Gene expression profiling in patients with multiple myeloma has identified gene signatures linked to prognosis. However, because of their heterogeneity, there is currently no consensus about which signatures represent the best predictive and prognostic markers. Novel computational tools are now helping investigators integrate heterogeneous data sets to identify universal and robust classifiers. *Clin Cancer Res; 17*(23); 7210–2. ©2011 AACR.

In this issue of *Clinical Cancer Research*, Agnelli and colleagues (1) report an ingenious application of the ARACNe algorithm (Algorithm for the Accurate Reconstruction of Cellular Networks) to disentangle critical nodes underlying the gene regulatory networks that drive the hematologic cancer known as multiple myeloma. Of importance, these authors were able to identify robust prognostic signatures across these independent data sets irrespective of the patient population, treatment modalities, and technological platform used for gene expression analysis.

Multiple myeloma, the second most frequent hematologic cancer in the United States, is a hematologic tumor characterized by clonal proliferation of neoplastic plasma cells in the bone marrow in association with elevated serum and/or urine monoclonal protein levels. Clinical manifestations may include lytic bone lesions, anemia, immunodeficiency, and renal impairment. Although it remains incurable in the vast majority of patients despite conventional high-dose chemotherapy with stem cell support, novel agents, including the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib, can achieve therapy with stem cell support, novel agents, including the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib, can achieve responses in patients with relapsed and refractory multiple myeloma. Moreover, these agents have now been incorporated into initial, consolidation, and maintenance strategies, with a consequent doubling of the median survival (2).

Multiple myeloma is a heterogeneous disease. Specifically, groups of patients can be subdivided into different prognostic subgroups based on the presence of specific genetic lesions in multiple myeloma cells, such as mutations of critical genes, chromosomal translocations, and gains or losses of whole chromosomes (or portions of them). Because most modifications at the DNA level can be accurately recounted by specific gene expression profiling (GEP) features (3), GEP has emerged as a comprehensive, highly sensitive approach for classifying patients with multiple myeloma. It can also identify subclasses of patients who show dysregulated expression of specific genes, such as cyclins, but lack chromosomal or sequence aberrations (4). In the past few years, investigators have derived hundreds of GEP profiles using multiple myeloma samples from patients participating in clinical trials around the world. These efforts led to the identification of gene signatures that can be used to distinguish patient subpopulations based on their prognostic outlook, including the UAMS 17-gene (5), IFM-15-gene (6), and myeloma IX 6-gene (7) classifiers. Disappointingly, even a cursory analysis of these studies shows that few genes, if any, are shared. As Dimopoulos and colleagues (8) recently noted, it is necessary to thoroughly gauge and assess the role of these classifiers and reach a consensus about which genes should be examined at the expression level before comprehensive GEP can be introduced into general clinical practice. The current study by Agnelli and colleagues (1) is an important step in this direction because it distills a few testable markers that appear to be highly relevant for the pathogenesis of multiple myeloma, are related to prognosis, and are independent of the assay platform and therapeutic protocol used (Fig. 1).

In their study, Agnelli and colleagues applied ARACNe across 7 publicly available multiple myeloma GEP data sets. This methodology is based on the theory of hierarchical, scale-free networks that was pioneered by Albert Barabási (as reviewed in ref. 9). In contrast to the established view posited in 1959 by mathematicians Paul Erdős and Alfréd Rényi that interconnected systems such as biologic networks are randomly wired together, Barabási postulated that certain real-life networks (e.g., the Internet and social networks) are organized around hubs (or nodes). In biologic systems, hubs are defined by genes that play central roles in cell physiology, such as the tumor suppressor TP53 (10). Of importance, modulation of these hubs by targeted therapies may uncover crucial liabilities for cancer cells. Building on this notion, ARACNe can identify statistically significant gene–gene coregulation while at the same time computationally eliminating indirect relationships between genes; thus, it can identify causal rather than associative interactions (11). This compiled
network provided by ARACNe is, therefore, a streamlined view of the most relevant nodes in the cell and their mutual connections. In comparison with other algorithms, a major advantage of ARACNe, and a critical asset highlighted in this study, is that it gives researchers the ability to analyze data from different sources. Indeed, ARACNe can be applied not only to GEPs from different platforms and patient populations, as described here, but also to any data set that contains interacting measurements, such as microRNAs (miRNA), proteins, and metabolites (11).

By sifting through 1,883 GEP profiles, Agnelli and colleagues were able to identify a restricted list of genes with a critical role in multiple myeloma. Reassuringly, cyclins D1 and D2, as well as WHSC1 and FGFR3, which have known roles in multiple myeloma pathogenesis, were among the most critical hubs identified across all data sets. The authors went on to test the prognostic relevance of the dysregulated expression of these genes across different patient populations, with the goal of designing a prognostic signature built on these nodes.
A model that included 4 probe sets (corresponding to FAM53B, KIF21B, WHSC1, and TMPO genes) emerged that was effective in discriminating prognostically distinct patient subgroups in all studies. Moreover, the authors showed that, in addition to the nodes themselves, the genes at the juncture between these nodes can provide critical pathogenetic and prognostic information. Using both the hubs and the neighboring genes shared by the hubs, they successfully identified a signature that was strongly linked with prognosis and was based on only 2 genes (CSGALNACT1 and SLC7A7). Of note, by testing this signature across different patient populations, they successfully distinguished patients with dissimilar prognostic outcomes, independently of the treatment modalities used. In addition, in multivariate analysis, both signatures showed their independence from other established prognostic signatures.

We anticipate 3 major applications of this methodology in the multiple myeloma field: First, the introduction in recent years of several novel U.S. Food and Drug Administration–approved drugs is redefining the prognostic and predictive significance of established markers, such as t(4:14), that apparently are less relevant in patients treated with bortezomib (3). Some of the prognostic signatures derived from GEP may also become obsolete once novel treatments based on different mechanisms of action are implemented. The flexibility of ARACNe will enable researchers to identify novel prognostic and predictive markers across studies of novel therapies and thus facilitate the rapid implementation of assays to guide the selection of appropriate therapeutic options for newly diagnosed patients.

Second, recent studies have delineated important roles for miRNAs in multiple myeloma pathogenesis, and novel technologies such as high-throughput proteomic analyses, whole-genome sequencing, and RNAseq are providing new, massive, orthogonal data sets. ARACNe seems ideally suited for integrating these new data into the existing framework based on GEP, thereby providing much-needed insights into the prognostic significance of miRNAs and the role they play in the pathogenesis of multiple myeloma.

Finally, ARACNe has provided essential insights into the process of carcinogenesis in other cancer types, for example by highlighting the importance of C/EBPβ and STAT3 transcription factors in glioblastoma multiforme (12). Most importantly, the major obstacle to obtaining personalized medicine that is closely tailored to the molecular features of an individual patient’s tumor remains computational. The information provided here by Agnelli and colleagues about the hubs in multiple myeloma represents an invaluable tool for both identifying the hallmark abnormalities that drive multiple myeloma pathogenesis and targeting them more effectively.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Disentangling the Myeloma Web

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