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Editorial

A broad-spectrum integrative design for cancer prevention and therapy: The challenge ahead

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ABSTRACT

Despite exciting advances in targeted therapies, high drug costs, marginal therapeutic benefits and notable toxicities are concerning aspects of today's cancer treatments. This special issue of Seminars in Cancer Biology proposes a broad-spectrum, integrative therapeutic model to complement targeted therapies. Based on extensive reviews of the cancer hallmarks, this model selects multiple high-priority targets for each hallmark, to be approached with combinations of low-toxicity, low-cost therapeutics, including phytochemicals, adapted to the well-known complexity and heterogeneity of malignancy. A global consortium of researchers has been assembled to advance this concept, which is especially relevant in an era of rapidly expanding capacity for genomic tumor analyses, alongside alarming growth in cancer morbidity and mortality in low- and middle-income nations.

1. Introduction

Targeted therapies, immunotherapy and precision medicine are coming to dominate oncology practice and research. From the early targeted therapies, such as trastuzumab and bevacizumab, to the newest United States Food and Drug Administration (USFDA)-approved immunotherapies, this paradigm has registered major achievements. The early tyrosine kinase inhibitor imatinib has converted some formerly fatal leukemias to medically manageable conditions [1]. The CLEOPATRA trial added pertuzumab to a control regimen of trastuzumab–docetaxel and recorded a 15.7 month increase in survival [2]. Immunotherapies, including pembrolizumab, nivolumab and ipilimumab, singly and in combination, are driving survivals higher in devastating melanomas and lung cancers [3,4]. All these advances are cause for celebration for clinicians, researchers and companies gaining approval for life-prolonging therapies. But a problem dogs the paradigm: therapeutic resistance is common, and often discouragingly rapid in onset. Driven by the inherent heterogeneity of cancers, resistance too often leaves single-target strategies with diminished efficacy, and overall survival is limited or not improved at all. Most melanoma patients treated with BRAF or MEK inhibitors relapse after 5–7 months [5]. Bevacizumab is typically added to chemotherapy regimens in colorectal cancer, but pivotal trials recorded increases in overall survival of only 4.7 months in first-line and 2.2 months in previously-treated patients [6]. Other second-line treatments, such as ramucirumab in gastric cancers [7] show similarly limited improvements in survival. Even the overall survival of 25 months recorded for a dafratinib–trametinib combination for metastatic melanoma must seem cruelly short to the recently diagnosed sufferer [8]. We have a long way to go before oncology can offer true comfort to most patients.

Multiple factors contribute to therapeutic resistance. Genomic instability results in genetically heterogeneous tumors, typically with 40–80 mutations per patient [9]. Selection pressures from a targeted therapy can result in evolutionary expansion of treatment-resistant clones already existing in the tumor. Other resistance mechanisms arise separately from the therapeutic target. These include, for instance, dysregulation of pro-apoptotic proteins, enhancement of DNA repair, and interactions with a tumor microenvironment that may shelter quiescent tumor cells as they develop resistant phenotypes.

The high costs of targeted therapies are well known. Most of the drugs approved in 2012 by the USFDA cost more than $100,000 per year per patient, perhaps not a surprise in view of the accelerating costs of drug development, which reached $1.8 billion for research and approval in recent years [10]. Clinicians drew attention to these high costs in 2013, when more than 100 experts in chronic myeloid leukemia called for lower prices and broader access to these drugs in the journal *Blood* [11]. A 2015 presentation at the American Society for Clinical Oncology estimated the yearly cost of combination immunotherapy at $1 million per patient [12]. Even bevacizumab, now standard of care in colon cancer, was recently found in a cost-effectiveness analysis to offer minimal benefit and high cost when taking into account the short survival increment it confers [13]. Moreover, at least half of cancer cases and mortality are now known to occur in low- and middle-income countries [14]. The World Health Organization recommends that the yearly cost of a drug should be no more than three times the average per capita income in a country to be considered cost-effective [15]. In

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low- to middle-income countries with per capita incomes ranging from $1045 to $12,746 in 2015 [16], costs for treatment reaching six-figure levels are unsustainable. Exploring lower-cost alternatives to high-cost therapies, specifically alternatives that may reduce therapeutic resistance through a broad-spectrum approach that seeks therapies with radically expanded sets of targets, is the goal of this special issue of *Seminars in Cancer Biology*.

2. Expanding our options: Exploring the rationale for a broad-spectrum approach

A broad-spectrum approach to cancer is one that addresses multiple pathways and targets relevant to prevention and therapy of malignancy, similar to the use of broad-spectrum antibiotics that kill multiple bacterial species. The select broad-spectrum concept presented in this special issue focuses on using a combination of agents to affect a broad range of relevant cancer-specific targets. Why consider such an approach in the face of the undeniable, albeit still limited, success of the targeted therapy paradigm? The major reason for considering this approach, which we propose as a complement rather than a replacement of targeted pharmaceutical therapies, is the problem of resistance to therapy. The complexity and heterogeneity of cancer in both preventive and therapeutic settings leads to resistance as clonal evolution under the selective pressure from narrowly targeted therapies implacably proceeds [9]. Combination therapies have long been recognized as a means to thwart resistance, leading to the widespread use of combination chemotherapy. Combining targeted therapies or immunotherapies can be effective [2,3]. However, ineffective combinations with elevated toxicity are often seen, and even successful immunotherapies have recorded rates of severe adverse events of over 50% [17–19].

Hepatocellular carcinoma (HCC), which occurs most commonly in less-developed countries, exemplifies the need for a broad-spectrum approach. HCC develops in the complex environment of the liver. Factors like alcohol and hepatitis infection induce immune-mediated inflammation, virally-mediated oncogenesis, mutations due to oxidative stress, and epigenetic damage in multiple cell types [20]. Expression of angiogenic factors by tumor stromal cells begins early in carcinogenesis. Stromal cells secrete inflammatory mediators and cytokines associated with metastasis. Cancer-promoting immune cells exert multiple detrimental effects. In this complex setting, especially in more advanced disease, targeting one signaling pathway results in selective pressures for clones responding to other stimulatory pathways [9]. And indeed, response to the standard-of-care sorafenib for advanced disease is modest [21]. Intervening with a broad-spectrum approach using low-cost and low-toxicity therapies may address the multiple defects of this tumor and its microenvironment.

3. The hallmarks of cancer: Framing the broad-spectrum concept and integrative stance

The complexity and heterogeneity of cancer have been recognized by many. Vogelstein and colleagues [22], for instance, describe 12 major signaling pathways relevant to cancer growth and 138 “driver” genes considered most important in oncogenesis. Block [23] proposes a broad-spectrum framework based on the insights of integrative medicine. Host environmental factors, termed “terrain factors”, such as inflammation, oxidation, immune regulation and glycemia, can be modulated by diet, exercise, mind-body medicine and carefully selected nutraceuticals. Twelve tumor-based “pathways of progression” also must be addressed, among them resistance to apoptosis, metastasis and cell-to-cell communication. Interventions like dietary change and exercise are inherently multi-targeted, and may reduce, for instance, inflammatory signaling or glycemic imbalance in a multi-faceted way [24]. They thus form a foundation for the clinical application of broad-spectrum approaches.

The conceptual framework selected for this exploration of broad-spectrum therapeutics is that of the cancer hallmarks. These were described by Hanahan and Weinberg [25], who proposed 6 hallmarks in 2000. They added two more hallmarks and two enabling characteristics in 2011 [26]. The concept of the cancer hallmarks is now widely recognized and influential. For the purposes of this project, we will treat both the hallmarks and the enabling characteristics as hallmarks of malignancy. We have also added an 11th characteristic that we will treat as a hallmark, the tumor microenvironment. The significance of the microenvironment is evident in the description of HCC above, but extends through many cancer types and is increasingly viewed as a critical setting for therapeutic targets [27].

The clinical message of the cancer hallmarks and our broad-spectrum design for cancer treatment is that we must broaden our concept of the “actionable target” for a therapeutic intervention, not simply relying on a limited set of molecular or immunologic targets with a correspondingly limited set of drug therapies. The rapid expansion of genetic testing enables us to obtain multi-faceted genetic profiles of tumors. Using such profiles, broad-spectrum approaches can and should be constructed that override the constraints of the existing single-target intervention model of treatment.

4. Getting to know cancer: The Halifax Project

The model of a broad-spectrum cancer therapy based on combination of low-cost, low-toxicity agents aimed at multiple therapeutic targets was independently introduced by Block in the volume *Life Over Cancer* [23], and by a non-profit organization, Getting To Know Cancer (GTKC). An initiative called the Halifax Project, organized by GTKC, undertook a project to assemble a set of reviews on the 11 cancer hallmarks, authored by an international team of experienced research scientists. These reviews are published in this special issue of *Seminars in Cancer Biology*. Each review summarizes one hallmark, explains the carcinogenic dysfunctions it involves, assesses its relation to other hallmarks, and suggests a set of potential drug targets and therapeutic approaches. The broad-spectrum model is then summarized in a capstone paper [28]. The approaches emphasize low-toxicity and low-cost agents, including phytochemicals, preferring those without current intellectual property protection so that broad-spectrum therapies composed of combinations of these agents would be widely accessible globally. Recognizing the network of signaling pathways involved in malignant processes [29,30], the project implemented a cross-validation literature review to help evaluate targets and approaches. This accounts for the possibility that manipulating one target, or exploiting one therapeutic approach, may have a carcinogenic or tumor-stimulating effect on another cancer hallmark. Tables of cross-validations are found in the hallmark reviews.

5. The hallmark reviews

The first hallmark, genomic instability, provides the basic means for a cell to gain selective growth advantages over its neighbors. As Christopher Maxwell and his team show, the fidelity of the genome, maintained by a series of checkpoints, is breached in cancer. This results in genetically and epigenetically heterogeneous malignancies that proliferate under selective pressures, resulting in cancer’s adaptability and therapeutic resistance. They propose five targets for improving cancer prevention and therapy: prevention of DNA damage, enhancement of DNA repair, targeting deficient DNA

repair, impairing centrosome clustering, and inhibition of telomerase activity.

Abnormal cell proliferation represents an important feature of cancer development and progression. Various signaling mechanisms are involved in uncontrolled cancer cell proliferation. The article by Mark Feitelson and colleagues highlights some of the widely studied targets in several pathways that regulate proliferation, such as hypoxia inducible factor 1, nuclear factor κ-B (NF-κB), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), insulin-like growth factor receptor 1, Wnt/β-catenin, cell cycle-associated proteins as well as androgen and estrogen receptor signaling.

The evasion of anti-growth signaling is an essential characteristic of cancer cells. In order to sustain proliferation, neoplastic cells must uncouple themselves from numerous signals that are known to slow down cellular growth. The article contributed by Dong Shin and his group eloquently describes the anti-growth signaling process and reviews several important pathways involved in growth signaling, namely p53, phosphatase and tensin homolog, retinoblastoma protein, Hippo, growth differentiation factor 15, AT-rich interactive domain 1A, Notch, insulin-like growth factor and Krüppel-like factor 5 pathways.

Ramzi Mohammad and colleagues describe various factors which contribute to apoptosis resistance in cancer. Apoptosis or programed cell death represents an endogenous process of removing defective cells from the body. Nevertheless, deregulation of apoptotic signaling facilitates cancer cells to escape this process, leading to uncontrolled proliferation resulting in tumor cell survival, drug resistance and recurrence of the disease. This article focuses on key resistance targets, namely Bcl-2 and Mcl-1 proteins, autophagy, necrosis and necroptosis, heat shock protein signaling, proteasome pathway, epigenetic mechanisms and aberrant nuclear export signaling.

Replicative immortality allows transformed cells to continuously self-renew, accumulating mutations that promote invasiveness and therapeutic resistance. Paul Yaswen and colleagues explore the use of senescence-inducing therapies that result in growth arrest. Consideration is given to the role of telomerase and to the search for agents promoting stable senescence. A number of potential targets are singled out for further research, including telomerase, human telomerase reverse transcriptase, mammalian target of rapamycin, cyclin-dependent kinase (CDK) 4/6, CDK 1/2/5/9, PI3K and Akt.

Dysregulated metabolism in cancer, often called the "Warburg effect", revolves around the reprogramed metabolic state of many cancer cells, allowing them to turn energy production toward biosynthesis and growth. Matthew Hirschey and colleagues point out hexokinase-2,6-phosphofructo-2-kinase/fructose-2,4,biphosphatase and pyruvate kinase isoform M2 as important regulators of glycolysis in cancer cells. In addition to altered glucose metabolism, glutamine oxidation is emerging as an attractive therapeutic target. Studies of targets for dysregulated metabolism are still preliminary but represent an exciting new area of cancer biology.

Chronic inflammation is linked to various phases of tumorigenesis, including transformation, apoptosis, invasion, angiogenesis and metastasis. Leroy Lowe and his team explore targeting of these effects in malignancy. They discuss the multi-faceted relationship of immunity and chronic inflammation in cancer. Macrophage migration inhibitory factor, cyclooxygenase-2, NF-κB, tumor necrosis factor-α, inducible nitric oxide synthase, Akt, and chemokines are important anti-inflammatory targets that might be suitable for a multi-pronged therapeutic approach.

Immune evasion by tumors is accomplished by several mechanisms including generating regulatory cells, defective antigen presentation, immune suppressive mediators, apoptosis, tolerance and immune deviation. Byoung Kwon and colleagues review the exciting work now emerging in this area. A broad-spectrum approach suggests use of nonspecific immune enhancers, targeting Th-1 responses, enhancing γδ T cells, activating macrophages, inhibiting Treg lymphocytes, induction of interleukin-2 and enhancing natural killer cells.

Microenvironment has been postulated as a cause as well consequence of tumorigenesis, influencing cellular proliferation, growth, metabolism, angiogenesis, hypoxia and innate and adapative immunity. Dean Felsher and his group elegantly describe how cholesterol synthesis and metabolites, reactive oxygen species and hypoxia, macrophage activation and conversion, indoleamine 2,3-dioxygenase regulation, vascular endothelial growth factor, fibrosis, as well as endoglin and Janus kinase signaling emerge as pivotal links in the regulation of tumorigenesis.

Angiogenesis – the growth of new blood vessels from an existing vasculature – is considered to be an essential pathologic feature of cancer and inhibition of tumor angiogenesis has become an important anti-cancer therapeutic strategy. Lasse Jensen and co-researchers identify 10 important aspects of tumor angiogenesis as targets for anti-angiogenic therapy. These include inhibiting endothelial cell migration/tip cell formation, reducing structural abnormalities of tumor vessels, reducing hypoxia, inhibiting lymphangiogenesis, reducing elevated interstitial fluid pressure, reversing poor perfusion, normalizing disrupted circadian rhythms, suppressing tumor-promoting inflammation, deactivating tumor-promoting fibroblasts and normalizing tumor cell metabolism/acidosis.

Understanding of the key clinical issue of cancer metastasis is still evolving. Establishment of the invasive phenotype, the invasive process itself, tumor establishment at secondary sites and the interaction between cancerous and non-cancerous cells play key roles in the complex cascade of metastatic dissemination. Factors explored by Wen Jiang and colleagues comprise disruption of E-cadherin and tight junctions, key signaling pathways, including urokinase-type plasminogen activator, PI3K/Akt, focal adhesion kinase, β-catenin/zinc finger E-box-binding homeobox 1 and transforming growth factor-β, together with inactivation of activator protein 1 and suppression of matrix metalloproteinase-9 activity.

We conclude this editorial with the hope that this special issue containing articles by our esteemed colleagues dedicated to discovering a successful means of managing cancer through an innovative new model represents a critical, effective and more sustainable effort in our fight against malignant disease. We believe that these contributions provide both resource and inspiration to the reader that a broad-spectrum integrative strategy may be our best hope to combat cancer.

Conflicts of interest statement

The authors declare no conflicts of interest.

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