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RESEARCH

# Altered MicroRNA Expression in Folliculotropic and Transformed Mycosis Fungoides

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**Abstract** Mycosis fungoides (MF) is a common, indolent primary cutaneous T-cell lymphoma (CTCL), with rare, more aggressive variants, such as folliculotropic MF (FMF). A minority of the MF cases may undergo large cell transformation (T-MF) associated with poor prognosis. A selection of microRNAs (miRs) contribute to the pathogenesis and progression of classic MF, and may also be useful in differential diagnostics. However, the molecular background of FMF and the mechanisms involved in large cell transformation are obscure. We analyzed the expression of 11 miRs in 9 FMF and 7 T-MF cases. Three miRs, including miR-93-5p, miR-181a and miR-34a were significantly upregulated in both FMF and T-MF. FMF also showed overexpression of miR-155 and miR-223, while miR-181b and miR-326 were overexpressed in T-MF cases compared to controls. These results by identifying a number of differentially expressed microRNAs add further insight into the molecular pathogenesis of folliculotropic MF and large cell transformation of MF.

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## Introduction

Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma (CTCL), representing approximately 50% of all CTCL cases. Generally, the conventional Alibert-Bazin type MF is a slowly progressive disease of the adults and the elderly, with favourable prognosis and survival of 10–35 years [1, 2] [3]. Folliculotropic MF (FMF) is a rare and more aggressive variant of the disease with 10 to 15 years median overall survival. Clinically FMF is characterized by a predilection for the head and neck region, the malignant lymphoid cells invade hair follicles and eccrine sweat glands with mild or no epidermotropism [1] [4]. A minority of the MF cases may undergo large cell transformation (T-MF) which is characterized by an aggressive clinical course, refractoriness to treatment and a median survival of 24 months [5, 6].

Despite MF is the most prevalent form of CTCLs, the pathogenesis and molecular characteristics remain largely unknown. Although multiple molecular changes, including chromosomal, genomic and gene expression aberrations, as well as altered microRNA (miR, miRNA) expression and methylation patterns have been described in classic MF [1, 7, 8], no distinct disease specific alteration has been identified so far. Moreover, little is known about the molecular background of FMF or T-MF.

MicroRNAs are short non-coding RNA molecules that regulate gene expression and contribute to biological processes including apoptosis, cell cycle, differentiation and normal haematopoiesis. Furthermore they have an important role in tumourigenesis, and depending on their target genes miRNAs may act as oncogenes or tumour suppressors [9, 10].

The possible role of miRNAs in the pathogenesis of MF and as a potential tool in differential diagnosis has been studied recently. Amongst others, miR-155, miR-92a, miR-93 and miR-326 were found to be overexpressed, while miR-203 and miR-205 were downregulated in MF compared to inflammatory skin diseases [11–13] [14], although, the exact role of these aberrantly expressed miRNAs in the pathogenesis of MF is yet to be defined.

The aim of this study was to gain further data on the molecular pathogenesis of MF with a focus on two rare forms, FMF and T-MF, by identifying aberrantly expressed miRNAs.

## Materials and Methods

### Materials

Formalin-fixed paraffin-embedded (FFPE) skin biopsy samples from 9 patients diagnosed with FMF (7 males, 2 females, age range 27–67 years, mean±SD: 47.5±14.1) and 7 patients diagnosed with T-MF (3 males, 4 females, age range 53–77 years, mean±SD: 69.3±8.3) were included in this study. T-cell receptor gene rearrangement demonstrated clonality in all MF cases (data not shown). The control group consisted of 5 cases of chronic eczema (E) (2 males, 3 females, age range 49–74 years, mean±SD: 64.0±10.6) and 3 cases of discoid lupus erythematosus (DLE) (1 male, 2 females, age range 40–72 years, mean±SD: 59.0±16.8). The study was conducted in accordance with the Declaration of Helsinki.

### Quantitative Real-Time Polymerase Chain Reaction Analysis Of miRNA Expression

Total RNA isolation was performed with RecoverAll™ kit (Life Technologies) according to the manufacturers' instructions. After reverse transcription of miRNAs using TaqMan® MicroRNA Reverse Transcription Kit (Life Technologies) the samples were preamplified with a TaqMan® PreAmp Master Mix Kit (Life Technologies). Quantitative real-time polymerase chain reaction analysis (Q-PCR) of miR-29b-1, miR-29b-2, miR-155, miR-223, miR-34a, miR-181a, miR-181b, miR-93-5p, miR-92, miR-326 and miR-122 was carried out using specific TaqMan® MicroRNA Assays (Life Technologies), with an ABI Prisms 7300 Sequence Detection System (Applied Biosystems). All samples were run in duplicate. Sequence Detection Software version 1.3 (Applied Biosystems) was used to analyze the data after amplification. Expression levels of miRNAs were normalized to the expression levels of the endogenous control U6snRNA ($\Delta Ct = Ct_{U6snRNA} - Ct_{miRNA}$). A higher $\Delta Ct$ value refers to a higher initial expression level of the analysed miRNA.

### Statistical Analysis

The Kolmogorov-Smirnov test was used for testing the normal distribution of $\Delta Ct$ values. Two-tailed Student's *t*-test was used for statistical analysis with the software package SPSS (version 20.0). P values 0.05 or below were considered statistically significant. Graphs (Fig. 1) were generated using Graphpad (version 5.0).

## Results

To examine the expression level of the different miRNAs, Q-PCR assays were performed in skin biopsy samples of 9 cases of FMF and 7 cases of T-MF. The miRNA expression of 5 skin biopsy samples of cases of eczema and 3 cases of DLE were measured and used as controls. The results are summarized in Tables 1 and 2 with relative expression of miRNAs represented by $\Delta Ct$ values.

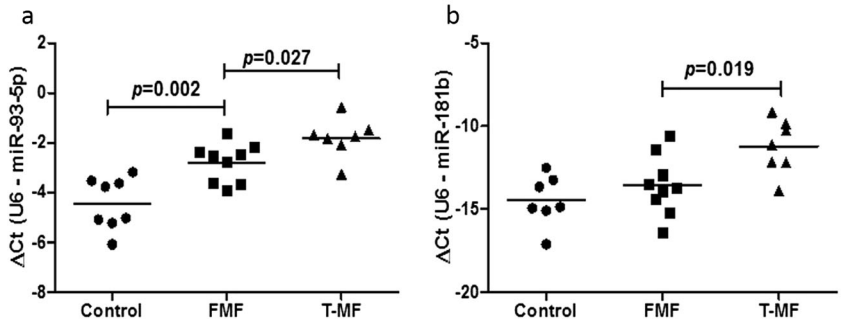


**Fig. 1** Differential expression of miR-93-5p and miR-181b in folliculotropic (FMF) and transformed mycosis fungoides (T-MF). a, Illustrated is the elevated expression of miR-93-5p in FMF ($n=9$) and T-MF ($n=7$) compared to the control group ($n=8$) with T-MF also displaying higher miR-93-5p expression compared to FMF. **b**, miR-181b demonstrated significantly higher expression in T-MF compared to the control and FMF groups, while the difference between FMF and the control group did not reach the level of statistical significance. (The expression levels are depicted as $\Delta Ct$ values relative to the endogenous control ($\Delta Ct = Ct(U6) - Ct(miR\text{-}93\text{-}5p \text{ or } miR181b)$ with higher $\Delta Ct$ values representing higher expression levels. P values 0.05 or below were considered statistically significant.)

**Table 1** Comparison of microRNA levels in folliculotropic mycosis fungoides and chronic inflammatory skin diseases

| MicroRNA | FMF | Control | *P*-value |
|---|---|---|---|
| ΔCt miR-29b1 | −12.4±1.1 | −12.8±1.2 | 0.462 |
| ΔCt miR-29b2 | −12.3±0.9 | −13.3±1.2 | 0.069 |
| **ΔCt miR-155** | 2.0±1.0 | −0.2±1.1 | **0.010** |
| **ΔCt miR- 223** | 2.1±1.0 | 0.8±1.5 | **0.049** |
| **ΔCt miR-34a** | −3.8±1.4 | −5.8±0.5 | **0.002** |
| **ΔCt miR-181a** | −5.2±1.1 | −6.7±0.7 | **0.004** |
| ΔCt miR-181b | −13.6±1.8 | −14.5±1.5 | 0.286 |
| **ΔCt miR-93-5p** | −2.8±0.8 | −4.4±1.0 | **0.002** |
| ΔCt miR-92 | 0.7±0.7 | 0.5±0.4 | 0.417 |
| ΔCt miR-326 | −15.9±1.4 | −17.3±1.5 | 0.067 |
| ΔCt miR-122 | −12.7±1.2 | −13.3±0.3 | 0.534 |

Bold letters highlight microRNAs with significantly different expression and related *p* values

Results are presented as mean±SD

Ct, cycle number at which the fluorescence crossed the fixed threshold; FMF, folliculotropic mycosis fungoides; P-values according to Student's *t*-test; $\Delta Ct = Ct_{U6snRNA} - Ct_{microRNA}$

In cases of FMF, expression of miR-155, −34a, −181a, −93-5p and −223 were significantly higher ($p<0,05$) compared to controls (Table 1). In cases of T-MF, expression of miR-34a, −181a, −181b, −93-5p and −326 were significantly higher ($p<0,05$) compared to the control group (Table 2). Interestingly, when comparing FMF to T-MF, only miR-181b ($p=0,019$) and miR-93-5p ($p=0,027$) showed significant up-regulation in T-MF (Table 3 and Fig. 1). The age and sex of patients had no significant influence on the level of any miRNAs (data not shown).

**Table 2** Comparison of microRNA levels in transformed mycosis fungoides and chronic inflammatory skin diseases

| MicroRNA | T-MF | Control | *P*-value |
|---|---|---|---|
| ΔCt miR-29b1 | 13.0±1.1 | −12.8±1.2 | 0.774 |
| ΔCt miR-29b2 | 12.7±1.3 | −13.3±1.2 | 0.380 |
| ΔCt miR-155 | 1.5±1.4 | −0.2±1.1 | 0.097 |
| ΔCt miR- 223 | 1.8±1.7 | 0.8±1.5 | 0.222 |
| **ΔCt miR-34a** | −3.6±1.3 | −5.8±0.5 | **0.001** |
| **ΔCt miR-181a** | −4.4±0.9 | −6.7±0.7 | **<0.001** |
| **ΔCt miR-181b** | −11.2±1.6 | −14.5±1.5 | **0.002** |
| **ΔCt miR-93-5p** | −1.8±0.8 | −4.4±1.0 | **<0.001** |
| ΔCt miR-92 | 0.5±0.6 | 0.5±0.4 | 0.910 |
| **ΔCt miR-326** | 15.1±2.1 | −17.3±1.5 | **0.046** |
| ΔCt miR-122 | −12.9±2.3 | −13.3±0.3 | 0.842 |

Bold letters highlight microRNAs with significantly different expression and related *p* values

Results are presented as mean±SD

Ct, cycle number at which the fluorescence crossed the fixed threshold; P-values according to Student's *t*-test; T-MF, transformed mycosis fungoides; $\Delta Ct = Ct_{U6snRNA} - Ct_{microRNA}$

**Table 3** Comparison of microRNA levels in folliculotropic mycosis fungoides and transformed mycosis fungoides

| MicroRNA | FMF | T-MF | *P*-value |
|---|---|---|---|
| ΔCt miR-29b1 | −12.4±1.1 | 13.0±1.1 | 0.298 |
| ΔCt miR-29b2 | −12.3±0.9 | 12.7±1.3 | 0.474 |
| ΔCt miR-155 | 2.0±1.0 | 1.5±1.4 | 0.431 |
| ΔCt miR- 223 | 2.1±1.0 | 1.8±1.7 | 0.706 |
| ΔCt miR-34a | −3.8±1.4 | −3.6±1.3 | 0.807 |
| ΔCt miR-181a | −5.2±1.1 | −4.4±0.9 | 0.165 |
| **ΔCt miR-181b** | −13.6±1.8 | −11.2±1.6 | **0.019** |
| **ΔCt miR-93-5p** | −2.8±0.8 | −1.8±0.8 | **0.027** |
| ΔCt miR-92 | 0.7±0.7 | 0.5±0.6 | 0.544 |
| ΔCt miR-326 | −15.9±1.4 | 15.1±2.1 | 0.395 |
| ΔCt miR-122 | −12.7±1.2 | −12.9±2.3 | 0.864 |

Bold letters highlight microRNAs with significantly different expression and related *p* values

Results are presented as mean±SD

Ct, cycle number at which the fluorescence crossed the fixed threshold; FMF, folliculotropic mycosis fungoides; P-values according to Student's *t*-test; T-MF, transformed mycosis fungoides; $\Delta Ct = Ct_{U6snRNA} - Ct_{microRNA}$

## Discussion

Mycosis fungoides is a relatively common and incurable primary CTCL, however it usually shows a slow progression and good prognosis. There are rare subtypes of MF distinguished by the WHO Classification of Tumours of hematopoietic and lymphoid tissues [1] including folliculotropic MF, pagetoid reticulosis and granulomatous slack skin, amongst which FMF is marked by a more aggressive clinical course and poorer outcome comparable to the tumour stage of classic MF [1] [2, 3]. The usual favourable prognosis of classic MF may also be hampered by transformation into large T-cell lymphoma.

Our understanding of the pathogenesis of MF is relatively scarce. Previous findings of genetic and gene expression alterations in MF suggested a central role of impaired Fas-mediated apoptosis in the pathogenesis of the disease [15] [16, 17]. Increased activity of transcription factors, such as STAT3 and JUNB has also been described, which may contribute to apoptosis resistance in MF [18, 19] [20, 21]. In addition, recurrent chromosomal aberrations and hypermethylation of the promoter region of different tumour suppressor genes have also been associated with the disease [22, 8].

Recent studies have revealed altered miRNA expression profiles in classic MF compared to normal skin, benign inflammatory skin diseases, primary cutaneous anaplastic large

cell lymphoma or Sezary syndrome [12, 11, 13, 14, 23]. These findings, in addition to shedding light on possible pathogenetic pathways, may also have a potential in differential diagnosis. Moyal et al. have shown that higher expression of miR-155 correlates with the progression of MF [14]. In a previous study of tumour stage MF, miR-155 and miR-92a showed the most significant upregulation compared to inflammatory skin diseases [11].

Despite the accumulating data on the pathogenesis of classic MF, the molecular background of the more aggressive folliculotropic MF and the molecular mechanisms by which a subset of MF undergoes transformation are hardly investigated. Prochazkova et al. have described frequent chromosomal imbalances associated with hypotetraploidy in transformed MF cases [24]. Combined CDKN2A-CDKN2B deletion was also observed in about 70% of transformed MF, and correlated with shortened survival [25]. However, there are no data on miRNA expression in cases of folliculotropic and transformed MF in the literature.

In this study, we analyzed the expression of 11 miRNAs which have previously been associated with lymphomagenesis or the pathogenesis of classic MF. Three miRNAs, including miR-93-5p, miR-181a and miR-34a were found to be significantly upregulated in both FMF and T-MF. FMF also showed overexpression of miR-155 and miR-223, while miR-181b and miR-326 were overexpressed in the transformed MF cases. In addition, miR-181b and miR-93-5p showed significantly higher expression in T-MF compared to FMF suggesting that these microRNAs together with miR-326 may have a possible role in the pathogenesis of large cell transformation of MF.

Elevated expression of miR-92 and miR-122 has been previously described in MF [11, 26]. In our study, no significant differences were detected in cases of FMF or T-MF. Moreover, miR-29b1 and miR-29b2 also seem to lack significant contribution in their pathogenesis.

In a recent study, downregulation of miR-223 has been confirmed in cases of early and advanced stages of MF [27]. Our results show that expression of miR-223 is significantly higher in cases of FMF compared to controls. This may be due to the presence of many Langerhans cells in cases of FMF, as Langerhans cells of the skin are known to highly express miR-223 [28].

In accordance with a previous microarray study demonstrating significantly higher expression of miR-326 in CTCL compared to chronic inflammatory skin diseases [13], our study revealed overexpression of miR-326 in cases of T-MF. Cases of FMF also showed slightly higher expression of miR-326 compared to controls, however, this difference was not statistically significant.

MiR-34a is accounted mainly as a tumour suppressor miR, however, it has recently been shown that miR-34a also has as a pro-proliferative or antiapoptotic effect in association with Myc on lymphoma cell lines [29, 30]. Since overexpression and amplification of Myc have been described in advanced stages of MF [31, 32], it can be speculated that miR-34a contributes to MF pathogenesis via oncogenic activity in FMF and T-MF.

Overexpression of the classic oncomir, miR-155 has already been linked to MF pathogenesis and progression [11, 13, 14, 12]. In keeping with this, FMF cases showed higher expression of miR-155 compared to the control group in our study. However, cases of transformed MF failed to show significantly elevated miR-155 expression, suggesting that miR-155 related gene expression regulation may not be involved in large cell transformation.

The oncogenic potential of miR-93-5p and the miR-181 family has been demonstrated in different types of tumours as well as in tumour cell lines [33–37]. MiR-93-5p and miR-181a were also found to be overexpressed in tumour stage MF [11]. Our study revealed higher level of miR-93-5p and miR-181a in both FMF and T-MF, as well as elevated expression levels of miR-181b in T-MF cases. The tumour suppressor PTEN, an essential member of the PI3K pathway, is a known target for miR-93-5p and the miR-181 family [38, 39]. Loss of heterozygosity of PTEN has been previously demonstrated in a subset of MFs [40]. In addition, a trend for loss of PTEN expression with histological progression of MF has been described [41]. Thus, miR-93-5p and miR-181a as well as miR-181b may exert their oncogenic effect through downregulation of PTEN both in FMF and T-MF, and in T-MF, respectively.

In summary, our results by identifying differentially expressed microRNAs add further insight in the molecular pathogenesis of folliculotropic mycosis fungoides and large cell transformation of MF.

**Declaration of Interests** The authors declare no conflicts of interest.

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