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Genomic Strategies for Personalized Cancer Therapy

The field of cancer genomics is developing rapidly with the emergence of new sequencing technologies that are enabling a dramatic expansion of our understanding of the disease. The complete genomes of many cancer types are being sequenced, providing a more comprehensive view of cancer development. "Hallmarks of cancer" outlining the biological capabilities acquired during the multistep development of human tumors have been identified to help rationalize the complexities of neoplastic disease (Hanahan and Weinberg, 2011). The power of cancer diagnostics is also advancing with the rapid discovery of new genes and novel biomarkers associated with cancer as a result of improvements in laboratory techniques and analytic methods (Vockley and Niederhuber, 2015). Ultimately, the goal is to translate what is learned into better diagnosis, treatment and prevention of cancer. While conventional therapies for cancer, such as chemotherapy, indiscriminately affect all tissues and thus damage normal cells, targeted approaches in cancer therapeutics utilize genomics to identify abnormalities in an individual's specific genes or pathways and develop drugs that selectively target those markers.

I. Overview of Mechanism-based Therapeutic Targeting

The introduction of mechanism-based targeted therapies to treat human cancers, made possible by the characterization of tumor genomic landscapes, is regarded as one of the major

advancements from decades of research (Hanahan and Weinberg, 2011). Comprehensive cancer genome sequencing has led to an understanding of the genomic landscapes of common forms of human cancers, consisting of many "hills," or genes altered infrequently in tumors, and fewer "mountains," or genes altered in a high percentage of tumors (Vogelstein and Kinzler, 2015). Only about 200 of the 20,000 genes in the human genome have been shown to act as "driver genes," genes that when mutated give the tumor cell a growth advantage over surrounding cells, for common cancers (Vogelstein and Kinzler, 2015). Furthermore, these driver genes appear to function through a limited number of pathways that regulate cells' growth and fate. Thus, focusing exclusively on driver-gene mutations and the pathways they control has made complex cancer-genome landscapes exploitable for therapeutic development.

Cancer therapeutics can be categorized according to their effects on the hallmark capabilities of cancer and associated pathways, as illustrated in the figure below.

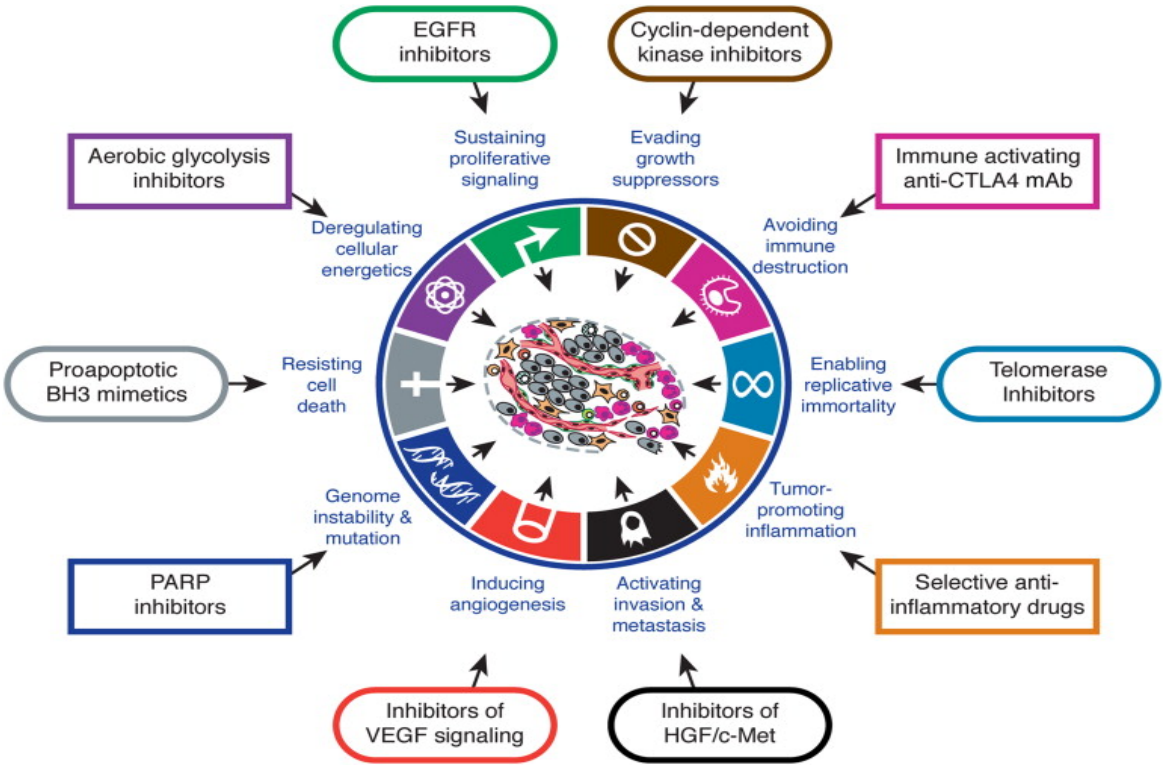

Figure 1. Therapeutic targeting of the hallmarks of cancer (Hanahan and Weinberg, 2011)

The acquired capabilities necessary for tumor growth and progression include the ability to sustain proliferative signaling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, and activate metastasis (Hanahan and Weinberg, 2011). Drugs that interfere with each of these capabilities are in clinical trials or, in some cases, approved for clinical use in treating certain forms of human cancer. Investigational drugs are also being developed to target each of the hallmark characteristics. The following discussion focuses on a subset of these therapies, proapoptotic BH3 mimetics and EGFR inhibitors, in the context of treatment of two specific human cancers.

II. Treatment Strategies Under Development for Two Specific Human Cancers

The availability of therapeutic agents and companion diagnostics from the categories above is making it increasingly possible to detect and treat individual patients on the basis of their cancer gene mutation profile (Vockley and Niederhuber, 2015). As a result, the standard of care for patients with advanced-stage cancers is shifting away from an empirical treatment strategy based on clinical–pathological profiles to one where a biomarker driven treatment algorithm based on molecular profiles of tumors is used (Kalia, 2014). Specifically, promising treatment strategies for chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and breast cancer are being developed based on new molecular targets. Each will be discussed below as useful examples of the broader evolution of cancer treatment toward biomarker-based methods.

Chronic Myelogenous Leukemia

Leukemia is a cancer of the bone marrow characterized by recurring chromosomal and genetic abnormalities. In one type of leukemia, chronic myelogenous leukemia (CML), a genetic

change takes place in immature myeloid cells, the cells that make red blood cells, platelets, and most types of white blood cells, and an abnormal gene called BCR-ABL is formed. CML was the first human malignancy found to be associated with a recurrent chromosomal abnormality (Nowell, 1960), and is treated using tyrosine kinase inhibitors. The tyrosine kinase BCR-ABL is the product of a reciprocal chromosome translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, and is a predictive biomarker for CML (Kalia, 2014). Five BCR-ABL inhibitors, imatinib, dasatinib, nilotinib, bosutinib and ponatinib, are approved by the FDA for the treatment of CML. The therapy imatinib (Gleevec) was successful in achieving a complete and long term cytogenic response in CML patients (Kalia, 2014). Imatinib works as a protein-tyrosine kinase inhibitor of BCR-ABL by occupying the ATP binding pocket of the BCR-ABL kinase domain, and thus preventing substrate phosphorylation, signaling, and proliferation.

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a type of cancer in which the bone marrow makes too many lymphocytes, a type of white blood cell. CLL is characterized by the accumulation of long-lived lymphocytes due to elevated expression of the anti-apoptotic protein BCL-2 (B-cell lymphoma 2), which makes CLL cells resistant to apoptosis. The recent introduction of targeted therapies that inhibit B-cell receptor signaling has improved the survival of patients with relapsed CLL (Roberts et al, 2015). Navitoclax was the first BH3-mimetic inhibitor of BCL-2 evaluated in clinical trials, and partial responses were observed in approximately 35% of patients with relapsed CLL (Roberts et al, 2015). The “BH3 mimetic” concept has recently prompted the development of small molecules that mimic the activity of BH3-only proteins, which trigger

apoptosis by binding to the prosurvival proteins, such as BCL-XL and BCL-2 (Billard, 2013). However, navitoclax was found to simultaneously inhibit BCL-XL, a protein critical for platelet survival, limiting the ability to escalate the dose of navitoxlax. A more potent BCL-2 inhibitor, venetoclax, is undergoing clinical trials and has proven to induce apoptosis in vitro against CLL cells, with minimal effects on platelets (Roberts et al, 2015). Venetoclax is a promising therapy with an overall response rate of 79% among patients with resistance to the first line drug Fludarabine and 71% among those with deletion 17p CLL, characterized by loss of function of the tumor suppressor TP53 which has been a major obstacle to successful therapy (Roberts et al, 2015).

Breast Cancer

Breast cancer, the second most common cancer among women, is a malignant tumor that starts in the cells of the breast. Conventional biomarkers for breast cancer include estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (Toss and Cristofanilli, 2015). Evaluation of conventional biomarkers in conjunction with molecular profiling can help in cancer classification, prognosis, and treatment planning. As a result of the large amount of information collected on disease subtyping, gene expression prognostic tests, including MammaPrint, MapQuant Dx, Oncotype DX, PAM50, and Theros Breast Cancer Index, have been developed (Toss and Cristofanilli, 2015).

Luminal cancers have the best prognosis and can typically be treated with anti-steroid compounds. Herceptin (trastuzumab) is approved for the treatment of human epidermal growth factor receptor 2-positive (HER2+) breast cancer. HER2 (Erb-B2) gene expression is a predictive and prognostic biomarker since increased expression of HER2 protein predicts a favorable response to trastuzumab(Kalia, 2014). Trastuzumab is an antibody that targets the human EGFR

protein, blocking both the intra- and extracellular domains of the HER2 receptor and thus inhibiting tumor growth. Additionally, there is recent evidence that breast cancer patients with HER2-positive tumors often benefit from topoisomerase II inhibitor-based chemotherapy such as doxorubicin or epirubicin (Kalia, 2014). Basal-like subtypes of cancer have the worst prognosis, and are primarily treated with surgery and chemotherapy.

III. Cancer Immunotherapy Research: Cancer Vaccines

In addition to cancer genomics, advancements in cancer immunotherapy research have led to further developments in immunotherapies, such as cancer vaccines. Whereas most traditional vaccines are designed to prevent a future illness, therapeutic cancer vaccines are used in people that already have a disease. The challenge in designing effective vaccines is that cancer cells escape recognition and attack by the immune system by displaying normal self-antigens. Currently, Sipuleucel-T (Provenge) is the only FDA approved cancer vaccine. However, Provenge doesn't cure patients of prostate cancer but only extends their lives by several months. Prostvac-VF is a poxvirus-based cancer vaccine in phase III clinical trials for prostate cancer. A recombinant poxvirus vector is engineered to express prostate-specific antigen (PSA) and then injected into the patient. The viral DNA is taken up by cells, which begin to manufacture the tumor-associated antigens and hopefully stimulate a strong immune response (Campbell, 2014).

Because clinical responses to vaccines vary from patient to patient for reasons that are often not understood, researchers aim to identify biomarkers that help predict the efficacy of the vaccine. In the study of Prostvac-VF, researchers used glycan microarrays to compare the serum antiglycan antibody levels in patients before and 2-4 months after initiating treatment with

Prostvac-VF (Campbell, 2014). The study identified three glycans people consistently had an antibody reaction to, and investigated them further to determine if they might be potential biomarkers informing how a patient will respond to the vaccine. Since carbohydrates are an essential class of antigens, changes in glycosylation is a common feature of disease, and cancer cells frequently display glycans, researchers were hopeful that antiglycan responses could be an early indicator of a favorable immune response to the vaccine. Antiglycan antibody responses were found to be induced by the Prostvac-VF vaccine and correlated with an increase in median survival of approximately nine months (Campbell, 2014). The identification of these glycan biomarkers has the potential to personalize treatment, allowing researchers and physicians to distinguish between patients who should continue with the vaccine or consider alternative treatments. Finding reliable indictors of a beneficial response could have a remarkable impact on clinical care.

IV. Challenges of Translating Personal Genomics into Clinical Practice

Despite rapid progress in research, the translation of genomic knowledge into clinical practice has been slow (Burke and Korngiebel, 2015). While numerous applications of genomic research in personalized medicine seem promising, few directly translate into clinical benefits. Although clinical testing for BRCA mutations moved rapidly into clinical practice, many genetic tests show no evidence of improving health outcomes, neither assisting decisions about drug use nor improving patient conditions (Burke and Korngiebel, 2015). Additionally, the issue of what is considered adequate evidence to justify clinical use of a new genetic test is controversial among expert groups. For example, experts disagree on the utility of gene expression profiling tests of breast tumors in identifying patients who can safely avoid chemotherapy. Even for tests

with strong evidence of clinical benefit, implementation remains slow, due to the need for informed consent procedures and education of point-of-care physics in genetics so they can explain the results of tests to patients (Burke and Korngiebel, 2015).

Efforts are needed to improve the body of evidence addressing clinical outcomes, in order to deliver the information most appropriate for particular clinical needs. Therefore, there is an increasing need for analytic and clinical strategies that extract the genomic information most relevant to improving health care from the growing volumes of genetic information now available (Burke and Korngiebel, 2015). At the same time, gene variants associated with common complex diseases that lack great clinical utility may still provide significant research value. They represent markers for biological pathways that may reveal unexpected mechanisms of disease, connections between different pathological processes, and interactions with environmental risk factors. Therefore, closing the translational gap relies not only on learning how to leverage individual genomes in clinical care but also using genomic knowledge to develop a better understanding of molecular physiology. Developing methods of prevention and therapy that provide benefits outside the context of genetic risk may also help expedite the translation of knowledge into clinical practice (Burke and Korngiebel, 2015).

V. Conclusion

Personalized medicine has changed the paradigms of oncology; it is now based on understanding molecular carcinogenesis, pharmacogenomics, and individual genetic differences that determine responses to chemotherapeutics. Knowledge of disease causing variants in cancer related genes, their impacts on cellular communication pathways, and the availability of drugs that can target altered genes within these pathways is the focus of study. New classes of drugs

and diagnostics are rapidly emerging with this transition from an empiric to a mechanism-based, molecular biomarker-driven therapeutic decision process (Kalia, 2014). As better analytic methods are developed to integrate and interpret the increasing volume of sequenced genomes, large scale cancer specific datasets, and ancestral information, new therapeutic biomarkers will continue to emerge at an increasing rate (Vockley and Niederhuber, 2015). Although not all genetic discoveries have proven or will prove to be clinically applicable, genetic analysis has illuminated cancer pathogenesis to a degree that was unimaginable not long ago, and will continue to provide unprecedented opportunities for better prevention and treatment.

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