miRNA Networks: Motif Prediction, Validation and Therapeutic Implications

Network biology is a conceptual shift from reductionist approaches in molecular signaling[1]. While reductionism has been powerful in elucidating the mechanisms of single events, a network view enables large-scale analysis of dynamic processes such as protein-protein interaction and gene regulatory networks[2]. These biological networks conform to common configurations, known as topologies, that exhibit distinct, emergent characteristics. One characteristic is recurrent arrangements of functional points, or network nodes, and their connecting links. These frequent arrangements are known as motifs. Common motifs include positive and negative feedback loops, as well as feed-forward loops[1].

microRNAs (miRNAs) have emerged as critical network nodes[3]. These small 19-22 nt, non-coding RNAs are endogenously expressed and target 3'-untranslated regions (3'-UTRs) in mRNA transcripts to facilitate inhibition of mRNA translation[4]. Some miRNAs have been identified as having a critical role in cancer by controlling apoptosis, proliferation and differentiation. These *oncomirs* have clinical relevance as diagnostic and prognostic indicators in various tumor types[5]. miRNAs are also intimately connected to transcription factors (TFs) in gene regulation by negating TF induced gene expression and also controlling TF levels in the cell[3].

miRNA and TFs are both key nodes in gene regulation networks. Studies employing a network approach are beginning to show that miRNA-TF interactions frequently form characteristic network motifs. Because of the critical role miRNAs play in these motifs and, as well as in disease, the hypothesis follows that **modulating critical transcription factor-miRNA network motifs is a therapeutic strategy for regulating human diseases**. To address this hypothesis, we consult the literature to determine if particular motifs are overrepresented in miRNA-TF networks, if these motifs exist in human gene regulatory networks, and whether or not targeting these motifs is feasible with emerging therapeutic technologies.

To determine whether or not miRNA-TF network motifs are overrepresented and if they exist in human, we examine studies that employ both informatics and experimental approaches to analyze transcriptional networks. First, Martinez *et al.*[6] provide a global analysis of *C. elegans* transcriptional networks. By using yeast one-hybrid experiments and *in silico* predictions this group shows how the interplay between TFs and miRNAs in the nematode conform to common network topologies, and also the emergence of a novel property, flux capacity, that can be used to predict whether or not a node participates in a network motif. Next, we explore a study by Re *et al.*[7] that uses bioinformatic tools to identify putative feed-forward loops (FFLs) in human. This study reveals the recurrence of FFLs as a frequent network motif containing nodes that control the activity of important transcription factors, and highlights motifs that are connected to cancer. We then turn to an experimental validation of a FFL in a human model that validates a motif in controlling cell proliferation[8]. Finally, we assess the potential for these motifs to be therapeutically exploited and discuss the pros and cons associated with the potential therapies[9,10].

References

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