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Characteristics of microRNA co-target networks

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ABSTRACT

The database of microRNAs and their predicted target genes in humans were used to extract a microRNA co-target network. Based on the finding that more than two miRNAs can target the same gene, we constructed a microRNA co-target network and analyzed it from the perspective of the complex network. We found that a network having a positive assortative mixing can be characterized by small-world and scale-free characteristics which are found in most complex networks. The network was further analyzed by the nearest-neighbor average connectivity, and it was shown that the more assortative a microRNA network is, the wider the range of increasing average connectivity. In particular, an assortative network has a power-law relationship of the average connectivity with a positive exponent. A percolation analysis of the network showed that, although the network is diluted, there is no percolation transition in the network. From these findings, we infer that the microRNAs in the network are clustered together, forming a core group. The same analyses carried out on different species confirmed the robustness of the main results found in the microRNA networks of humans.

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1. Introduction

Belonging to a class of non-coding RNAs, microRNAs (miRNAs) [1,2] are small single-stranded RNA molecules of approximately 21–23 nucleotides in length. Although miRNAs are encoded by genes of the corresponding DNA, they are not translated into proteins. Instead, a primary transcript miRNA is processed into a functionally matured miRNA by way of forming a short stem-loop structure called pre-miRNA. Mature miRNAs are partially complementary to one or more messenger RNAs (mRNAs) so that they can interact with the 3′ untranslated region (UTR) of a target gene. The name "microRNA" was coined [2] several years after it was first described by Ambros and his colleagues in 1993 [1], and since then miRNAs have been widespread in biology.

Recently, miRNAs have been the subjects of intensive studies, and they have attracted a great deal of attention from the scientific community, primarily due to the discovery of the regulating gene expression, which has long been thought of as an exclusive function of proteins. The discovery of its regulatory function is more prominent as a scientific breakthrough than initially predicted [3]. miRNAs regulate various important biological processes, including cell growth and death, development, and differentiation. Although, in some cases, they are found to increase the expression of target genes [4], the interaction mostly results in down-regulating gene expressions either by degrading mRNAs or inhibiting the protein translations of target mRNAs.

While a theoretical analysis proposed that about 30% of genes in the human genome could be the target of miRNAs [5], a recent study predicts this percentage to be as high as 90%, although experimental validation of such a prediction has not been provided [6]. It was shown that miRNAs can alter gene expression by binding to either the coding region or the 5′ UTR [7], although the canonical binding is to the 3′ UTR. In addition, the phenotypical diversity of miRNAs has been investigated by

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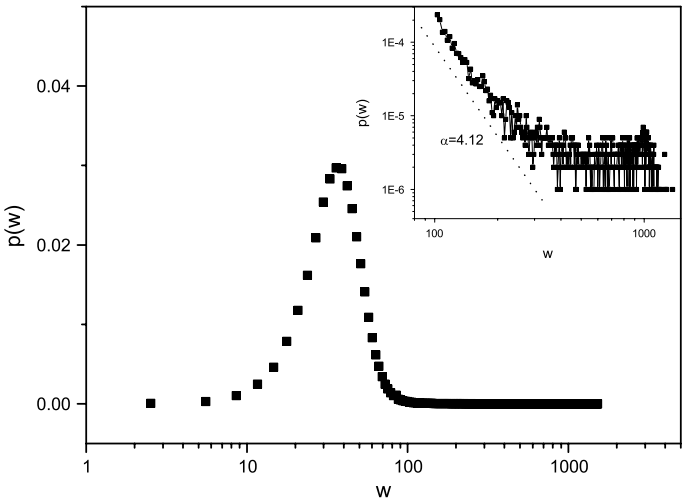

Fig. 1. The relative frequency distribution $p(w)$ of the number of co-targeted genes w for *H. sapiens*. The mean and standard deviation of w are 41.6 and 26.2, respectively. The distribution for $w > 100$ is plotted in a log–log scale in the inset.

mutating miRNAs, and the significant functional redundancy of miRNAs has also been reported [8]. These studies suggest that miRNAs and their target genes form a complex regulatory network.

Different functional roles of miRNAs in gene regulation have been found. For instance, by constructing the co-regulation network of *Homo sapiens*, in which the correlation between the gene silencing scores of miRNAs is considered, modules for co-regulating miRNAs are investigated [9]. From the finding of a miRNA regulating two transcription factors in a regulated feedback loop, it was demonstrated that miRNAs and transcription factors extensively interact with each other [10]. In addition, intronic miRNAs, which are located within introns of protein coding genes, have been studied to uncover the linkage between their expression and the promoter-driven regulation of genes [11]. The correlation between miRNA regulation and the protein–protein networks has also been investigated to elucidate how miRNAs regulate the networks [12].

In addition to the regulation of miRNAs, the deregulation of miRNAs has been shown to be associated with diseases, such as various types of cancer and heart failure [13–18]. For instance, an experimental study of mice shows the effect of miRNA on the development of cancer: mice that have a surplus miRNA in lymphoma develop cancer, and they were found to live much shorter lives than those without a surplus of miRNA [13]. miRNA involvement in cardiomyopathies was demonstrated in the expression levels of specific miRNAs that change in abnormal human hearts through miRNA expression profiling studies [16–18]. In addition, by constructing miRNA co-target networks, it can be identified that specific clusters of miRNAs are associated with specific diseases [19]. Thus, miRNAs' association with diseases has led to the increase of not only academic research opportunities, but also the development and commercialization of miRNA-related diagnostics and therapeutics.

Despite the rapid advance in the understanding of the functional aspect of miRNAs in numerous biological processes and human diseases, quantitative analyses of miRNA–gene interaction from a computational viewpoint is relatively lacking and is still in its infancy. Notable quantitative studies on the role played by miRNAs have been carried out from the systems biology (or complex networks [20]) perspective. For instance, the miRNA regulation of cellular networks, including cellular signal networks, gene regulatory networks, and metabolic networks, has been investigated [21]. These studies addressed the regulation of miRNAs by analyzing interactions between miRNAs and the cellular networks in cells in terms of complex regulatory networks of miRNAs and their targets. To partially, if not entirely, complement the study on the miRNA from the perspective of complex networks, in this paper, we propose a method of constructing a miRNA functional co-target network and analyze it from the perspective of complex networks. This elucidates topological characteristics of the miRNA co-target network and may suggest an implication of regulation on the targets. To this end, we analyze 851 miRNAs and 34,788 predicted target genes of *H. sapiens* in the miRBase database (http://microrna.sanger.ac.uk/) [22]. We also analyze the data of other species to test the robustness of our main analysis results.

2. Construction of a miRNA co-target network

A miRNA co-target network can be constructed based on the finding that more than two miRNAs can target the same genes [19]. Not only does each miRNA interact with a certain number of genes as targets, but each gene can be targeted by multiple miRNAs. To quantify this characteristic, we define w_{ij} as the number of genes that two different miRNAs (i and j) share as targets, that is, two miRNAs co-target. With this definition of w_{ij}, we evaluate w_{ij} for all pairs of miRNAs. It turns out that, in the case of *H. sapiens*, w_{ij} ranges from $1 \leq w_{ij} \leq 1519$. As can be seen from the frequency distribution of w, shown in Fig. 1, w is the most probable around $w \approx 40$ and there is a small but finite frequency at large w. In particular, for $w > 100$, the distribution approximately follows a power-law expression with an exponent close to $\alpha = 4.12$. We have tried various

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