ELSEVIER

Deciphering molecular determinants of chemotherapy in gastrointestinal malignancy using systems biology approaches

Q2 Li-Ling Lin[1], Hsuan-Cheng Huang[2] and Hsueh-Fen Juan[1,3,4] the 2013 Taida Cancer Systems Biology Study Group

[1] Institute of Molecular and Cellular Biology, Department of Life Science, National Taiwan University, Taipei, Taiwan
[2] Institute of Biomedical Informatics, Center for Systems and Synthetic Biology, National Yang-Ming University, Taipei, Taiwan
[3] Genome and Systems Biology Degree Program, National Taiwan University, Taipei, Taiwan
[4] Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan

Gastrointestinal cancers are asymptomatic in early tumor development, leading to high mortality rates. Peri- or postoperative chemotherapy is a common strategy used to prolong the life expectancy of patients with these diseases. Understanding the molecular mechanisms by which anticancer drugs exert their effect is crucial to the development of anticancer therapies, especially when drug resistance occurs and an alternative drug is needed. By integrating high-throughput techniques and computational modeling to explore biological systems at different levels, from gene expressions to networks, systems biology approaches have been successfully applied in various fields of cancer research. In this review, we highlight chemotherapy studies that reveal potential signatures using microarray analysis, next-generation sequencing (NGS), proteomic and metabolomic approaches for the treatment of gastrointestinal cancers.

UNCORRECTED PR

Introduction

The stomach, pancreas and large intestine are organs of the gastrointestinal system, and cancers in these organs are usually advanced when they are diagnosed because the early stages are asymptomatic and difficult to detect [1,2]. Although surgical resection is an important curative treatment for such cancers, the long-term survival rate of patients is poor because of unresectable tumors, drug resistance and recurrent cancer. In addition, mortality rates associated with these cancers remain high because of the scarcity of effective therapeutic biomarkers. In this review, we focus on using systems biology approaches in deciphering molecular determinants of anticancer drugs that have been approved by the US Food and Drug Administration (FDA) for the clinical treatment of gastrointestinal cancer (Table 1).

Systems biology is an interdisciplinary field that explores systems at different levels, from pathways to networks, across scales, from single cells to entire organisms. In cancer research, many investigators have attempted to use systems biology to reveal disease-related components within complex biological networks and to identify novel therapeutic candidates [3]. For instance, differentially expressed genes can be interpreted through functional annotation (e.g., Gene Ontology) and pathway analysis in drug discovery (e.g., Kyoto Encyclopedia of Genes and Genomes Pathways) [4]. To maximize the therapeutic effects of potential anticancer drugs, it is important to identify the target precisely and to minimize the adverse effects. A systems biology approach can be used to integrate interdisciplinary fields to provide new methods for discovering anticancer drugs and for understanding the mechanisms behind their effects [5]. In this article, we demonstrate the application of this approach in investigating the relation between anticancer drugs and their targets (Figure 1). Moreover, we describe how this approach can be used to examine regulatory mechanisms for improving therapeutic strategies (Table 2).

Systems biology and omics

Cancer research using a systems biology approach currently uses technologies such as microarray analysis, proteomics, and metabolomics. Microarray analysis, a major method of high-throughput genetic profiling, has commonly been used to investigate molecular

Corresponding authors: Huang, H.-C. (hsuancheng@ym.edu.tw), Juan, H.-F. (yukijuan@ntu.edu.tw)

1359-6446/06/$ - see front matter © 2014 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.drudis.2014.04.016

Please cite this article in press as: L.-L. Lin, et al., Deciphering molecular determinants of chemotherapy in gastrointestinal malignancy using systems biology approaches, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.04.016

TABLE 1

Profiles of gastrointestinal cancer drugs featured in this review[a]

Drug	Phase	FDA first approval*	Target[b]
5-Fluorouracil	II/III	Before 1984[c]	HER2
Bortezomib	II	2003	Ubiquitin–proteasome pathway
Capecitabine	II/III	1998	HER2
Cetuximab	II	2004	EGFR
Cisplatin	II/III	Before 1984[c]	DNA
Doxorubicin	II	Before 1984[c]	Topoisomerase II
Erlotinib	II	2004	Tyrosine kinase
Etoposide (VP-16)	II	Before 1984[c]	Topoisomerase II
Irinotecan	II/III	1996	Topoisomerase I
Leucovorin	I/II/III	Before 1984[c]	DNA
Oxaliplatin	III	2002	EGFR
Trastuzumab	III	1998	HER2

[a] Based on the US FDA (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm).
[b] *NCI Drug Dictionary* published by the National Cancer Institute [59].
[c] FDA unable to verify dates of drugs approved before 1984.

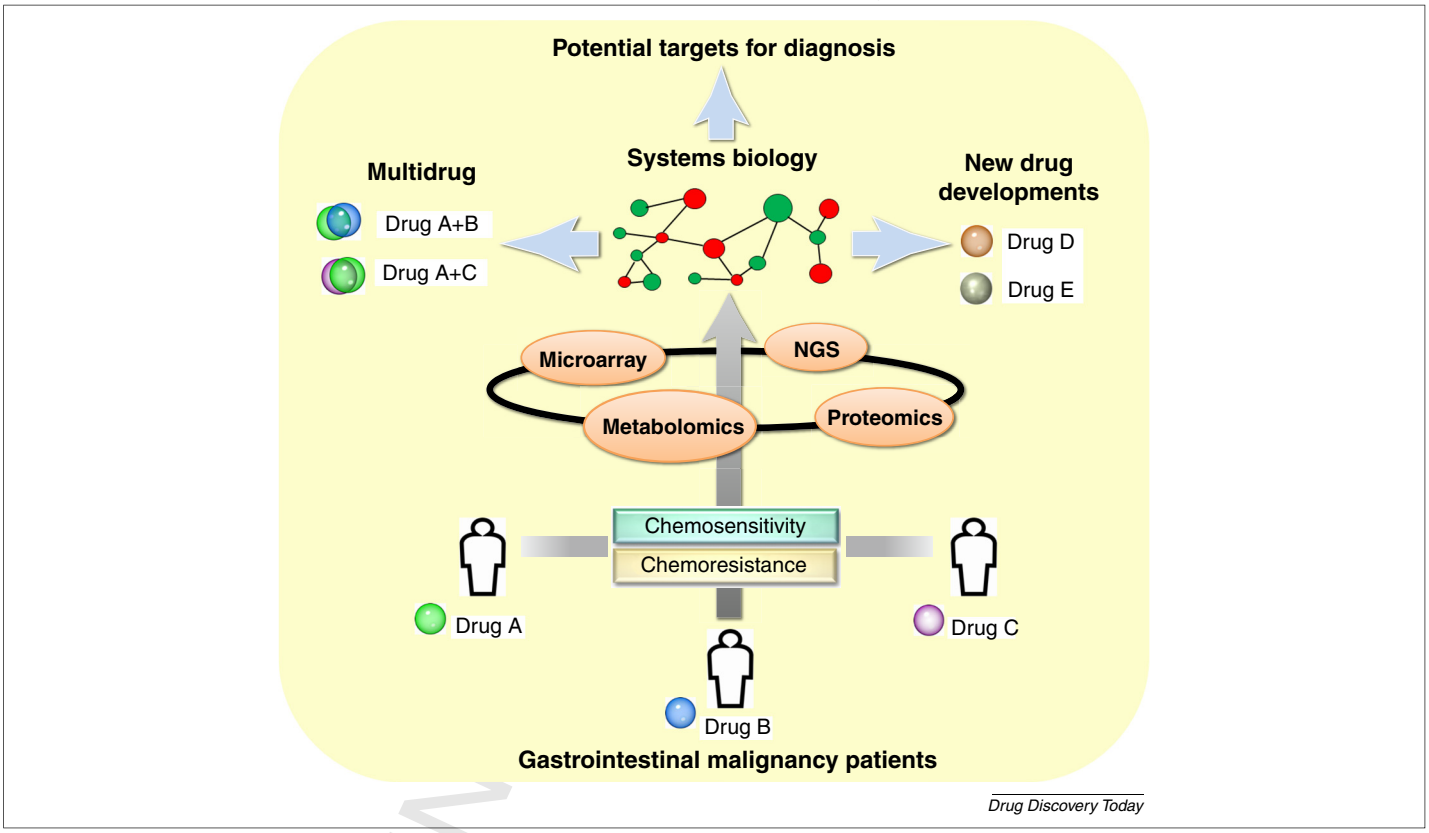

FIGURE 1

Schematic representation of the application of a systems biology approach to identify new cancer drugs and drug combinations. A systems biology approach combining microarray, next-generation sequencing (NGS), proteomics and metabolomics analyses can be used to develop treatment strategies that reduce adverse effects, enhance chemosensitivity, or reduce chemoresistance. Moreover, it can be used to identify potential biomarkers for the diagnosis or prediction of cancer progression.

mechanisms. It involves hybridization with oligonucleotide probes to enable detection of DNA and RNA, and has many applications. Examples of methods that use this approach are those based on DNA methylation status, DNA variations and miRNA expression profiles [6]. The extended application of microarrays has yielded biological insights from comprehensive genomic and proteomic studies. Through computational modeling of high-throughput data produced by these methods, scientists can explore the molecular mechanisms and biological signaling pathways in cancer development [7,8].

Please cite this article in press as: L.-L. Lin, et al., Deciphering molecular determinants of chemotherapy in gastrointestinal malignancy using systems biology approaches, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.04.016

Download English Version:

https://daneshyari.com/en/article/10886125

Download Persian Version:

https://daneshyari.com/article/10886125

Daneshyari.com