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Review

Predictive genomics: A cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data

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ABSTRACT

Tumor genome sequencing leads to documenting thousands of DNA mutations and other genomic alterations. At present, these data cannot be analyzed adequately to aid in the understanding of tumorigenesis and its evolution. Moreover, we have little insight into how to use these data to predict clinical phenotypes and tumor progression to better design patient treatment. To meet these challenges, we discuss a cancer hallmark network framework for modeling genome sequencing data to predict cancer clonal evolution and associated clinical phenotypes. The framework includes: (1) cancer hallmarks that can be represented by a few molecular/signaling networks. 'Network operational signatures' which represent gene regulatory logics/strengths enable to quantify state transitions and measures of hallmark traits. Thus, sets of genomic alterations which are associated with network operational signatures could be linked to the state/measure of hallmark traits. The network operational signature transforms genotypic data (i.e., genomic alterations) to regulatory phenotypic profiles (i.e., regulatory logics/strengths), to cellular phenotypic profiles (i.e., hallmark traits) which lead to clinical phenotypic profiles (i.e., a collection of hallmark traits). Furthermore, the framework considers regulatory logics of the hallmark networks under tumor evolutionary dynamics and therefore also includes: (2) a self-promoting positive feedback loop that is dominated by a genomic instability network and a cell survival/proliferation network is the main driver of tumor clonal evolution. Surrounding tumor stroma and its host immune systems shape the evolutionary paths; (3) cell motility initiating metastasis is a byproduct of the above self-promoting loop activity during tumorigenesis; (4) an emerging hallmark network which triggers genome duplication dominates a feed-forward loop which in turn could act as a rate-limiting step for tumor formation; (5) mutations and other genomic alterations have specific patterns and tissue-specificity, which are driven by aging and other cancer-inducing agents.

This framework represents the logics of complex cancer biology as a myriad of phenotypic complexities governed by a limited set of underlying organizing principles. It therefore adds to our understanding of tumor evolution and tumorigenesis, and moreover, potential usefulness of predicting tumors' evolutionary paths and clinical phenotypes. Strategies of using this framework in conjunction with genome sequencing data in an attempt to predict personalized drug targets, drug resistance, and metastasis for cancer patients, as well as cancer risks for healthy individuals are discussed. Accurate prediction of cancer clonal evolution and clinical phenotypes will have substantial impact on timely diagnosis, personalized treatment and personalized prevention of cancer.

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1. Introduction

Tumor genome sequencing has generated information on thousands of mutations and other genomic alterations. To date, more than 10,000 tumor genomes have been sequenced and as

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sequencing costs drop, many more genomes will be determined in the near future. Recently, Illumina released a high-throughput genetic sequencing machine, the HiSeq X Ten that can sequence a whole human genome for $1000. New technologies such as Quantum Sequencing platform and Oxford Nanopore systems hold promise for further reducing genome sequencing cost in the near future. This trend suggests that genome sequencing could be used as a diagnostic tool in clinical practice.

Tumor genome sequencing has cataloged many 'driver-mutating genes' and will continue to catalog more. However, the biological complexity of cancer combined with a vast amount of genome sequencing data presents a significant challenge on how to extract useful information and translate them into mechanistic understandings and predictions for cancer phenotypes [1], thus enabling management of cancer patient treatment in a more efficient manner. If one looks at a cancer cell genome, it is abundant with gene mutations, deletions and amplifications, chromosome gains and losses. Though seemingly random, there could in fact be patterns for mutations and chromosomal changes and by uncovering these patterns, we could in turn gain more insight into the mechanisms which drive cancer progression. By accessing the complete, precise genomic and clinical information from cancer patients, future advances will depend on exploiting the natural genetic complexity through uncovering key components of the cancer system. The genetic complexity observed can be described in a mathematical manner and models computed as a result. Moreover, the key components of cancer could be experimentally perturbed to test their characteristics. Ultimately, we could predict evolutionary path of the tumor clones and their phenotypes associated with progression, metastases and drug resistance.

In this review, we discuss a cancer hallmark network framework that can be used to model key components of cancer system and then link mutant genotypes (i.e., mutations and other genomic alterations) to cellular and clinical genotypes. Using this framework, we illustrate strategies for predicting of cancer drug targets, probability of tumor recurrence, and cancer risks based on individual patient's genome sequencing profile. Predictions derived from cancer hallmark network-based modeling could ultimately be used in diagnosis and optimized patient management and prevention of cancer.

2. Cancer hallmarks and their networks

Although the biology of cancer is extremely complex, key traits have been revealed during the past decade. The complexity of cancer can be reduced and represented by a few distinctive and complementary capabilities ('cancer hallmarks') that enable tumor growth and metastasis dissemination. These hallmarks constitute an organizing principle that provides a logical framework for understanding the remarkable diversity of neoplastic diseases. In 2000, Weinberg and Hanahan proposed six cancer hallmarks [2]: (1) cancer cells self-stimulate their own growth; (2) they resist inhibitory signals that might prevent their growth; (3) they resist their own programmed cell death; (4) they stimulate the growth of blood vessels to supply nutrients to tumors; (5) they can multiply forever; and (6) they invade local tissue and spread to distant organs. These are the core common traits that govern the transformation of normal cells to cancer (malignant or tumor) cells. In 2011, Weinberg and Hanahan updated the cancer hallmarks by adding 4 more hallmarks [3]: (7) abnormal metabolic pathways; (8) evading the immune system (escaping from immunosurveillance); (9) chromosome abnormalities and unstable DNA (genome instability); and (10) inflammation.

2.1. Genome duplication is an emerging cancer hallmark

Cancer hallmarks are evolving as we understand more about cancer. For example, from genomic point of view, the most striking characteristic of cancer genomes is extensive aneuploidy. Cancer genomes carry extremely high frequency of somatic copy number alterations, most of which are large-scale at chromosomal level. For example, several chromosomal arms can be amplified or deleted. It has been proposed that genome duplication could play a critical role for generating cancer aneuploidies and most likely be a rate-limiting step for tumor development [4,5]. This assumption is based on the observations that genome duplication occurs only one time and routinely at the last round of gene amplification/deletion events during the transformation from normal to cancer cells [4,5]. Aneuploidy is extensive in cancer [6]. We and others have shown that a large fraction (~50%) of solid tumors has undergone genome duplication (Milanese et al. unpublished data; [7]). Therefore, we regard genome duplication as an emerging cancer hallmark trait which not only drives cancer aneuploidies but also a rate-limiting driving force during tumor formation. Genome duplication enables subtle changes in the activity of many different genes simultaneously and could facilitate the activation of several hallmark networks in one shot [4,5]. In particular, the capabilities of interactions/regulations between hallmark networks could easily be acquired through genome duplication. Therefore, activation of genome duplication network could represent a 'perfect storm' of extreme changes of genes in the cancer genome so that a cell could acquire a set of cancer hallmark traits at one time and then transform a 'slow-growing' cancer clone into 'fast-growing' one and therefore speed up tumor formation.

2.2. Mapping of cancer hallmark traits onto cancer hallmark networks

Over the past few years it has been argued that network or a systems approach should be adopted for modeling of cancer genomic data so as to further understand cancer biology and translate the information into clinical practice [1,8,9]. In the article of '*The Roadmap of Cancer Systems Biology*' [10], we proposed that a signaling network could be constructed for an individual tumor and modeling efforts could then be made ascribing cancer hallmark networks to that particular tumor. Substantial efforts have been made in this direction recently and have generated interesting results. For example, patient-specific whole signaling pathways have been constructed using a graphical model (PARADIGM) based on genomic alteration data and used for predicting drug targets [11]. We have developed an algorithm, which focuses on modeling cancer hallmark gene modules, and successfully identified highly robust cancer biomarkers [12]. Moreover, by the modeling of genomic alterations on the core cancer hallmark network – the cell survival and proliferation network – we are able to effectively predict (with 80% accuracy) breast cancer subtype-specific drug targets [13]. Theses examples are encouraging for modeling of tumor genomic data and complex cancer systems using a framework that consists of a set of hallmark networks representing underlying principles and mechanisms of tumorigenesis.

The mechanisms of cancer etiology attributed to signaling pathways of some cancer hallmarks are closely intertwined. Therefore, the hallmarks whose underlying signaling pathways are highly intertwined can be collected into one hallmark network. For example, the signaling processes of Hallmarks 1, 2 and 3 are highly interactive, which one can define as a cancer cell survival and proliferation network (for simplicity, the survival network). This survival network collects the interactions and signaling processes of above three hallmarks. Using this principle, we mapped cancer hallmark

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