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PERSPECTIVE

Gene Regulation by Transcription Factors and MicroRNAs

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The properties of a cell are determined by the genetic information encoded in its genome. Understanding how such information is differentially and dynamically retrieved to define distinct cell types and cellular states is a major challenge facing molecular biology. Gene regulatory factors that control the expression of genomic information come in a variety of flavors, with transcription factors and microRNAs representing the most numerous gene regulatory factors in multicellular genomes. Here, I review common principles of transcription factor– and microRNA-mediated gene regulatory events and discuss conceptual differences in how these factors control gene expression.

Transcription factors (TFs) and microRNAs (miRNAs), the largest families of trans-acting, gene regulatory molecules in multicellular organisms, share a common regulatory logic (*1*) (Fig. 1 and figs. S1 and S2). Sets of combinatorially expressed TFs ("TF codes") and miRNAs ("miRNA codes") precisely delineate individual cell types. By binding to discrete cis-regulatory elements, individual TFs and miRNAs can control dozens, if not hundreds, of target genes. Moreover, most, if not all, genes in the genome are controlled not by a single, but by a combination of trans-acting factors (Fig. 1). Many TFs bind cooperatively to their cognate DNA sequences and/or cooperatively recruit transcriptional cofactors (*2*, *3*). Similarly, cooperative action of miRNAs has also been defined through reporter gene assays (*4*). Cooperativity therefore provides the mechanistic basis for reading out combinatorial expression patterns of both TFs and miRNAs (Fig. 1).

Binding site accessibility provides an additional layer of gene regulatory control (Fig. 1). In vivo occupancy of TF binding sites depends on nucleosome coverage of the site, with nucleosome positioning and remodeling being regulated processes (*5*). Similarly, the accessibility of a miRNA recognition site is controlled by a member of a large (>100) family of RRM domain–containing RNA binding proteins (*6*). Other family members may control other miRNA/target interactions. Apart from protein-regulated site accessibility, miRNA binding site accessibility is also controlled by folding of the mRNA target sequences into secondary structures (*7*). Mere coexpression of a miRNA and its mRNA target, therefore, does not always lead to a functional interaction—a notion to be kept in mind when considering computer-predicted miRNA/target interactions.

The Importance of Repression

Whereas TFs are known to positively or negatively regulate transcription, miRNAs appear to regulate gene expression mostly, but not always, through repression (*8*, *9*). Gene repression is an important mechanism to shape cell-specific gene regulatory programs. Broad and non–cell type–specific transcriptional activation events, evoked by broadly expressed TFs, gain specificity through the action of cell type–specific transcriptional repressors, which restrict gene expression to a smaller subset of cells (*1*). Moreover, in many developmental contexts, activating effects of TFs often turn out to be double-negative, derepression effects in which a TF "activates" transcription by repressing expression of a transcriptional repressor (*1*, *10*). The repressive mode of miRNA action therefore fits neatly into the overall importance of gene repression in defining cell-specific gene expression programs.

Regulating Regulators—Networks and Modifications

The ability of TFs to define, either alone or in combination, cell type–specific gene expression programs rests on cell type–specific expression profiles of the TFs themselves. Such profiles are controlled by more upstream layers of gene regulatory programs. Developmental processes can therefore be considered as a succession of hierarchically acting regulatory states (*11*). Consequently, transcriptional regulatory programs have been placed into well-defined regulatory networks that are characterized by specific, small network motifs such as positive and negative feedback and feedforward motifs that endow the system with specific properties such as signal amplification, dampening, persistence detection, and oscillation (*12*). Because the expression of many TFs themselves is subject to miRNA regulation and the cell type–specific expression profiles of miRNAs are brought about largely by conventional TF-dependent transcriptional control mechanisms, it does not come as a surprise that miRNAs and TFs are linked to one another in gene regulatory networks (*13*, *14*). As with TF-only networks, prevalent motifs within these networks include feedforward and feedback loops (Fig. 1 and fig. S2).

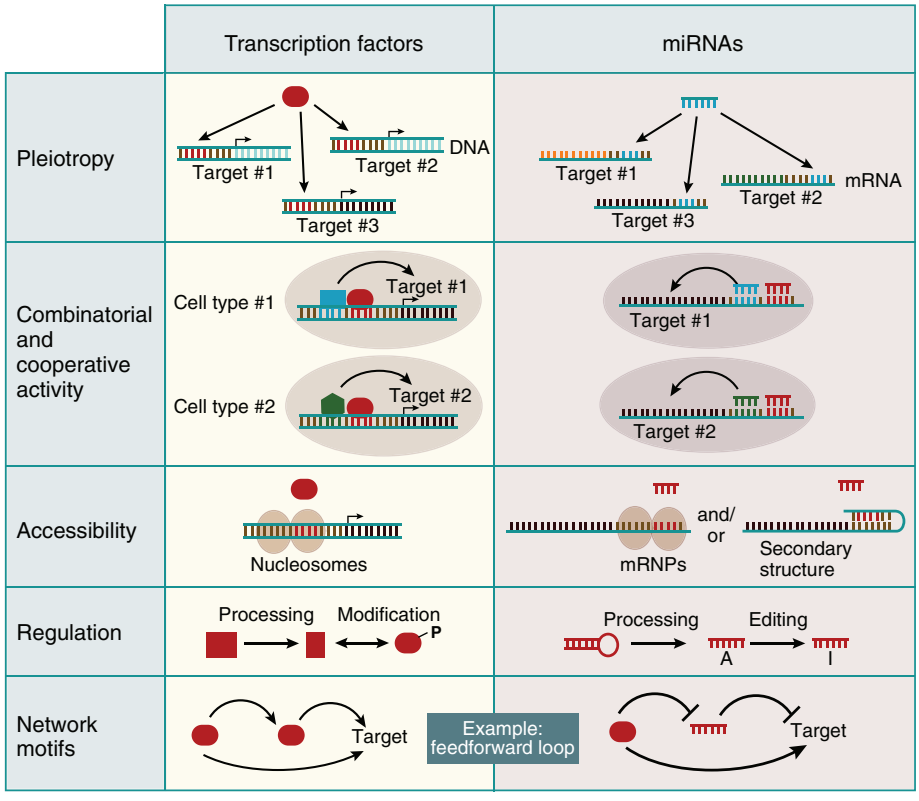

Fig. 1. A schematic visualization of some shared principles of TF and miRNA action. See also fig. S2.

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Besides being regulated at the level of gene expression, TF activity is prominently regulated via posttranslational events such as protein phosphorylation, processing, or localization. miRNA-mediated control of gene expression may also be subject to posttranscriptional regulation (Fig. 1). For example, the processing of miRNAs from their primary transcript to their mature form is subject to regulation in various cell types (*15*, *16*). Modifications of miRNA species by RNA editing also control miRNA activity in a cell type–specific manner (*17*). Posttranslational modifications of additional protein factors involved in miRNA function may introduce an additional layer of regulatory complexity in miRNA function.

Phenotypic Spectrum

The points raised above provide a somewhat biased view in which many features of miRNA- and TF-mediated regulatory events appear quite similar (Fig. 1). But are miRNA and TFs really on par in terms of their importance for gene regulatory events? Genetic analysis in unicellular and multicellular organisms has amply demonstrated the importance of TFs in controlling development and homeostasis (*11*). Elimination of specific animal miRNAs can also produce striking phenotypes in multiple patterning events (*18*). However, the deletion of >80% of individual miRNA loci in *Caenorhabiditis elegans* revealed that less than 10% of miRNA knockouts result in clear developmental or morphological defects (*19*). In contrast, RNA interference–mediated loss-of-function analysis shows that about 30% of all *C. elegans* TF losses cause easily observable phenotypes (*20*). Redundancy between closely related miRNA family members may mask essential functions (*19*), but as exemplified by the miRNA *lsy-6*, which diversifies the functional capacities of two very similar chemosensory neurons (*21*), miRNA use may be more biased toward controlling specific aspects of terminal differentiation programs of individual cell types. In support of this notion, miRNAs tend to have highly cell type–specific expression profiles, both during normal development and in specific disease states, such as cancer (*22*, *23*). Are there intrinsic features of miRNAs that would explain why they may cover a more restricted regulatory niche as compared to TFs?

Unique Features of miRNA-Mediated Gene Regulation

The gene regulatory region of TF targets is often complex and can span dozens of kilobases, whereas miRNA-controlled 3′-untranslated regions are, on average, <1 kb in size (*11*). Not only does this limit the amount of regulatory inputs that a gene can sample from miRNAs versus TFs, but it also provides less substrate for evolution to "play on," i.e., to evolve new regulatory inputs, a major driving force in evolution (*24*). This inherent size restriction may disfavor the evolution of miRNA-dependent gene expression programs. On the other hand, inherent features of miRNA-mediated gene regulation may also provide unique evolutionary opportunities. Whereas, in principle, expression of a gene can become more restricted on an evolutionary time scale by acquiring a novel repressive TF binding site in its promoter, such an acquisition may be constrained by features of the transcriptional activation program. For example, evolving a negative regulatory input into a promoter that is combinatorially activated by several distinct transcriptional activators may be mechanistically more difficult—and evolutionarily more improbable—than evolving a miRNA input into the mRNA product of the transcriptional event. By acquiring a miRNA binding site or evolving a novel miRNA gene de novo that matches a given mRNA, evolution is essentially provided with an independent opportunity to diversify a gene expression program. In sum, the fact that miRNAs can only serve to further modify transcriptional programs—because they require an mRNA substrate to work on—and the more restricted size of their regulatory control regions may explain the more restricted phenotypic spectrum of miRNAs compared to TFs.

Speed and reversibility are other distinguishing features of miRNA-mediated gene regulation that may result in a more specialized regulatory niche of miRNAs. For transcription to be repressed, a sophisticated machinery needs to be set in place in a subcellular compartment—the nucleus—that is distinct from the production site of the protein product, the cytoplasm. The stability of already transcribed mRNA species sets another limit to the speed with which transcriptional repression can wipe out the expression of a target gene. In contrast, miRNAs can rapidly turn off protein production right at the site of protein production, the ribosome. Another factor that speeds up miRNA-mediated control of gene expression is that, owing to their small size and noncoding nature, miRNAs may be produced more rapidly than TFs, thereby decreasing response times to stimuli that induce gene repression. Lastly, a miRNA-repressed target can also be reactivated more rapidly than a transcriptionally repressed target, because such reactivation may merely involve the translocation of an already present mRNA to an active ribosome (*25*–*27*).

Another important conceptual difference between miRNA- and TF-mediated gene regulation is that miRNA action can be compartmentalized within a cell to rapidly alter gene expression locally. For example, highly compartmentalized neurons face the challenge of translationally regulating gene expression on a synapse-specific, rather than cell-wide, level (*28*). TFs cannot provide such subcellular specificity in their regulatory effects. In contrast, ribosomes, the likely site of miRNA action, distribute to various subcellular compartments, including the synapse, thereby providing potential subcellular resolution for miRNA-mediated regulatory control. miRNAs have indeed been recently implicated in synapse-specific functions (*26*, *27*). Taken together, speed, reversibility, and compartmentalization of miRNA-mediated control mechanisms predestine miRNAs to be involved in rapid, adaptive changes in gene expression to maintain homeostasis and to respond to specific environmental, nutrient, or neuronal signals.

In conclusion, TFs and miRNAs share many similarities and are broadly used in many different contexts. However, specific features of miRNA function may bias their use into more specialized regulatory niches, a notion that requires confirmation through detailed and comprehensive analyses of miRNA gene knockouts in the future.

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Supporting Online Material

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Figs. S1 and S2

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