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## miR-155 expression in Primary Cutaneous T-Cell Lymphomas (CTCL)

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Mycosis fungoides (MF) and Sezary syndrome (SS) represent around 70% of cutaneous T-cell lymphomas (CTCL).<sup>1,2</sup> Several hypothesis have been proposed to explain their etiopathogenesis, but to date, the role of miRNAs –a class of short length double strand genome-encoded RNAs produced to repress posttranscriptionally the expression of cellular mRNAs– in CTCL is largely unknown.

miRNA expression in CTCL is a matter of debate in the literature; some authors demonstrated an up-regulation of miR-21, miR-214 and miR-486 in SS,<sup>3,4</sup> while in other studies the majority of SS-associated microRNAs resulted downregulated.<sup>5</sup>

We performed miR-155 analysis on MF/SS patients to evaluate the MIR expression pattern with the aim of identifying differences with normal subjects and get further insights into the molecular pathogenesis of these diseases.

Peripheral blood mononuclear cells were obtained from 42 CTCL (23 MF and 19 SS) patients. The diagnosis of CTCL was made according to standard clinical and immunopathological findings.<sup>6</sup> Among the 19 patients with peripheral blood involvement (stage IVA1, all affected by SS), evaluated on whole blood by means of flow cytometry, the amount of circulating atypical cells ranged from 18% to 98% of total lymphocytes (median 69%). All SS patients showed an identical clone in both skin and blood. Results were compared with those obtained in a cohort of 20 healthy donors from the same geographical area, matched for sex and age.

The expression of miR-155 was measured using the cycle quantification (Cq) value, the fractional cycle number at which the fluorescence of each sample passed a fixed threshold. The fold change was calculated using the equation  $\text{fold change} = 2^{-\text{DCq}}$ . Mann–Whitney test was employed for the results analysis.

The 42 MF/SS patients enrolled were diagnosed, treated and followed up at Dermatologic Clinic of the University of Turin. Patients (28 males and 14 females) presented with different clinical stages, including early- (9 stage IA, 4 stage IB, 5 stage IIA) and advanced-phase disease (5 stage IIB) and 19 stage IVA1 (SS patients). Median age was 70 years (range 41–101). All patients were receiving an active treatment depending on their stage, ranging from skin-directed to systemic treatments.

miR-155 was significantly over-expressed in SS patients when compared with healthy donors ( $P = 0.0004$ ) and MF (Fig. 1a,b). No differences in the overall amount of miR-155 were found in MF when compared with healthy subjects. miR-155 levels increased from early (IA–IIA) to advanced (IIB–IVA1) stages ( $P = 0.0084$ )

(Fig. 2). Moreover, in patients with peripheral blood involvement (stage IVA1), no differences were found in miR-155 levels regarding age, gender and type of treatment. Our data show that SS is characterized by an over-expression of miR-155 sequences in blood compared to MF. In contrast to Van Kester and colleagues, we did not find any correlation between upregulated miR-155 in MF patients and healthy control;<sup>7</sup> otherwise, it must be considered that the detection technique for quantification of miRNAs is extremely variable in different papers. Recent data demonstrated that MF and SS patients differ in gene expression profiles; in addition, Campbell and colleagues recently suggested that MF and SS arise from different T-cell subsets, underlining the different molecular pathogenesis.<sup>8-10</sup>

Actually, no differences in miR-155 expression levels according to clinical stage and number of circulating Sezary cells were found, even if the small number of our series limited the statistical power.

These data suggest that microRNAs are important in SS pathogenesis and could provide new options for disease diagnosis and for clinical outcome definition. It should be interesting to evaluate the presence of miR-155 amplification in both lesional skin and blood of the same patient to ascertain the possible existence of a CTCL-specific miRNA transcription profile.

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Caption Figure

Figure 1 (a, b) miRNA-155 expression in MF/SS.

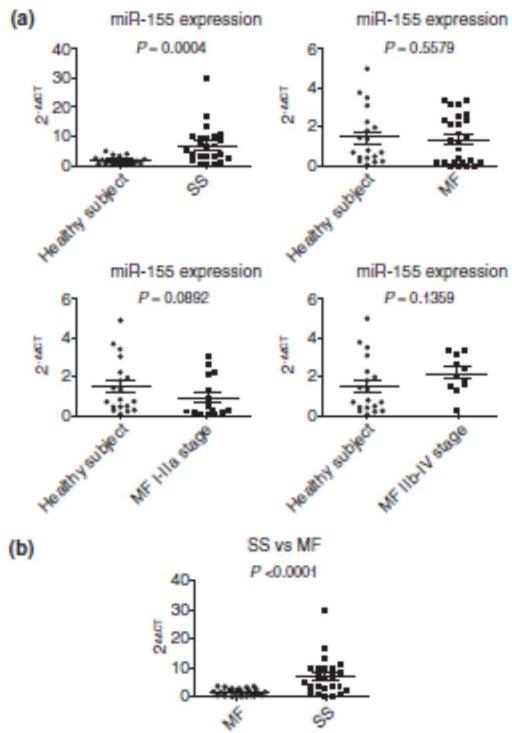


Figure 2 miRNA-155 expression among MF disease stages.

