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Review Article

The Complex Challenge of Targeted Therapy in Cancer

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Abstract

Extensive efforts are being made to improve approaches to cancer prevention, diagnosis and treatment. However, data show that during the most recent decade both the rate of new cancer diagnoses and cancer death rate declined only marginally. While many new mechanistic pathways in cancer are being discovered and utilized in developing new drugs, effective concepts for targeting cancer cells have not emerged, highlighting a need for a greater understanding of the mechanisms of cancer.

It is argued that the available resources should be channeled less toward finding cures by addressing pathway that are common both to cancer as well non-cancer cells, and more toward finding unique differences between cancer and other cells. Further, that effective therapy of cancer is likely not to target a single but a multiplicity of mechanistic targets involved in cancer development and progression.

Keywords: Drug; Disease Target; Magic Bullet; Cancer; Precision Drug; Artificial Intelligence

Abbreviations

ADP: Adenosine Diphosphate; AML: Acute Myeloid Leukemia; ATP: Adenosine Triphosphate; ATR: Serine/Threonine Kinase; BCL-2: B-Cell Lymphoma 2; BCR-ABL: BCR-ABL Fusion Protein from BCR-ABL Fusion Gene; C98: Apoptosis Regulator Bcl-2-Like Protein; CD20: B-Lymphocyte Antigen Protein; CHK1: Checkpoint Kinase 1; CDK: Cyclin-Dependent Kinase; CDK9: Cyclin-Dependent Kinase 9; CML: Chronic Myeloid Leukemia; DNA: Deoxyribonucleic Acid; ECM: Extra-Cellular Matrix; EGFR: Epidermal Growth Factor Receptor; HIV: Human Immunodeficiency Virus; MCL-1: Differentiation Protein Mcl-1; MPA: Microscopic Polyangiitis; NADPH: Co-Factor Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NOX2: NADPH Oxidase 2; P16INK4a: Cyclin Dependent Kinase (CDK) Inhibitor; PARP: Poly (ADP-ribose) Polymerase; PV: Pemphigus Vulgaris; RA: Rheumatoid Arthritis; RNA: Ribonucleic Acid; STAT3: Signal Transducer and Activator of Transcription 3; TKI: Tyrosine Kinase Inhibitor; TME: Tumor Microenvironment; VEGF: Vascular Endothelial Growth Factor.

Introduction

More than some 100 years ago, Paul Ehrlich had an idea that it could be possible to kill specific disease-causing agents such as bacteria without harming the body itself [1].

His development of drug Salvarsan for the treatment of syphilis was the first drug that put the idea into practice, and became the first step towards the concept of chemotherapy [2], and ultimately the establishment of discipline of pharmaceutical research [3]. The idea of "targeting" the cause of disease has since attracted much research effort. Search of PubMed for "drug AND target" generated (as of 13 February 2019) 327596 items, with 105248 of these focusing on cancer. In the year 2018 alone, 8783 publications were devoted to targeting drugs in cancer.

Advances in treating various cancers are being made. In particular, the application of target-specific antibodies approaches the ideal behavior of a hypothetical "magic bullet". Rituxan is a monoclonal antibody drug that binds specifically to CD20 protein found only on B cells. This helps the cells to be identified by the immune system which can attack and remove cells associated with diseases such as in low-grade or follicular CD20-positive Non-Hodgkin's lymphoma, CD20-positive chronic lymphocytic leukemia, rheumatoid arthritis, Wegener's granulomatosis, microscopic polyangiitis, pemphigus vulgaris [4], and others. Similarly, Cetuximab monoclonal antibody recognizes receptors on cancer cells and blocks incoming (epidermal growth factor) signals; this may slow down or stop the growth of cancer cells [5]. The monoclonal antibody bevacizumab (Avas-

tin) acts in a similar way by intercepting growth signals associated with the vascular endothelial growth factor (VEGF) [6]. A key feature of envisaged "magic bullets" is to avoid acting on non-disease tissues and hence exhibit no (or at least minimum of) undesirable side effects [7]. However, many currently approved "targeted" drugs including Rituxan exhibit side effects [4] such as increased risk of infections, body aches, tiredness, nausea and also serious and even life-threatening such as chest pain, irregular heartbeats, heart attack, kidney failure and stomach and bowl problems. Effective targeting specifically to cancer cells remains elusive. Although claims are frequently being made that novel approaches such as that "nanomedicines have been evolved as an effective and cost-effectual alternative for treatment of cancer" [8], the use of these and earlier delivery systems has repeatedly been shown as being ineffective. Most-recent data (2006 – 2015) show the rate of new cancer diagnoses decreasing by some 2% per year in men and remain about constant for women. However, during the same period, cancer death rate declined by 1.4% / year in women and 1.8%/ year in men, suggesting that new therapies are not very effective [9].

Fundamentals of effective drug delivery to disease targets

It is "carrying coals to Newcastle" to argue that effective targeting needs a clear target definition. Previously we examined the essential requirements to be met by precision medicine for tumor-cell-targeted drug-delivery systems [10]. General rules derived from earlier steady-state considerations using a three-compartment model [11] dictate that it is essential for a drug–carrier conjugate not to be removed too rapidly from circulation, further that the drug is not released from the conjugate away from the target site, that a sufficient amount of the drug conjugate reaches the target site, and that the released drug must accumulate at the target to reach its effective pharmacodynamic concentration. Most existing drugs have a tendency to diffuse away from the site when converted into their free, non-conjugated form, and hence most of the drug-delivery system examined so far have not been clinically effective. In general, we argued that in order to limit the action of drugs to cells that carry the disease, unique molecular targets associated with the disease must be available. In the pursuit of developing targeted drugs, researches need to take full account of these essential conditions that need to be met for such effective human therapies to be possible [12].

We also pointed out that the term "targeted" is being used to describe various new drugs and therapies with an intent to suggest that such drugs exhibit higher specificity with respect to the disease to be treated. The reality, however, is that the use of all such recently denoted drugs is associated with large number often very serious undesirable side effects. It is concluded that using the term "targeted" when it relates to the intent of what the drug is to do and ignoring the fact that the drug's action is generally distributed throughout the body rather than acting on the locus of the disease is misleading [13].

Consequently, "targeting" drugs to molecular structures or cell mechanisms shared by normal and cancer cells does not remove the requirement of "not harming the body itself".

When considering drug targeting, there are two basic approaches to use

Design and make drugs the structure of which interacts specifically with the intended disease target (for example monoclonal antibodies), and 2. Drugs that interact both with the target present both on the disease as well as the normal cells, in which case the drug needs to be delivered to the intended target of disease. We previously discussed essential requirements for delivering drugs to target [14,15].

We argued repeatedly that the approaches currently employed in developing disease-site specific delivery systems are inadequate, wrongly conceived, and hence ineffective. We are no longer alone having such an opinion [16]. Rauch et al. argue that finding a "magic bullet" to cure cancer has failed despite huge efforts in that direction. They offer several reasons for this lack of success; further, they contrast the failure of cancer research with the success of developing drugs that target and suppress the human immunodeficiency virus (HIV)-1 based on "good understanding" of this disease. Here lies the crux of the matter. First, HIV is a single retrovirus that is molecularly distinct from human cellular material. The HIV-specific components allow target-specific drugs to be developed for which efficacy can be maximized without necessarily bringing about unacceptable side effects. A second consideration is also based on distinctive viral features, namely an ability to detect and measure quantitatively viral load and therefore measure the impact of antiviral drug regimen efficiently and rapidly, allowing for early detection of disease relapse and appropriate modification of treatment regimen before full relapse can occur. Finally, even though HIV is a single virus, the effective suppression and potential eradication of the infectious agent requires a multi-targeted approach that incorporates drugs with complementary activities directed against diverse viral enzymes. Rauch et al. foresee that progress towards treating cancer would benefit from the field adopting a transdisci-

plinary (as different from an interdisciplinary) approach, wondering "whether a single cell line in a dish is really representative of what cancer is all about" (sic). While Rauch et al. suggest that, in order to progress, cancer should be "conceptualized" not only as a scientific object but also as an "object of life", we base our considerations on science alone, i.e., on technical aspects of developing targeted drugs.

Delivery to cancer disease targets

So, what do we know about cancer cells that could serve as a target of drug action? What information is currently available about targets of cancer disease? There is a vast amount of information available showing how cancer cells differ from other cells. Can we find effective molecular targets on cancer cells, molecular features that are unique to cancer cells, or at least features that are present in cancer cells in substantially larger quantities than in other, normal cells? Let us look at few examples offered here in a way of illustration; a thorough analysis of what is currently available will no doubt require the use of artificial intelligence.

Most cancers fall into one of three main groups: carcinomas, sarcomas, and leukemias or lymphomas. Here we examine mainly leukemias and lymphomas involving blood-forming cells and cells of the immune system, respectively, and to some extent also carcinomas that are malignancies of epithelial cells. According to Jockers [17], cancer cells remain undifferentiated and continue to survive, lack normal cell signaling responses such as contact inhibition and normal apoptosis, contain abnormal nuclei, have altered energy metabolism, and induce a number of pathways and mechanisms in the microenvironment that enhance survival of the aberrant clone, for instance, angiogenesis and CD8+ T cell exhaustion and senescence.

The transformed cell population has an ability to survive the occurrence of DNA damage that allows it to persist despite numerous molecular abnormalities. The underlying defect in DNA damage response permits the accumulation of survival-enhancing genomic lesions as the clonally aberrant population expands [18]. Further, cells of malignant tumors formed this way are capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic systems (metastasis). At least in theory, malignant tumors develop over time from a stem cell that has acquired an extensive and impressive collection of genomic and molecular lesions that allow that cell and its progeny to survive unchecked [18]. Identification and elimination of such cells could in principle prevent cancer development; Jordan reported [19] that some of the features of leukemia stem/progenitor cells appear to be unique and are not found in normal hematopoietic stem cells.

Tumor tissues generally express only one allele of a heterozygous X chromosome gene [20]. While the mechanism of how genes are silenced in human cancer are not understood, their elucidation would likely increase our understanding of human cancer pathogenesis, and might broaden the ground for developing successive therapies in future. Cancers develop gradually through the progressive accrual of alterations and abnormalities that accumulate over periods of many years [18]. It is hard to visualize that identifying such initial step, eliminate it and thus prevent cancer development is within our capabilities. Instead, developing our understanding of subsequent steps leading to abnormalities in the mechanisms that regulate normal cell proliferation, differentiation, and survival that are displayed by cancer cells are more likely to provide means of drug targeting.

Let us examine some of such abnormalities. Many cancer cells have reduced requirements for extracellular growth factors [18,21]. While loss of homeostasis and tumor initiation are derived from oncogenic mutations, growth factors are key regulators of all subsequent steps of tumor growth. Malignant epithelial cells may have reduced expression of cell-surface adhesion molecules [22]. In consequence of lower adhesivity, tumor cells continue moving after contact with their neighbors migrating over adjacent cells, and growing in disordered, multilayered patterns. Movement and proliferation of many normal cells is inhibited by cell-cell contact, but cancer cells are insensitive to such contact inhibition of growth. Could this be utilized in designing new cancer specific drugs? For example, could preventing loss of E-cadherin, the principal adhesion molecule of epithelial cells, arrest the development of carcinomas (epithelial cancers)? The possibilities of employing adhesion molecules for drug targeting has been reviewed by Huang et al. [23].

Secretion of collagenase has been reported to be an important determinant of the ability of cancer cells to digest and penetrate through basal laminae, thus invading associated connective tissue [24]. It may be worth revisiting observations made even decades ago and evaluate lessons that can be learned from past experimentation.

Also, cancer cells secrete growth factors that promote angiogenesis. The U.S. Food and Drug Administration (FDA) has already approved a number of vascular endothelial growth factor (VE-

GF)-targeted angiogenesis inhibitors to treat cancer [25]. Since these drugs can access equally normal as well as cancer cell, their side effects are extensive and include coagulation abnormalities, increased blood pressure, and interference with wound healing. Here again, finding ways of delivering VEGF inhibitors exclusively to cancer cells and finding ways of keeping it there would represent a major step forward.

Abnormal differentiation of cancer cells leads to the cells being blocked at an early stage of differentiation thus continuing with their active proliferation. Leukemic cells fail to undergo terminal differentiation and retain their capacity for continuing proliferation. The possibility of inducing terminal differentiation in leukemic cells has been discussed by Matushansky *et al*. [26]. Similarly, many cancer cells fail to undergo apoptosis, and have a longer lifespan compared to non-cancerous cells. This failure of cancer cells to undergo programmed cell death contributes substantially to tumor development. Consequently, tumor cells are often able to survive in the absence of growth factors that are required by normal cells [27].

Any concept for targeting drugs to cancer needs to consider the environment in which the disease target is located. Tumors are surrounded by extracellular matrix (ECM) and stromal cells, and the physiological state of the tumor microenvironment (TME) that contains a range of cells such as fibroblasts, myofibroblasts, neuroendocrine cells, adipose cells, immune and inflammatory cells, the blood and lymphatic vascular networks, and ECM. All of these components play a role in the ability of the malignant clone to escape normal regulatory mechanisms and to survive multiple insults including cytotoxic chemotherapy [28-30].

Perhaps most significantly, tumorigenesis is a multi-step process that involves a complex orchestration of intracellular and extracellular factors leading to survival of a molecularly aberrant clone that evolves and expands over time [31]. Such survival relates at least in part to activation of multiple interactive pathways rather than a single molecular lesion, with the result being a "cascade" of molecular activations that converge on central determinants of cellular survival [31-33]. Given the multiplicity of signaling intermediaries that are activated in the malignant cell, if one pro-survival intermediary is blocked, another can take over to maintain the cell's ability to survive. This compensatory ability suggests that the use of single "targeted" agents may well be suboptimal – a concept that, unfortunately, is supported by clinical experience in all malignancies. Moreover, such activation and resultant compensatory activity exist not only within the tumor cell per se, but also within the multiple cellular and humoral components of the tumor microenvironment [33-36].

Taken all together, the multifactorial nature of the tumorigenesis process requires a multifactorial approach directed toward diverse aspects of tumor cell survival and aimed at tumor eradication via early detection, treatment and, ultimately, prevention [31,33].

With regard to intracellular pathways, there are multiple examples to support the notion of compensatory activation of pro-survival pathways resulting from cellular stress including cytotoxic chemotherapies. Exposure to cytarabine, which targets DNA replication and therefore cell-cycle progression through S phase, results in activation of the ATR-CHK1 pathway which, in turn, arrests cell-cycle progression for the purpose of repairing the lethal drug-induced DNA lesions [39]. The CDK9 inhibitor Alvocidib (Flavopiridol) abrogates the activity of RNA Polymerase II and critical downstream molecules including STAT3, VEGF, and MCL-1 but also is accompanied by a "rebound" in BCL-2 expression [38]. Likewise, alterations in components of the microenvironment can occur in response to the presence of an aberrant population and may provide a survival advantage for that malignant clone [34-36]. As a case in point, AML blasts induce both exhaustion and senescence of CD8+ T effector cells due to expression of multiple coinhibitory molecules present at the time of diagnosis [34]. In functional studies, AML blasts directly alter CD8+ T cell viability, expansion, co-signaling and senescence-marker expression. A major hallmark of these findings may be the increased suppressive activity of regulatory T cells (Tregs), which accumulate in leukemic sites and impede the activity of cytotoxic T lymphocytes [34]. In addition, AML blasts induce senescence in bone-marrow stromal cells by generating NOX2-derived superoxide and resulting in increased stromal-cell expression of p16INK4a which, in turn, promotes AML cell survival [35]. Further, it is tempting to speculate that perhaps this or another AML-induced superoxide could be a contributing factor to T-cell senescence [34]. Perhaps these findings may open up the possibility that strategies to decrease AML blast-triggered oxidative stress might have therapeutic value, particularly in the setting of clinical remission with minimal residual disease. Malignant cells can also acquire genetic lesions that confer resistance to the agents used for initial therapies. This type of clonal progression is exemplified by development of mutations in the ATP binding site in the kinase domain of the chronic myelogenous leukemia (CML)-associated BCR-ABL fusion gene, leading to resistance to one or more of the tyrosine kinase inhibitors (TKIs) used for CML treatment. In a similar vein, mutations in the epidermal growth factor receptor

(EGFR) gene can be acquired during initial TKI therapy with first- and second-generation drugs for breast and other epidermal cancers and confer resistance which, in turn, can be overcome by later-generation TKIs.

On the other hand, malignant cells may exhibit a dependency on selected survival intermediaries and pathways that can be exploited to enhance the cytotoxicity of DNA-damaging chemotherapeutic agents. In this context, inhibitors of DNA damage response/repair enzymes of the poly (ADP-ribose) polymerase (PARP) family [39], the antiapoptotic BCL-2 family [40,41], and cyclin dependent kinases (CDK) 4/6 [42,43] exert synergistic effects when combined with agents cytotoxic and/or hormonal agents for a spectrum of malignancies including ovarian cancers, breast cancers, and myeloid malignancies.

Conclusions

New small molecule drugs continue to be developed. Frequently, the best outcome is seen when such new molecularly targeted entities are combined with standard chemotherapy [44]. Many new mechanistic pathways in cancer are being discovered and some are being utilized in developing new drugs. However, clear and valid concepts for therapy have not been developed for many of the old and new pathways, highlighting a need for a greater understanding of the mechanisms of cancer [45].

Available resources should be channeled less toward finding cures by addressing pathway that are common both to cancer as well non-cancer cells, and more toward finding unique differences between cancer and other cells. Such differences may include defining and exploiting a relatively increased dependency of malignant cells on normal growth and survival pathways. Once such targets have been identified, we anticipate that addressing several key pathways of cancer-cell biology by using corresponding highly specific targeted drugs in combination would offer a new paradigm for generating new highly successful human therapies.

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