Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

# Effects of dermal wounding on distal primary tumor immunobiology in mice

*Leah M. Pyter, PhD,*[a,b,c,d,*] *Daniel B. McKim, PhD,*[a] *Yasmin Husain, MD,*[d] *Humberto Calero, BS,*[d] *Jonathan P. Godbout, PhD,*[a,c] *John F. Sheridan, PhD,*[a,e] *Phillip T. Marucha, DMD, PhD,*[d,1] *and Christopher G. Engeland, PhD*[d,2]

[a] *Institute for Behavioral Medicine Research, Ohio State University Wexner Medical Center, Columbus, Ohio*
[b] *Departments of Psychiatry and Behavioral Health, Ohio State University, Columbus, Ohio*
[c] *Department of Neuroscience, Ohio State University, Columbus, Ohio*
[d] *Center for Wound Healing and Tissue Regeneration, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois*
[e] *Department of Biosciences, College of Dentistry, Ohio State University, Columbus, Ohio*

ARTICLE INFO

*Article history:*
Received 7 April 2017
Received in revised form
4 August 2017
Accepted 15 September 2017
Available online 17 October 2017

*Keywords:*
Oral cancer
Tissue repair
Myeloid cells
Trafficking
Cytokines

ABSTRACT

*Background:* Before primary oral tumors are treated, various prophylactic procedures that require tissue repair are often necessary (e.g. biopsies, tooth extractions, radiation, and tracheotomies). Wound healing and tumor growth harness similar immune/inflammatory mechanisms. Our previous work indicates that tumors impair wound healing, although the extent to which tissue repair conversely influences tumor growth is poorly understood. Here, we test the hypothesis that dermal wound healing exacerbates primary tumor growth and influences tumor immunobiology.

*Materials and methods:* Female, immunocompetent mice were inoculated subcutaneously with murine oral cancer cells (AT-84) to induce flank tumors. Half of the mice received dermal excisional wounds (4 × 3.5 mm diameter) on their dorsum 16 days later, whereas the skin of controls remained intact. Tumor and blood tissues were harvested 1 and 5 days post wounding, and tumor myeloid cell populations and inflammatory gene expression were measured. Circulating myeloid cells, cytokines, and corticosterone were also quantified.

*Results:* Wounding increased tumor mass, early tumor infiltration of macrophages, and tumor inflammatory gene expression. While wounding attenuated tumor growth–induced increases in circulating myeloid cells, no effects of wounding on circulating cytokine/endocrine measures were observed.

*Conclusions:* These results indicate that modest skin immune/inflammatory processes can enhance distal tumor growth and alter innate tumor immunity. The implication for this work is that, in the presence of a tumor, the benefits of tissue-damaging procedures that occur clinically must be weighed against the potential consequences for tumor biology.

© 2017 Elsevier Inc. All rights reserved.

* *Corresponding author*. IBMR Room 219, 460 Medical Center Dr, Columbus, OH, 43210. Tel.: +614 293 3496; fax: +614 366 2097.
E-mail address: leah.pyter@osumc.edu (L.M. Pyter).
[1] Current address: College of Dentistry, Oregon Health and Sciences University, Portland, OR, USA.
[2] Current address: Department of Biobehavioral Health, Pennsylvania State University, University Park, PA, USA.

0022-4804/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jss.2017.09.016

## Introduction

Oral cancer is diagnosed most often in >40-year-olds who use tobacco/alcohol, although a new and rapidly growing population of young adults with human papilloma virus–positive oral cancer has also emerged. Despite treatment improvements, the 5-year survival rate has stagnated around 50% for the last 40 years.[1] Diagnosis of oral cancer is often relatively late and it is a diffuse cancer; hence, tissue-damaging treatments (e.g. surgery and radiation) are common, extensive, and numerous. Prophylactic procedures that require healing (e.g. tooth extractions and other dental surgery, portacaths, feeding tubes, tracheotomies, and biopsies) are often part of the early stages of treatment to stabilize oral health before attempting to treat the tumor.[2] Even for operable oral tumors, primary tumor recurrence is common,[3] indicating that cancer cells remain *in situ* after surgery. Taken together, wound healing is a frequent clinical occurrence in the presence of primary tumor cells. Partly because these tissue-damaging procedures are the *status quo* and considered unavoidable, there is little understanding of how these two concurrent processes involving the innate immune system (i.e. tissue repair and tumor growth) may interact with each other. In our recent article, we reported a detrimental effect of tumors on the rate of skin repair.[4] Conversely, here, we focus on the effects of modest dermal wounding on primary tumor size, as well as, innate tumor immunobiology and signaling.

Dermal tissue repair is a coordinated and complex innate immune process involving rapid recruitment of neutrophils and then macrophages to the wound site.[5,6] Mounting evidence indicates that these same myeloid cells modulate tumor initiation, growth, and metastasis.[7-9] Indeed, solid tumors have been dubbed as the "wounds that never heal".[10] Therefore, both wounds and tumors solicit overlapping innate immune resources, which potentially create a competitive immune energetic trade-off scenario and/or an overall heightened state of inflammation. These immune processes are largely studied independently of one another, even though clinically they co-occur in cancer patients. One relevant line of basic and clinical research indicates that surgery incites metastases via the shedding and enriching of tumor cells, the neuroendocrine responses to surgery, and by causing suppression of cell-mediated immune function (e.g. natural killer cells [NK] and T-cells).[11-14] Given the frequency of tissue damage that occurs before and during primary oral cancer removal, this study aimed to test the hypothesis that active wounds promote primary tumor growth by activating proneoplastic myeloid-cell resources in tumors. This investigation is important because standard tissue-damaging clinical treatments may have a larger impact on primary tumor growth than is currently assumed. Understanding these mechanistic interactions will inform both presurgery and surgery treatment strategies and will provide insight into targets/plans for limiting or preventing unnecessary complications.

## Materials and methods

### *Animals*

Nulliparous female C3H mice (Charles River Laboratories Inc, Wilmington, MA) were housed 3-5 per cage and acclimated to the temperature-controlled (21 ± 1°C) vivarium for 1-2 weeks under a 14:10 light:dark cycle (lights on at 06:00 h). Female mice were used to prevent nonexperimental wounding due to fighting. Rodent chow (Harlan 7912) and water were available *ad libitum* throughout the study, and shredded paper was provided for nest building. All animal experiments were approved by the University of Illinois at Chicago or Ohio State University Institutional Animal Care and Use Committees and carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.[15] All efforts were made to minimize animal suffering and to reduce the number of mice used. Experiment 1 assessed tissue masses, tumor gene expression, and circulating cytokines and corticosterone ($n = 40$). Experiment 2 assessed immune-cell populations in the blood and tumors using flow cytometry ($n = 21$). Figure 1 is an illustration of the experimental timeline.

### *Cells*

The murine oral cancer cell line AT-84, originating from C3H mice,[16] was generously provided by Dr Shulin Li at MD Anderson, Houston, TX and grown in RPMI-1640, with 10% fetal bovine serum, 2-mM L-glutamine, 0.1-mM nonessential amino acids, 10-mM N-2-HEPES buffer, 100 units penicillin/ml, and 100 μg streptomycin/ml at 37°C with 5% $CO_2$. As this cell line is not commercially available, its authenticity has been tested using microscopic morphological assessment, as well as, growth curve analyses and mycoplasma testing (IDEXX BioResearch, Columbia, MO).

### *Tumor induction*

Aged between 8-10 weeks, the mice were acclimated to handling three times over 2 weeks. Next, all mice were anesthetized (100 mg/kg ketamine mixed with 10 mg/kg xylazine, i.p.) and injected in the flank (s.c.) with a 150 μL suspension of $1.5 \times 10^6$ AT-84 cells. Flank tumors were used to avoid both the potentially confounding complications of oral tumors (i.e.

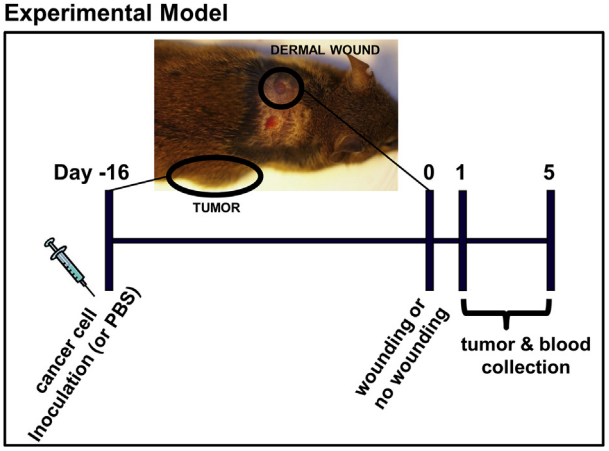


**Fig. 1 – Experimental timeline. Temporal sequence of tumor and wounding treatments, tissue collection, and related photograph. (Color version of figure is available online.)**

Download English Version:

https://daneshyari.com/en/article/5733674

Download Persian Version:

https://daneshyari.com/article/5733674

Daneshyari.com