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MicroRNA-mRNA Regulation Networks

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Synonyms

Bipartite network; Gene regulation network; MiRNA; Post-transcriptional gene regulation (PTGR); Regulatory network

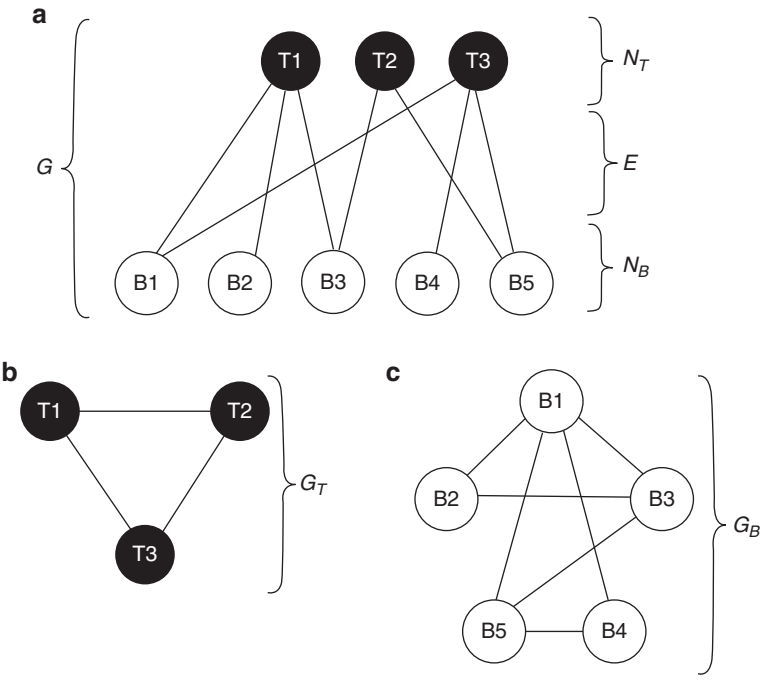
Definition

MicroRNA (miRNAs) modulate gene expression post-transcriptionally through binding at the 3′-untranslated region of target mRNAs. Thus, the miRNA-mRNA network represents a particular layer in the landscape of gene regulation (Djuranovic et al. 2011). This network is based on the specificity of the interaction between miRNAs and their specific mRNA targets. Briefly, a miRNA-mRNA network is the graph that captures the relation by which mature miRNAs control the translation of target mRNAs (additionally compromising mRNA stability) (Kanitz and Gerber 2010). Properties such as a fat tail degree distribution, the abundance of cybernetic motifs, and a modular behavior have been reported as descriptors of the topological organization of this miRNA-mRNA regulation network.

Characteristics

Study System

MiRNAs involve a particular subset within the general set of small ▶ non-coding RNAs. MiRNAs block mRNA translation into proteins by binding to the so-called ▶ RNA-induced silencing complex (RISC) and driving it to specific miRNA sites in the target mRNA. MiRNAs are among the most abundant regulatory factors in the human genome (Griffiths-Jones et al. 2008). Bioinformatic and experimental predictions indicate that every miRNA may target multiple mRNAs, as well as every particular mRNA is likely regulated by synergic co-targeting of several miRNAs (Bartel 2009), thus suggesting that miRNAs may play a pervasive and coordinated role in the regulation of gene expression. This pleiotropic behavior of miRNAs justifies their involvement, as fine-tuning regulators, in the coordination of many cellular processes related to development, differentiation, growth, metabolism, and many others (Inui et al. 2010), even though the amount of repression conferred by miRNAs tends to be modest for any single target (Baek et al. 2008). To deep further in the knowledge of this regulatory layer, interactions between miRNAs and the corresponding target mRNAs are abstracted as graphs whose topological organization give insights about the logic of their fine-tuned relationships and the precision of the regulatory output (Kanitz and Gerber 2010).



MicroRNA-mRNA Regulation Networks, Fig. 1 Representation of a bipartite graph (**a**). The edges (*E*) establish the connection between the members of two disjoint sets: *top nodes* (N_T) and *bottom nodes* (N_B). Connections between nodes of the same set are forbidden. Two alternative projections: *top nodes* (**b**) and *bottom nodes* (**c**) are possible by considering nodes of one set as connectors of the other one

Graph Abstraction

Within the framework of graph theory, elements involved in systems are reduced to nodes that are connected by an edge if some kind of relationship has been defined between them. Considering the nature of the system, different graphs can be obtained, being the ► bipartite graph one of the most intuitive representations. In a bipartite graph $G = (N_T, N_B, E)$, miRNAs and mRNAs are tow disjoint sets of nodes, top (N_T) and bottom (N_B) nodes, and the set of edges (E) commonly captures the interaction by specific sequence site recognition between miRNAs and mRNAs. Therefore, edges between two miRNAs or two mRNAs are not allowed in this bipartite representation. In addition, this bipartite representation can be simplified by producing two alternative graphs. A miRNA graph is a one-type node graph with only miRNAs. In this graph, two miRNAs are bound by an edge if they co-target the same sequence in the bipartite graph. The other one defines a network where nodes are mRNAs. Two mRNAs are linked if they are regulated by a common miRNA in the bipartite network. These last graphs are known as projections of the bipartite graph (Fig. 1).

Furthermore, other abstractions can be established. Examples of them are the multidimensional regulatory networks in which transcription factors (TFs) interact with each other and with miRNAs to build up cybernetic motifs (Kanitz and Gerber 2010). Another possibility is to consider miRNAs and disease networks by combining the diseasome and the PTGR. In this resulting network, mRNAs are the edges and two kinds of nodes (miRNAs and diseases) are connected if targeted mRNAs are associated with health disorders (Murray et al. 2010). Other interesting possibility is the multigraph regulation network in which miRNAs and mRNAs are connected by two kinds of edges: specific miRNA-mRNA target interactions and physical interactions between proteins codified by these mRNAs (Tsang et al. 2010). The choice of the type of representation depends on the purpose of the study. All of them inevitably introduce some kind of limitation to the interpretation of the results.

Topological Organization

Topology, applied to the branch of graph theory developed from the field of statistical mechanics, commonly indicates the pattern of organization of a graph. By using this approximation, the organization of a number of very large interconnected systems, spanning from metabolism and protein interaction networks to the Internet, has been successfully uncovered, becoming paradigmatic study cases of this branch of physics.

The application of such an analysis to the miRNA regulatory network allows us to uncover some notable features giving clues about the logic of cellular functions. An interesting topological property is related to the degree (k) – the number of connections of a node – and, in particular, to the degree distribution, i.e., the probabilities of finding nodes with degree (k). It has been observed that PTGRs follow a fat tailed distribution in both types of nodes. This means that a handful of nodes (the hubs) have many connections, whereas the vast majority of them have very few ones. Many authors link this fat-tailed degree distributions, in particular a power-law decay, with the Barabási and Albert's model of growth and preferential attachment to explain the evolution of miRNAs (Murray et al. 2010). It is worth noting that miRNAs and mRNAs have not the identical degree distribution. In general, miRNAs have higher degree values than mRNAs. In other words, each miRNA may bind and regulate dozens to hundreds of mRNAs, whereas each mRNA may be only regulated by one to tens of miRNAs. This is reflected in their average degrees: about 50 for miRNAs and around 6 for mRNAs (Murray et al. 2010; Kanitz and Gerber 2010). According to the observed topological properties, the idea that miRNAs can rewire the genetic network at the system level is reinforced.

They both, bipartite graph and multigraph, share a comparable topology with respect to TFs network but more densely connected. This favors short average path lengths in spite of the high locality (degree to which nodes in a graph tend to cluster together) in their connections (Kanitz and Gerber 2010; Shirdel et al. 2011). The direct interpretation of these results reveals a small-world behavior. This property agrees with the commonly accepted idea in metabolism that an optimization process of regulation and information flux keeps local structures in which changes are quickly transmitted within a system where short paths permit a fast coordination.

▶ Modularity is a measure that quantifies the quality of a partition of a network into modules or communities, in which there are more connections between the nodes within modules than between different modules, only sparsely connected. It has been said that modular structures may facilitate functional and evolutionary versatility. In fact, modularity has been observed in miRNA diseases, miRNAs-cancer and miRNAs-protein function networks. Furthermore, analyses of multidimensional networks suggest that the overrepresentation of cybernetic motifs, along with modular configuration in miRNAs gene regulatory networks, confer regulatory buffering of gene expression and tones down the impact of noise. In this way, the coordination of protein expression levels allow higher specificity in developmental processes (Herranz and Cohen 2010).

All these evidence support the idea of a kind of evolutionary optimization in the PTGR system.

Dynamic Implications

Has been verified that miRNA levels change dynamically in time, and their changes condition the functional state of the cell, their behavior, and tissue coordination. In order to delve into how PTGR network is conditioned by their topology, network motifs have been explored. It has been found that feedback loops, in which two TFs regulate each other and a miRNA regulates both, are the most significant overrepresented network motif. In this context, miRNAs act as stabilizers of the feedback loop, thus resisting environmental perturbations (Yu et al. 2008). Moreover, on the basis of this network motif profile analysis, the occurrence of two classes of miRNAs with distinct network topological properties (depending on the number of TFs involved on its regulation) has been demonstrated. The class I is regulated by a high number of TFs, whereas class II is regulated by only a few of TFs (Yu et al. 2008). Class I might be involved in complex developmental programs in which a combinatorial coordination of TFs must be fine-tuned. In contrast, class II miRNAs may be involved in the maintenance of tissue identity. To understand how miRNA-associated feedback loops work, mathematical analysis of the dynamics behavior of the motifs has been performed (Yu et al. 2008; ▶ MicroRNA Regulation, Feed-Forward Loops). These models suggest that the repressive function of miRNAs, when combined with other regulatory factors, can build up more complex and higher-order functions, such as canalization and fine-tuning of development. This reinforces the suggestions presuming that miRNAs contribute to the canalization of genetic programs, play a role in stabilizing development by maintaining phenotypic reproducibility of development, differentiation, growth, metabolism, and many other processes (Inui et al. 2010).

As mentioned above, a network is an abstraction of reality and its construction and analysis can

determine the conclusions derived from it. At this point, the type of representation used for the topological analysis acquires special importance. However, we must be aware that PTGR networks should be expected to be highly fragmented due to the differential expression of genes and miRNAs, according to cell types and environmental conditions. Therefore, the interpretations must be taken with due care, taking into consideration the still considerable gaps of knowledge that characterize this emerging field.

Cross-References

- ▶ Bipartite Graph
- ▶ Gene Regulatory Networks
- ▶ MicroRNA Regulation, Feed-Forward Loops
- ▶ MicroRNA-mRNA Regulation Networks
- ▶ Modularity
- ▶ Network Motifs of Gene Regulatory Networks
- ▶ Non-coding RNA
- ▶ Post-transcriptional Gene Networks
- ▶ RNA-Induced Silencing Complex (RISC)

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Microsatellite Repeats

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Synonyms

Short tandem repeats (STRs); Simple sequence repeats (SSRs)

Definition

These are the variations brought about by a variable number of tandemly repeated DNA sequences. The repeat motif is generally two to nine base pairs in length. It is represented as $(CA)_n$ repeat, where n is the variable between alleles. The variable number of repeats is seen due to strand slippage during DNA replication. The variations in repeat numbers are responsible for variable gene expression as well as creating poor and hypermetabolizer phenotypes in individuals. They can be polymorphic in the population (meaning that two individuals in the population would not share the same genetic profile for microsatellite markers) and, hence, used as landmarks on the genome for genotyping populations. They are also extensively used in forensic science.

Cross-References

- ▶ Epigenetics, Drug Discovery

Microspectroscopy

- ▶ Spectroscopy and Spectromicroscopy