

The Promise of Cancer Pain Research

The prospect of a medical cure for oral cancer is poor; each new iteration of genomic technology reveals greater molecular complexity in oral cancer. This disease is genomically heterogeneous and cannot be readily broken down into subtypes. A variety of dysregulated genetic pathways lead to many variations on the theme that fit into the “oral squamous cell carcinoma” category. Similarly, myriad mechanisms are responsible for cancer pain. A unifying pain mechanism appears unlikely.

While significant effort has been expended to understand oral carcinogenesis, few researchers investigate the neurobiologic factors responsible for cancer pain. Recently; however, the investigation of carcinogenesis and pain have converged. Some of the most significant recent advances (from a clinical standpoint) involve discoveries concerning the interplay between neurons and cancer cells. In work that confirms interaction between malignant cells and neurons, investigators found that adrenergic and cholinergic stimulation are requisite for carcinogenesis in the prostate [22]; the nervous system is not only responsible for pain but also contributes to carcinogenesis. To exploit these important findings we must attract a cadre of investigators to the problem. The talent and knowledge of cancer biologists, neuroscientists and clinicians must be utilized to investigate the interface between oral cancer and the peripheral nervous system. This nontraditional approach to studying cancer and cancer pain is likely to reveal fascinating mechanisms behind a terrifying disease.

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