Title: Disentangling the myeloma web

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Running title, ARACNe in Multiple Myeloma

Summary:

Gene expression profiling in multiple myeloma patients have identified gene signatures linked to prognosis. However, due to their heterogeneity, no consensus has been reached on the best predictive and prognostic markers to be used. Novel computational tools are now helping to integrate heterogeneous datasets to identify universal and robust classifiers.
Main text

In this issue of *Clinical Cancer Research*, Agnelli et al used an ingenious application of the ARACNe algorithm to disentangle critical nodes underlying the gene regulatory networks which drive the hematological cancer Multiple Myeloma (MM). Importantly, these authors have successfully identified robust prognostic signatures across these independent datasets irrespective of patient population, treatment modalities, and the technological platform used for gene expression analysis (1).

Multiple Myeloma (MM), the second most frequent hematological cancer in the US, is a hematological 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, anaemia, 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 immunomodulatory agents thalidomide and lenalidomide as well as the proteasome inhibitor bortezomib can achieve responses in patients with relapsed and refractory MM. Moreover, these agents have now been incorporated into initial, consolidation, and maintenance strategies, with a consequent doubling of the median survival (2).

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

These authors have applied ARACNe (Algorithm for Accurate Reconstruction of Cellular Network) across seven publicly available MM GEP datasets. This methodology is based on the theory of hierarchical scale-free networks, pioneered by Albert Barabási (9). In contrast to the established view posited in 1959 by mathematicians Pál Erdős and Alfréd Rényi that interconnected systems like biological networks are randomly wired together, Barabási postulated in his scale-free network theory that several real-life networks, as is true for the internet and social networks, are organized around hubs (or nodes). In biological systems, hubs are defined by genes exerting central roles in cell physiology, such as the tumor suppressor TP53 (10). Importantly, modulation of these hubs by targeted therapies may uncover crucial liabilities for cancer cells. Building upon this notion, ARACNe identifies statistically significant gene-gene coregulation, while at the same time computationally eliminating indirect relationships between genes; 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. When compared with other algorithms, a major advantage of ARACNe, and a critical asset evidenced in this study, is 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 containing interacting measurements, such as microRNAs, proteins, metabolites and so on (11).

Sifting through 1883 GEP profiles, Agnelli et al. here have identified a restricted list of genes with a critical role in MM. Reassuringly, cyclins D1 and D2 as well as WHSC1 and FGFR3, with known roles in MM pathogenesis, were among the most critical hubs identified across all datasets. 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 upon these nodes. A model including five probe sets (corresponding to FAM53B, KIF21B, WHSC1, TMPO, and TXNDC13 genes) emerged, which was effective in discriminating prognostically distinct patient subgroups in all studies. Moreover, the authors further showed that not only the nodes themselves, but also genes at the juncture between nodes, represent critical pathogenetic and prognostic information. Using not only the hubs, but also these neighboring genes shared by the hubs, they successfully identified a signature strongly linked with prognosis which was based upon only two genes, CSGALNACT1 and SLC7A7. Importantly, testing this signature across different patient population successfully distinguished patients with dissimilar prognostic outcomes, independent of the treatment modalities. In addition, in multivariate analysis both signatures demonstrated their independence from other established prognostic signatures.

We anticipate three major applications of this methodology in the MM field. First, the introduction in recent years of several novel FDA-approved drugs is redefining the prognostic and predictive significance of established markers such as t(4:14), apparently 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. ARACNe flexibility will swiftly identify novel prognostic and predictive markers across studies of novel therapies,
and thereby help to provide for the rapid implementation of assays to guide selection of appropriate therapeutic options for newly diagnosed patients.

Second, recent studies are delineating important roles for miRNAs in MM pathogenesis, and novel technologies such as high-throughput proteomic analyses, whole-genome sequencing and RNAseq are providing new, massive, orthogonal datasets. ARACNe seems ideally suited to integrate these new data into the existing framework based upon GEP, thereby providing much-needed insights into their role in MM pathogenesis and prognostic significance.

Finally, ARACNe has provided essential insights into the understanding of carcinogenesis in other cancer types, such as highlighting the importance of C/EBPβ and STAT3 transcription factors in Glioblastoma Multiforme (12). Most importantly, the major obstacle to obtaining personalized medicine which is closely tailored to the molecular features of individual patient’s tumor remains computational. Exploiting the knowledge of the hubs defined here in MM (1) represents an invaluable tool to both identify hallmark abnormalities driving MM pathogenesis and to target them more effectively.

References:


Several studies have examined the gene expression profiling of MM patients. However, no consensus has been reached concerning gene signatures able to prognostically classify patients, due to heterogeneity in the technological platforms utilized, in the patient population and in the treatment protocols. The computational tool ARACNe could overcome these limitations, providing critical information not only on prognostic and predictive markers but also on the mechanisms responsible for the pathogenesis of the disease. Within each network, red indicates critical nodes/hubs, blue neighboring genes shared between networks.
Prognostic and predictive signatures

Disease mechanisms

Cumulative survival

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