Accepted Manuscript

Title: Improving cancer therapies by targeting the physical and chemical hallmarks of the tumor microenvironment

Author: Jill W. Ivey, Mohammad Bonakdar, Akanksha Kanitkar, Rafael V. Davalos, Scott S. Verbridge

PII: S0304-3835(15)00770-3
DOI: http://dx.doi.org/doi: 10.1016/j.canlet.2015.12.019
Reference: CAN 12671

To appear in: *Cancer Letters*

Please cite this article as: Jill W. Ivey, Mohammad Bonakdar, Akanksha Kanitkar, Rafael V. Davalos, Scott S. Verbridge, Improving cancer therapies by targeting the physical and chemical hallmarks of the tumor microenvironment, *Cancer Letters* (2015), http://dx.doi.org/doi: 10.1016/j.canlet.2015.12.019.

Improving cancer therapies by targeting the physical and chemical hallmarks of the tumor microenvironment

Jill W. Ivey[1*], *Mohammad Bonakdar*[2*], *Akanksha Kanitkar*[1], *Rafael V. Davalos*[1,2], *Scott S. Verbridge*[1†]

[1]*Department of Biomedical Engineering and Mechanics, Virginia Tech-Wake Forest University, Blacksburg VA 24061*

[2]*Department of Mechanical Engineering, Virginia Tech, Blacksburg VA 24061*

Highlights

- We propose that key physical and chemical hallmarks of the tumor microenvironment (TME) should be further considered as presenting therapeutic target opportunities, as opposed to barriers for effective treatment.
- We outline the chemical (low pH, low oxygen) and physical (altered tissue and cell mechanics, thermal conductivity, and electrical properties) characteristics of the TME.
- We review the prior work, and suggest future studies in the targeting of each of these hallmarks, including the altered pH, oxygen, electrical, mechanical and thermal properties of the TME.

Abstract

Tumors are highly heterogeneous at the patient, tissue, cellular, and molecular levels. This multi-scale heterogeneity poses significant challenges for effective therapies, which ideally must not only distinguish between tumorous and healthy tissue, but also fully address the wide variety of tumorous sub-clones. Commonly used therapies either leverage a biological phenotype of cancer cells (e.g. high rate of proliferation) or indiscriminately kill all the cells present in a targeted volume. Tumor microenvironment (TME) targeting represents a promising therapeutic direction, because a number of TME hallmarks are conserved across different tumor types, despite the underlying genetic heterogeneity. Historically, TME targeting has largely focused on the cells that support tumor growth (e.g. vascular endothelial cells). However, by viewing the intrinsic physical and chemical alterations in the TME as additional therapeutic opportunities rather than barriers, a new class of TME-inspired treatments has great promise to complement or replace existing therapeutic strategies. In this review we summarize the physical and chemical hallmarks of the TME, and discuss how these tumor characteristics either currently are, or may ultimately be targeted to improve cancer therapies.

1. Introduction

Tumors are marked by a high degree of heterogeneity both within as well as between patients. This multi-scale heterogeneity drastically diminishes the treatment efficacy of many classical cancer therapies. The most commonly used chemotherapies target a biological phenotype of cancer cells, specifically their highly proliferative nature. However such therapies leave behind

* These authors contributed equally to this work.
† Corresponding author, Email: sverb@vt.edu