Seminars in Cancer Biology 35 (2015) S199–S223

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Cancer prevention and therapy through the modulation of the tumor microenvironment

Stephanie C. Casey[a], Amedeo Amedei[b], Katia Aquilano[c], Asfar S. Azmi[d], Fabian Benencia[e], Dipita Bhakta[f], Alan E. Bilsland[g], Chandra S. Boosani[h], Sophie Chen[i], Maria Rosa Ciriolo[c], Sarah Crawford[j], Hiromasa Fujii[k], Alexandros G. Georgakilas[l], Gunjan Guha[f], Dorota Halicka[m], William G. Helferich[n], Petr Heneberg[o], Kanya Honoki[k], W. Nicol Keith[g], Sid P. Kerkar[p], Sulma I. Mohammed[q], Elena Niccolai[r], Somaira Nowsheen[s], H.P. Vasantha Rupasinghe[t], Abbas Samadi[u], Neetu Singh[v], Wamidh H. Talib[w], Vasundara Venkateswaran[x], Richard L. Whelan[y], Xujuan Yang[n], Dean W. Felsher[a,*]

[a] *Division of Oncology, Departments of Medicine and Pathology, Stanford University School of Medicine, Stanford, CA, United States*
[b] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*
[c] *Department of Biology, University of Rome "Tor Vergata", Rome, Italy*
[d] *Department of Oncology, Wayne State University School of Medicine, Detroit, MI, United States*
[e] *Department of Biomedical Sciences, Ohio University, Athens, OH, United States*
[f] *School of Chemical and Biotechnology, SASTRA University, Thanjavur 613401, Tamil Nadu, India*
[g] *Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom*
[h] *Department of Biomedical Sciences, School of Medicine, Creighton University, Omaha, NE, United States*
[i] *Ovarian and Prostate Cancer Research Laboratory, Guildford, Surrey, United Kingdom*
[j] *Department of Biology, Southern Connecticut State University, New Haven, CT, United States*
[k] *Department of Orthopedic Surgery, Nara Medical University, Kashihara, Japan*
[l] *Physics Department, School of Applied Mathematics and Physical Sciences, National Technical University of Athens, Athens, Greece*
[m] *New York Medical College, Valhalla, NY, United States*
[n] *University of Illinois at Urbana-Champaign, Champaign-Urbana, IL, United States*
[o] *Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic*
[p] *Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States*
[q] *Department of Comparative Pathobiology, Purdue University Center for Cancer Research, West Lafayette, IN, United States*
[r] *University of Florence, Florence, Italy*
[s] *Medical Scientist Training Program, Mayo Graduate School, Mayo Medical School, Mayo Clinic, Rochester, MN, United States*
[t] *Department of Environmental Sciences, Faculty of Agriculture, Dalhousie University, Nova Scotia, Canada*
[u] *Sanus Biosciences, San Diego, United States*
[v] *Advanced Molecular Science Research Centre (Centre for Advanced Research), King George's Medical University, Lucknow, Uttar Pradesh, India*
[w] *Department of Clinical Pharmacy and Therapeutics, Applied Science University, Amman, Jordan*
[x] *Division of Urology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*
[y] *Mount Sinai Roosevelt Hospital, Icahn Mount Sinai School of Medicine, New York City, NY, United States*

ARTICLE INFO

Article history:
Available online 10 April 2015

Keywords:
Tumor microenvironment
Cancer biology
Cancer therapy
Cancer prevention

ABSTRACT

Cancer arises in the context of an *in vivo* tumor microenvironment. This microenvironment is both a cause and consequence of tumorigenesis. Tumor and host cells co-evolve dynamically through indirect and direct cellular interactions, eliciting multiscale effects on many biological programs, including cellular proliferation, growth, and metabolism, as well as angiogenesis and hypoxia and innate and adaptive immunity. Here we highlight specific biological processes that could be exploited as targets for the prevention and therapy of cancer. Specifically, we describe how inhibition of targets such as cholesterol synthesis and metabolites, reactive oxygen species and hypoxia, macrophage activation and conversion, indoleamine 2,3-dioxygenase regulation of dendritic cells, vascular endothelial growth factor regulation of angiogenesis, fibrosis inhibition, endoglin, and Janus kinase signaling emerge as examples of important potential nexuses in the regulation of tumorigenesis and the tumor microenvironment that can

* Corresponding author at: Division of Oncology, Departments of Medicine and Pathology, Stanford University, Stanford, CA 94305, United States. Tel.: +1 6507256353.
E-mail address: dfelsher@stanford.edu (D.W. Felsher).

http://dx.doi.org/10.1016/j.semcancer.2015.02.007

be targeted. We have also identified therapeutic agents as approaches, in particular natural products such as berberine, resveratrol, onionin A, epigallocatechin gallate, genistein, curcumin, naringenin, desoxyrhapontigenin, piperine, and zerumbone, that may warrant further investigation to target the tumor microenvironment for the treatment and/or prevention of cancer.

1. Introduction

1.1. Tumor microenvironment as a therapeutic target

The tumor microenvironment is critical to both the initiation and maintenance of tumorigenesis [1,2]. The tumor microenvironment is composed of a complex network that includes multipotent stromal cells/mesenchymal stem cells, fibroblasts, blood vessels, endothelial cell precursors, immune cells, and secreted factors such as cytokines [2]. During tumor progression, changes in the microenvironment occur through effects on a molecular as well as cellular level and involve interactions between incipient cancer cells and host structural as well as adaptive and innate immune cells [3]. Many of the "hallmarks of cancer" are related to the tumor microenvironment, including the ability to induce proliferation and inhibit apoptosis, to induce angiogenesis and avoid hypoxia, to inhibit the immune system and avoid immune detection, and to activate immune cells to support invasion and metastasis [4]. Specific oncogenic pathways can be associated with dramatic changes in the tumor microenvironment [5–8]. Hence, the manipulation of the tumor microenvironment could be used as an approach to prevent as well as treat cancer.

Identification of therapeutic targets in the tumor microenvironment could be useful in the treatment and prevention of cancer. The typical biological approach has been to investigate specific molecular and cellular mechanisms and then to examine whether or not the inhibition or activation has the expected consequences for tumorigenesis. However, there are caveats to this approach. The same molecules and effector cells can have roles in both the prevention and initiation of tumorigenesis. Different cancers can occur through disparate mechanisms. What is limiting in some contexts may be in other circumstances of no importance. Some targets may have effects on multiple pathways and programs that can counteract their overall effectiveness. Hence, the ability to reconcile how to target the microenvironment and identify suitable therapies is daunting.

In this review, we have taken a different approach. Through an initiative supported by the Halifax Project, a group of investigators worked together as a team to identify both specific targets and novel approaches to therapeutically inhibit specific aspects of the tumor microenvironment. Through an integrative approach we have identified strategies for the treatment and prevention of cancer. Then, we examined the literature and thereby identified possible agents, in particular natural products, which could potentially inhibit some or several of these targets. Our goal was to identify existing agents that may be exploited for the prevention and/or treatment of cancer. Finally, the team utilized a cross-validation approach to examine how these targets and approaches, either alone or in combination, could be useful for the prevention and/or treatment of cancer.

We identified 10 programs that could be or definitely appear to be targets and 10 existing natural agents that may mediate their reported anti-cancer effects through the tumor microenvironment (Figs. 1 and 2, Tables 1 and 2). Our list is not a complete examination of all possible targets or therapeutic approaches but rather an attempt to identify existing broad-spectrum, lower toxicity therapeutics that could be combined with existing therapeutics.

The targets identified include metabolic programs that may broadly influence many cell biology programs that impact tumorigenesis and the tumor microenvironment, including (cholesterol synthesis and metabolites, reactive oxygen species (ROS) and hypoxia, inflammation, innate and adaptive immunity related programs (macrophage conversion, dendritic cell (DC) activation, immune signaling), host microenvironment associated cellular programs (fibrosis, angiogenesis), and cytokine mediated regulatory programs (interleukin (IL)-6, endoglin, and Janus-associated kinase (JAK)) (Fig. 1, Tables 1 and 2).

We particularly focused on identifying approaches for inhibiting these targets, including natural products that may have significant anticancer activity. Some of these molecules may more generally influence tumorigenesis and the microenvironment (berberine), others more specifically target ROS (resveratrol, desoxyrhapontigenin) macrophage conversion (onionin A), indoleamine 2,3-dioxygenase (IDO) regulation of dendritic cells (epigallocatechin-3-gallate (EGCG)), cholesterol synthesis (genistein), fibrosis (naringenin), inflammation and immune signaling (piperine), vascular endothelial growth factor (VEGF) inhibition (curcumin), and JAK signaling (zerumbone). These approaches may warrant further investigation (Fig. 1, Tables 1 and 2). These agents generally have low toxicity, suggesting that they could be combined with each other or existing therapies.

1.2. Cross-validation of approaches and targets

We identified approaches and targets through the analysis of the scientific literature *via* a team of investigators from a multitude of subspecialties. We made several assumptions. First, the complex biology and heterogeneity of cancer suggested that the most effective therapeutic approach may require simultaneous actions on mechanisms that are important for many of the hallmarks of cancer. Second, we anticipated that synergies would be achieved by combining specific targets with specific approaches. Third, we considered that we could validate both targets and approaches through a cross-validation through the analysis of literature. Finally, we considered it was important to examine the relevance of the identified targets and the nominated approaches across different aspects of cancer biology.

Notably, the targets and approaches that we identified for the tumor microenvironment have been shown to be relevant to other cancer hallmarks. These are noted as having "complementary" effects, while those that were found to have pro-tumorigenic actions were noted as having "contrary" effects. Instances where reports on relevant actions in other aspects of cancer biology were mixed, where reports showing both pro-cancer potential and anti-tumorigenic potential, we have used the term "controversial." Finally, in instances where no literature support was found to document the relevance of a target site or approach in a particular aspect of cancer's biology, we documented this as "no known relationship." These validation results are shown in Tables 1 and 2.

Our priority was to choose targets and approaches after consideration of potential cross-hallmark effects. We examined for possible incidental actions from therapeutic interventions. We assembled a reasonably complete view of the literature. However,