MicroRNAs (miRNAs) are short, noncoding RNA molecules capable of regulating gene expression at transcription and translation levels (1). Conserved throughout evolution, miRNAs participate in fundamental biologic processes including cell cycle, differentiation, development, metabolism, patterning, and aging. The human genome contains approximately 1000 miRNAs that are estimated to regulate a third of all genes. These regulatory molecules originate, by transcription of distinct genes in the noncoding portions of chromosomes, as precursor RNA molecules containing hundreds to thousands of nucleotides, which undergo distinct nuclear and cytoplasmic processing. Specifically, miRNAs originate in the nucleus as pri-miRNAs, precursors transcribed by RNA polymerase II (Fig. 1). Subsequently, cleavage by a ribonuclease III called Drosha and the double-stranded DNA binding protein DGCR8/Pasha generates a hairpin-shaped premiRNA. These intermediates are transported by the nuclear export factor exportin 5/Ran GTP into the cytosol, where they are processed into 19- to 25-nucleotide miRNA duplexes by the ribonuclease III Dicer, in association with the transactivation-responsive RNA-binding protein. These duplexes incorporate as the targeting core of RNA-induced silencing complexes, inducing translational inhibition by cleavage and degradation of messenger RNA or by blocking translation, thereby defining the pool of available genes (1). In this way, miRNAs represent an increasingly recognized component in the multidimensional complexity characterizing information processing at the interface of nucleus and cytoplasm. Importantly, their function has provided novel insight into the integrated genetic circuitry specifying cell fate.

Commonly, miRNAs are located in cancer-associated genomic regions, including minimal regions of amplification, loss of heterozygosity, fragile sites, and common breakpoint regions in or near oncogenes or tumor suppressor genes (1). There is increased evidence in human tumors of abnormal expression of miRNAs that have been assigned oncogenic and/or tumor suppressor functions. Although some miRNAs commonly exhibit altered expression across tumors, more often different tumor types express unique patterns of miRNAs, referable to their tissues of origin. In fact, patterns of miRNA expression appear to be a richer source of pathognomonic tumor information.
than messenger RNA expression profiling. The role of miRNAs in tumorigenesis underscores their value as mechanism-based therapeutic targets in cancer. Similarly, unique patterns of altered microRNA expression provide complex fingerprints that may serve as molecular biomarkers for tumor diagnosis, prognosis of disease-specific outcome, and prediction of therapeutic response (2).

The potential value of miRNAs as prognostic and predictive biomarkers in cancer is elegantly highlighted in the recent work of Schetter et al. (3), who compared miRNA expression patterns in colon adenocarcinoma and adjacent normal tissue using a test set and validation cohorts. Specific miRNA signatures distinguished colon cancer from normal colon, and a subset of miRNAs was further demonstrated to exhibit prognostic value. In particular, one specific species of miRNA, miR-21, was expressed in 87% of patients with colon cancer and was revealed as an independent prognostic marker of poor survival (3). In addition, high miR-21 expression predicted worse survival in treated colon cancer patients and poor responsiveness to adjuvant chemotherapy. Beyond prognosis and prediction, miRNAs associated with neoplastic transformation may mediate pathophysiological mechanisms underlying tumorigenesis. Indeed, miR-21 may play a role in tumor growth, invasion, and metastasis by targeting multiple tumor/metastasis suppressor genes (4). These studies of miRNA profiles in colon adenocarcinoma reinforce the utility of these biomarkers in defining the molecular taxonomy of tumors. Similarly, they highlight the potential of miRNA profiling for defining prognosis, stratifying risk, and identifying low- and high-risk populations of patients with cancer. Moreover, they underscore the potential value of miRNAs as mechanism-based therapeutic targets in cancer, an unmet need in the management of colon cancer, the second leading cause of cancer-related mortality (1–3).

The utility of miRNAs as prognostic and predictive markers accentuates the future practice of medicine, reflecting the beginning of the continuum integrating discovery, development, regulatory review, and evidence basis of medicine required to translate advanced technology into clinical practice (5). Whereas marker discovery has driven biomedical innovation, systematic validation to define performance metrics, including reproducibility, sensitivity, and precision, is required for broad application. Moreover, analytes can be evaluated using different platforms whose performance and compatibility have not been verified. The absence of assay performance metrics reflecting standardization underlies issues of reproducibility that undermine uniform clinical application. In the case of miRNAs, analyses have been performed historically on microarray or bead-based platforms (2). More recently, quantitative reverse transcription PCR, Northern analysis, and in situ hybridization have been adapted to quantify miRNAs. Although results from microarray and bead analyses generally concur, the challenge remains to cross-validate performance metrics of analytical platforms. Similarly, quantitative and qualitative relationships between biomarkers, patient management, and disease outcomes have not yet undergone clinical qualification. Ultimately, relationships defining the clinical utility of a biomarker should be assessed in appropriately designed and powered prospective blinded and randomized clinical trials, and subsequently validated in follow-up trials.

Regulation by miRNAs is fundamental to the integrated organization of gene expression. Corruption of miRNA-dependent regulatory circuits contributes to the genetic dysfunction underlying neoplasia. The discovery of unique patterns of miRNA expression in colon cancer (3) and other tumors (1) offers the opportunity to develop biomarkers for diagnosis, prognosis, and prediction in cancer. These considerations emphasize a central role for clinical chemistry in accelerating the discovery-to-translation of miRNA panels for clinical application.

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