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MicroRNAs and the butterfly effect

Gerald W. Dorn II*

Center for Pharmacogenomics; Department of Internal Medicine; Washington University School of Medicine; St. Louis, MO USA

MicroRNAs are nature's dimmer switches for protein translation. When expressed in sufficient abundance, these single-stranded small RNAs bind to complementary nucleotide sequences in the 3' untranslated regions of target mRNAs and direct them to RNA-induced silencing complexes (RISCs) for translational suppression and degradation.[1] Although much has been learned about the molecular mechanisms of microRNA activity, understanding their system-wide effects has lagged. Thus, striking end-organ phenotypes provoked by artificial manipulation and/or natural regulation of a given microRNA are not readily explained by modest in vivo suppression (typically 30–50%) of direct mRNA targets.[2] Our laboratory has gained insight into this issue using whole-genome microRNA, mRNA and RISC sequencing to examine the global consequences of microRNA-mRNA interactions in a model of stress-adaptation, the early cardiac response to pressure overload:[3] Deep sequencing identified approximately 370 cardiac-expressed microRNAs and approximately 8,500 cardiac-expressed mRNAs. Although bioinformatics has indicated that one-third of all mRNAs are potential microRNA targets,[4] deep sequencing of mRNAs captured within microRNA RISC complexes (RISC-Seq)[5] revealed that only ~1,200 of the 8,500 cardiac-expressed mRNAs (e.g., ~15%) were being directly targeted by cardiac microRNAs. Likewise, in our studies the steady-state abundance of > 600 cardiac microRNAs was significantly altered by acute hemodynamic stress, but only 63 (~10%) of these appeared to be directly targeted and regulated by microRNAs.[3] Given the modest effects of microRNAs on suppression of their direct mRNA targets and the limited number of mRNAs that are directly targeted by microRNAs in vivo, the overarching question that arises is, "What is the role of microRNAs in stress adaptation?"

The apparent paradox of limited microRNA direct activity exerting dramatic systemic effects echoes the famous question posed by Edward Lorenz at the 139th Annual Meeting of the American Association for the Advancement of Science (1979): "Does the flap of a butterfly's wings in Brazil set off a tornado in Texas?" (This lecture, describing a real-world application of mathematical chaos theory, was based on Lorenz's seminal description of the unexpected sensitivity of computer weather simulations to fractional variability in numerical inputs).[6] The answer to both questions is the same: microRNAs (and butterflies) are optimally positioned to alter processes whose end-effects are exquisitely sensitive to the initial conditions. While microRNAs may seem to be peripheral "fine-tuners" of cell biology (not being enzymes, structural cell components or biochemical signaling factors), their incomplete suppression of direct mRNA targets helps define the initial conditions of critical cell pathways directing, for example, metabolism and proliferation, cell morphometry and migration and stress response. Regulated microRNA expression levels, as during a tissue stress response, induce small changes in initial conditions that are sequentially amplified through secondary and higher-order interactions, producing a systemic ripple effect that ultimately invokes disproportionately large (and frequently unanticipated) phenotypes. Our study describes one molecular mechanism that explains this microRNA butterfly effect: preferential stress-regulated microRNA targeting of transcriptional and post-translational pathways whose effects resonate system-wide through indirect modulation of gene expression and protein function. Because a major end-organ effect of microRNAs is indirect regulation of pathways that orchestrate gene expression, we called this systemic microRNA behavior "epitranscriptional regulation."[3]

As microRNAs are products of transcription subject to many of the same regulatory influences as mRNAs, stress-regulation of microRNAs does not occur in isolation. Rather, levels of a given microRNA are increased or decreased in the context of regulated expression of other microRNAs and of their respective mRNA targets. Thus, the aggregate effects of regulated microRNAs within multiply interactive biochemical pathways rapidly achieves extreme complexity when viewed from the perspective of thousands of primary, secondary and tertiary molecular interactions. By contrast, when viewed at the whole cell, organ or organism level, specific microRNAs reproducibly elicit system-wide biological behavior that derives from comparatively straightforward rules of microRNA target selection and suppression. Even though there are aspects to these rules that are not yet fully understood (such as the effects of seed and non-seed sequence mismatches on thermodynamic stability of microRNA-mRNA duplexes),[7] and the possible biological outcomes can vary depending upon initial conditions (e.g., microRNA and mRNA expression levels), the systemic behavior is chaotic rather than stochastic. In other words, it is complicated, but not random, and therefore can be predicted. From this perspective (i.e., that of the entire woods rather than the proverbial individual tree), a specific focus on one or a few microRNA-mRNA target interactions tends to ignore the characteristic multidimensional molecular and systemic consequences of microRNA

*Correspondence to: Gerald W. Dorn; Email: gdorn@dom.wustl.edu
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activity. Extreme reductionism will not only provide incomplete, but possibly misleading, mechanistic models. Our results suggest that, rather than artificially assigning special importance to suppression of one or a few direct mRNA targets and protein products, microRNA activity is better assessed through characterization of end-organ phenotypes complemented by genome- and/or proteome-wide analyses of the relevant pathways and penultimate responsible molecular events.

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