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The pharmacogenomics of drug resistance to protein kinase inhibitors

Nancy K. Gillis[a,b], Howard L. McLeod[b,c,*]

[a] Eshelman School of Pharmacy, Center for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC, United States
[b] H. Lee Moffitt Cancer Center and Research Institute, DeBartolo Family Personalized Medicine Institute, Tampa, FL, United States
[c] Xiangya Hospital, Central South University, Changsha, China

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ABSTRACT

Dysregulation of growth factor cell signaling is a major driver of most human cancers. This has led to development of numerous drugs targeting protein kinases, with demonstrated efficacy in the treatment of a wide spectrum of cancers. Despite their high initial response rates and survival benefits, the majority of patients eventually develop resistance to these targeted therapies. This review article discusses examples of established mechanisms of drug resistance to anticancer therapies, including drug target mutations or gene amplifications, emergence of alternate signaling pathways, and pharmacokinetic variation. This reveals a role for pharmacogenomic analysis to identify and monitor for resistance, with possible therapeutic strategies to combat chemoresistance.

1. Introduction

Cancer is a genetic disease that arises primarily from the accumulation of genetic changes in genes regulating cellular growth, proliferation, and survival. Gain of function alterations inducing hyperactivity of oncogenes or loss of function alterations leading to inactivation of tumor suppressor genes cause deregulation of cellular signaling, a fundamental trait of cancer cells. In healthy cells, homeostasis is conveyed via growth factors binding to cell surface receptors, primarily protein kinases, which then activate intracellular signaling pathways and regulate cell cycle progression (Hanahan and Weinberg, 2011). Deregulation of these signals results in uncontrollable cellular proliferation, metabolism, survival and, ultimately, cancer. Somatic (acquired, or tumor) mutations lead to constitutive activation of these signaling pathways. For example, mutations in the B-raf proto-oncogene, *BRAF*, a serine/threonine kinase, cause constitutive signaling through the mitogen-activated protein kinase (MAPK) pathway and are commonly observed in melanoma, colorectal (CRC), and papillary thyroid cancers (Araya et al., 2016). Identification of the genes and pathways deregulated in cancer, such as *BRAF*, has led to a rapid increase in the design and approval of therapies targeting these genetic drivers of oncogenesis. Targeted anti-cancer therapies function by interfering with specific molecular alterations that regulate cellular signaling and drive tumor growth. By binding to or inhibiting a known molecular driver, targeted therapies interrupt the signaling pathways, causing cellular deregulation and leading to cancer cell apoptosis or cell death. For example, vemurafenib selectively inhibits *BRAF V600*-mutated cancer cells, abrogating MAPK-mediated signaling, preventing proliferation of *BRAF*-mutated cells, and ultimately resulting in apoptosis (Tsai et al., 2008).

To optimize the use of targeted therapies, the genetic alterations causing pathway deregulation in each patient's tumor must be identified. This is the modern concept of personalized cancer medicine (or precision medicine). Pharmacogenomics is the study of how genetic variations influence the response of an individual to drugs. In the context of cancer, there are two genomes relevant to predicting drug response or resistance: (1) germline, or inherited, genetics may affect drug exposure, potentially causing variability in efficacy and/or toxicity, and (2) somatic, or tumor, genetics are the acquired alterations that may initiate and perpetuate cellular deregulation. Generally, it is the somatic germline that is interrogated to identify alterations driving oncogenesis and to select targeted therapies. It should be emphasized that drug resistance phenomena continue to be a primary hindrance to curative chemotherapy of solid tumors and hematologic malignancies (Fletcher et al., 2016; Niewerth et al., 2015; Wicki et al., 2016). Hence, deciphering the molecular mechanisms underlying chemoresistance should enhance targeted individualized cancer medicine (Assaraf et al., 2014; Livney and Assaraf, 2013; Swanton et al., 2016).

* Corresponding author at: H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, MRC-CANCONT, Tampa, FL 33612, United States. Tel.: +1 813 745 8435; fax: +1 813 745 6525.
E-mail address: Howard.McLeod@moffitt.org (H.L. McLeod).

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Due to their critical role in regulating cellular signaling, >20 protein kinase inhibitors (PKIs) have been developed and approved across a wide range of tumor types. Despite their overall high response rates, many patients for whom the drugs are indicated will not have any evidence of disease control, while others will have transient benefit followed by tumor growth. This lack of complete and durable responses is indicative of drug resistance phenomena. If the correct alteration driving tumor growth is not identified from the outset, intrinsic resistance may be observed. When the tumor cells evolve to overcome targeted inhibition, the patient develops acquired resistance and stops responding to therapies that were previously effective. In this review, we will elaborate on the various classifications of cancer drug resistance, provide examples of how pharmacogenomics plays a role in resistance to PKIs, and discuss possible therapeutic strategies to overcome cancer drug resistance.

2. Classifications of drug resistance mechanisms important in cancer

Drug resistance can be defined as the lack of therapeutic benefit or response to a medication. In the cancer setting, drug resistance is apparent with an increase in tumor size or metastasis (i.e. disease progression). Various mechanisms of chemoresistance can result in lack of complete or durable response to cancer therapies (Fig. 1). An overview of the common classifications is provided below. It is important to note that a single pharmacogenomic biomarker may represent multiple mechanisms of drug resistance.

2.1. Pharmacological vs. biological resistance

Pharmacological resistance reflects inadequate drug exposure at the drug target, and can be caused by environmental factors (e.g., drug–drug interactions, non-compliance), germline pharmacogenomics (i.e., inter-individual variability in drug metabolism or pharmacokinetics) (Fig. 1A and C) as well as drug sequestration away from its target (Goler-Baron and Assaraf, 2011; Zhitomirsky and Assaraf, 2016). For example, addition of an antacid to alleviate gastroesophageal reflux caused by some PKI therapies will affect gastric absorption and exposure to the PKI, thereby leading to pharmacological resistance (Budha et al., 2012). Additionally, the observation that PKI-sensitive clones reemerge post-PKI discontinuation demonstrates the cytostatic, rather than cytotoxic, nature of some targeted therapies (Browning et al., 2013; Sequist et al., 2011). Therefore, inconsistent suppression of the drug target due to missed doses may lead to upregulation of the cancer-driving pathways and, ultimately, cancer progression.

Biological resistance results from cancer cell evolution in the presence of adequate drug exposure (Fletcher et al., 2016; Liu et al., 2016; Niewerth et al., 2015). In the context of cancer, biological resistance can arise from somatic alterations in drug targets or pathways (Fig. 1B and C). Examples include genetic alterations in the drug target itself, activation of alternative signaling pathways (bypass tracks), alteration in signaling proteins downstream of the drug target, or phenotypic switch. Most known mechanisms of resistance to targeted cancer therapies are of the biological resistance subtype; hence, these will be the primary focus of this article.

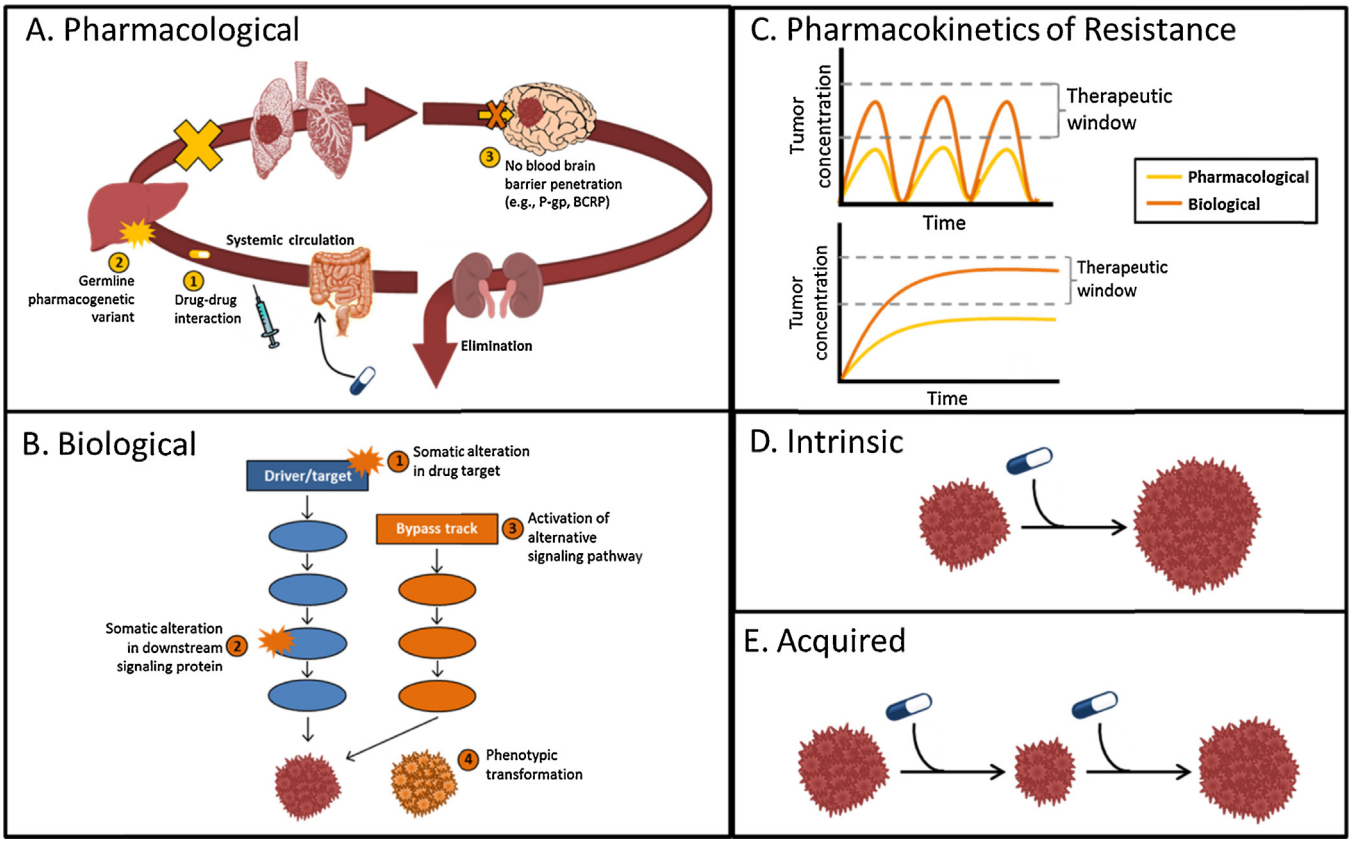

Fig. 1. Mechanisms of oncology drug resistance. (A) Pharmacological resistance. Drug–drug interactions and germline pharmacogenetic variants can affect drug exposure at the tumor site. Pharmacological properties can affect drug penetration into the central nervous system. (B) Biological resistance. Somatic (acquired) mutations in the drug target can affect the drug's ability to effectively inhibit oncogenesis. Somatic alterations downstream of the drug target can result in constitutive upregulation of oncogenic pathways. Genetic alterations may also activate alternative oncogenic signaling pathways. Some tumor types have been shown to transform into other tumor types (e.g., non-small cell lung cancer to small cell lung cancer). (C) Pharmacological drug resistance results from inadequate drug levels at the site of action, whereas biological drug resistance results despite adequate drug levels at the site of action. (D) Intrinsic resistance is the lack of even transitory clinical benefit – the tumor continues to progress despite treatment. (E) Acquired resistance is the lack of tumor response to medication despite initial benefit.