Association Between Modular Organization of Cancer Signaling Networks and Patient Survivability

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1 Introduction

Cancer is a complex and robust system; thus, it may remain an incurable disease despite the efforts to develop effective anticancer therapies [1]. Since cancer behaviors are governed and coordinated by these interactions between biomolecules (i.e., cancer signaling networks), investigators have been able to actively carry out comprehensive data analyses in an ongoing attempt to shed light on the understanding of cancer robustness. The data on signaling networks are accumulated in several databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) [2].

Although cancer patient survivability was reported to correlate with the degree entropy, characterizing heterogeneous connectivity, of the signaling networks [3] inspired by theoretical studies on the increase of network robustness due to the heterogeneous connectivity, other theoretical and data analytic studies suggest an alternative explanation: the impact of modular organization of networks on biological robustness or adaptation to changing environments (modularity–robustness hypothesis) (see [4] for details). In this study, thus, we evaluate whether this hypothesis is applicable to cancer using network analysis [4].

2 Method and Results

2.1 Cancer signaling networks and patient survival rates

We manually downloaded the KGML files containing the signaling network data of 14 cancer types from the KEGG database [2], and constructed the cancer signaling networks in which nodes and edges are proteins and relations between proteins such as protein–protein interactions and signaling flows.

We obtained the average 5-year survival rate of cancer patients according to the previous study by [3]. The survival rate of cancer patients was originally extracted from the Surveillance Epidemiology and End Results (SEER) Program database (http://seer.cancer.gov/), which provides information on cancer statistics compiled by the National Cancer Institute.

2.2 Network modularity

We focused on 2 types of parameters for characterizing network modularity: the *Q-value*, which is defined as the fraction of edges that lie within, rather than between, modules relative to that expected by chance, and the *clustering coefficient*, which denotes the density among neighbors of a node (i.e., the ratio of the number of edges among the neighbors to the number of all possible connections among the neighbors) (see [4] for details).

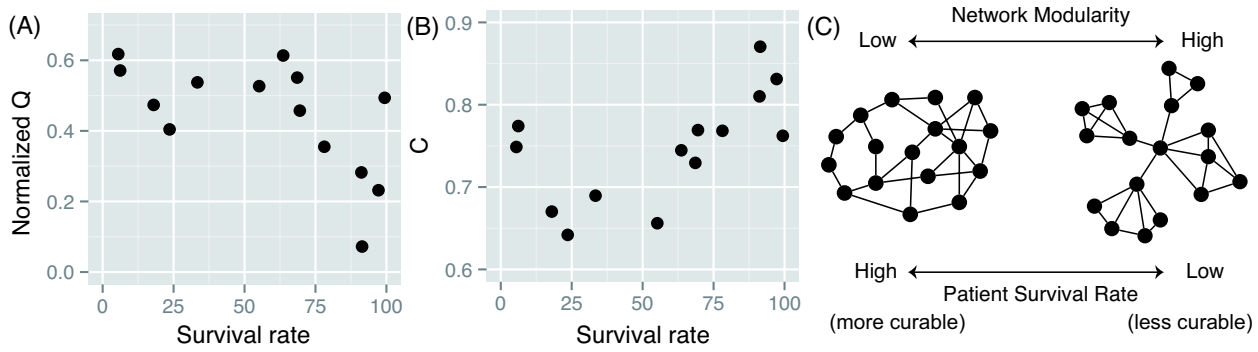

Figure 1: Correlation of patient survival rates with (A) Q-value (normalized version) (Spearman's rank correlation coefficient $r_s = -0.65$ and $p = 0.014$) and (B) clustering coefficient ($r_s = 0.57$ and $p = 0.036$). (C) Schematic diagram of the association between the network modularity and the survival rates.

As expected from the modularity–robustness hypothesis, these network parameter for characterizing modularity correlate with patient survival rates (Figures 1A and 1B). In particular, the cancers with less modular signaling networks are more curable (or less robust) (Figure 1C).

Moreover, the normalized Q-value and the degree entropy are different structural properties because of no correlation between them ($r_s = 0.39$ and P-value $p = 0.17$).

3 Discussions

This finding provides new and different insights into cancer robustness from the heterogeneous connectivity. In particular, modularity may facilitate an adaptation to changing environments. Discrete modules in systems (e.g., networks) may archive particular functions; thus, systems are expected to acquire more modules when they have to robustly respond (e.g., cancer cells grow and survive) under more various conditions. Thus, a cancer with more modular signaling networks is more robust to multiple treatments such as the dosage of multiple drugs and radiation exposure. This interpretation is consistent with multidrug resistance in cancer.

Although data analysis has several limitations, these findings provide new insights into the relationship between cellular networks (a microscopic view) and phenotypes (a macroscopic view) in cancer, and they enhance our understanding of adaptive and evolutionary mechanisms of cancer cells. We believe that these findings are also helpful for network-based cancer treatments.

References

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