A three miRNA-classifier as a new prognostic tool in mycosis fungoides

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Comment on: Lindahl LM, Besenbacher S, Rittig AH, *et al.* Prognostic miRNA classifier in early-stage mycosis fungoides: development and validation in a Danish nationwide study. Blood 2018;131:759-70.

Received: 22 May 2018; Accepted: 20 June 2018; Published: 21 June 2018.

doi: 10.21037/jlpm.2018.05.07

View this article at: http://dx.doi.org/10.21037/jlpm.2018.05.07

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL), corresponding approximately 50% of all lymphomas originated in the skin (1). The disease commonly presents an indolent clinical course but some patients progress to more advanced stages with an aggressive behavior. Different studies have provided information in the comprehension of the molecular pathogenesis of MF and identified probable prognostic markers some of them possible targets for future therapeutic intervention (2-5). Interestingly, patients with genomic imbalances have shown shorter overall survival, supporting an association of genomic instability and worse clinical outcome. However, genetic aberrations did not appear to be sufficient to explain the molecular complexity of MF biology and epigenetic changes emerge as another important factor.

In this context, results of interest the study of microRNAs (miRNAs), a type of small noncoding single-stranded regulatory RNAs of ~22 nucleotides that negatively regulate gene expression by mRNA degradation and/or translational interference (6). They are involved in different biological processes, including cell growth and proliferation, differentiation, development, metabolism and apoptosis. MiRNA deregulation has been associated with the pathogenesis of several diseases and cancer development, including solid tumors and hematological malignancies (7). Some miRNAs are located in chromosome regions related to cancer and causally implicated in oncogenesis, acting as tumor suppressor genes or oncogenes. In addition, a subset of miRNAs has specific epigenetic functions. Thus, they participate in the epigenetic regulation of multiple biological processes as well as in the control of the expression of important epigenetic regulators, cooperating to determine the gene expression profile of different types of cells, including malignant cells (8).

Several reports have focused on the identification of miRNA differential profiles in MF patients and demonstrated significant differences compared to inflammatory benign skin biopsies as well as between early and advanced stages, suggesting a role of aberrant miRNA expression in the development and progression of this disease (5,9-11). Furthermore, few reports found an association between different miRNA expression profiles and the prognosis of MF (12,13). Most studies have analyzed tumoral MF (9,14-16) and only two reports include the evaluation of other histological variants, like folliculotropic MF (5,16). The number of miRNAs analyzed varies widely among the studies and the results are not completely concordant, situation that could be related with the characteristics of different cohorts analyzed. Furthermore, some miRNAs, like miR-155, appears as particularly involved in tumor progression in MF (5,9,10,13).

As known, MF is an indolent disease with a favorable prognosis but in some patients the disease progress in a multistep process from patches and plaques to tumor development (1,17). Although clinical classifications have been very useful in guiding disease management and treatment decisions, they are not accurate enough to predict

patient outcome at early-stage disease and new diagnostic tools are needed to identify cases that are at risk of disease progression. This determines the search for new parameters focusing research on the identification of biological markers capable to detect which patients will have an aggressive behavior with higher risk of progression and probable need a more severe treatment at the time of diagnosis. In this context, in a recent report, Lindahl *et al.* (18) have evaluated miRNA expression profiles in a very well characterized cohort of 154 Danish patients with early-stage MF and 20 age- and sex-matched healthy controls, using a quantitative reverse transcription polymerase chain reaction (qRT-PCR) miRNA panel covering 384 human miRNAs. Interestingly, a combination of three miRNAs: miR-106b-5p, miR-148a-3p and miR-338-3p, was selected as the best discriminator between MF patients at high or low risk of disease progression at diagnosis. In addition, a significantly decreased overall survival (OS) was observed in the group of patients with poor prognosis according to the three-miRNA classifier compared to those with low risk of disease progression. In addition, this miRNA classifier was detected as an independent predictor of disease evolution from early to advanced stage MF and OS at diagnosis. This very interesting approach adds prognostic value to the known clinical prognostic factors of this disease, allowing the earlier detection of high risk patients, being of importance in the way to a personalized medicine. However, to date there are some difficulties to apply miRNA analysis as a routine diagnostic test in all laboratories, which complicate its translation into clinical practice.

There are some previous miRNA classifiers reported in the literature. Among solid tumors, a six-miRNA-based classifier were described in patients with colon carcinoma (19), being a useful tool to discriminate cases with stage II into groups with low and high risk of disease recurrence. Furthermore, Brand *et al.* (20) identified a five-miRNA expression classifier capable to detect pancreatic ductal adenocarcinoma that might aid in the diagnosis of this pathology. In reference to non-Hodgkin lymphomas, a three-miRNA classifier including miR-155, miR-203 and miR-205, that discriminate between CTCL and benign inflammatory skin diseases was described (21). In addition, Goswami *et al.* (22) found that the combination of miRNAs and current clinical indicators, like Ki-67 and MIPI (international prognostic index), may add prognostic information in patients with mantle cell lymphoma (MCL). More recently, Roisman *et al.* (23) explored the transcriptional profiles of SOXC and miR-17-92 clusters in this pathology, revealing two subsets of MCL with significant differences in important clinical variables, such as blastoid morphological variant, nodal presentation, CD5 positivity and OS, contributing to distinguish MCL patients with aggressive and indolent outcome. These results support the important role of miRNA expression in cancer development and evolution.

Particularly, the new findings described by Lindahl *et al.* (18) constitute a novel prognostic tool for early stratification of MF patients in different groups of disease progression, contributing to the understanding of MF pathobiology. Simultaneously, these findings may have an impact on the care of MF patients, with possible importance in treatment decisions, and could also serve as potential therapeutic targets in the future.

Acknowledgments

Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Dao-Jun Hu (Department of Clinical Laboratory, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Chongming Branch, Shanghai, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2018.05.07). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2018.05.07
Cite this article as: Slavutsky I. A three miRNA-classifier as a new prognostic tool in mycosis fungoides. J Lab Precis Med 2018;3:56.

