ORIGINAL ARTICLE

Expression of FK506-binding protein 51 (FKBP51) in Mycosis fungoides

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Abstract

Background Mycosis fungoides (MF) is the major subtype of cutaneous T-cell lymphomas (CTCL). It usually has a prolonged indolent clinical course with a minority of cases acquiring a more aggressive biological profile and resistance to conventional therapies, partially attributed to the persistent activation of nuclear factor-kappa B (NF-κB) pathway. In the last decade, several papers suggested an important role for the FK506-binding protein 51 (FKBP51), an immunophilin initially cloned in lymphocytes, in the control of NF-κB pathway in different types of human malignancies.

Objectives We aimed to investigate the possible value of FKBP51 expression as a new reliable marker of outcome in patients with MF.

Methods We assessed by immunohistochemistry (IHC) FKBP51 expression in 44 patients with MF, representative of different stages of the disease. Immunohistochemical results were subsequently confirmed at mRNA level with quantitative PCR (qPCR) in a subset of enrolled patients. In addition, IHC and qPCR served to study the expression of some NF-κB-target genes, including the tumour necrosis factor receptor-associated factor 2 (TRAF2).

Results Our results show that FKBP51 was expressed in all evaluated cases, with the highest level of expression characterizing MFs with the worst prognosis. Moreover, a significant correlation subsisted between FKBP51 and TRAF2 IHC expression scores.

Conclusions We hypothesize a role for FKBP51 as a prognostic marker for MF and suggest an involvement of this immunophilin in deregulated NF-κB pathway of this CTCL.

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Conflicts of interest

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Competing interests

The authors declare that they have no competing interests.

Introduction

Primary cutaneous T-cell lymphomas (CTCL) are a wide group of non-Hodgkin lymphomas, characterized by a clonal expansion of skin-homing T lymphocytes, primarily presenting in the skin without extra-cutaneous involvement at diagnosis.[1] Mycosis fungoides (MF) represents the most common form of CTCL and usually has an indolent stage-related clinical outcome. Only a small subset of patients progresses to an advanced disease characterized by more aggressive behaviour (5-year overall survival is 15–40% in stage IV).[2] The identification of those patients likely to progress remains a challenge.[3–6] Neoplastic T lymphocytes evade apoptotic stimuli, resulting in frequent failure of therapeutic treatment.[7–11] In the last decade, among several signalling pathways reported to be deregulated in CTCL,[12–15] including PI3K/AKT, JAK/STAT,[16,17] RAS and nuclear factor-kappa B (NF-κB) pathways, a major role has been attributed to

the persistent activation of NF-κB in chemoresistance of MF malignant cells.[18–22] NF-κB is a key expression regulator of genes involved in inflammation and innate immune response.[23,24] Moreover, this transcription factor has a well-documented role in the processes of carcinogenesis, tumour progression, metastasis and resistance to chemotherapy in different types of human cancers.[25,26] Specifically, in CTCL, NF-κB promotes the expression of pro-inflammatory and anti-apoptotic genes, thus contributing to increased proliferation and survival of neoplastic cells.[21] In recent years, several experimental evidences have shown that FK506-binding protein 51 (FKBP51), an immunophilin resident in T lymphocytes, plays a relevant role in NF-κB activation,[27,28] Bouwmeester firstly identified FKBP51 as an IκB kinase (IKK) α-cofactor[27] and some years later Romano *et al.*[28] demonstrated that FKBP51 acts with its scaffold and isomerase activity on the IKK kinase complex, allowing its correct assembly and function. Upon activation, IKK phosphorylates IκB and promotes the ubiquitination and degradation of such inhibitor, leading to NF-κB nuclear translocation and activity.[28–34] Increasing evidence supports a role for FKBP51 in the induction and maintenance of chemoresistance in human malignancies,[35] mediated by aberrant NF-κB activation[33,34,36,37] and proposes this factor as a reliable marker of outcome and progression-free survival in several human solid malignancies.[38–40] Recently, several studies have shown a pathogenic role for TNF receptor-associated factor 2 (TRAF2) in human lymphomas.[41] It mediates the NF-κB signal transduction activation from a wide range of members of the TNF receptor superfamily. The interaction of TRAF2 with TRADD, a TNF receptor-associated apoptotic signal transducer, ensures the recruitment of IAPs for the direct inhibition of caspase activation.[42] The aim of this study was to address the involvement of FKBP51 in the progression of MF from an indolent to a more aggressive phase of disease. To this end, we investigated by IHC and qPCR expression levels of FKBP51 in a series of MF at a different stages of the disease. Moreover, to strengthen the association between FKBP51 and deregulated NF-κB, we measured levels of the NF-κB-regulated gene namely TRAF2. MF examined by IHC showed increased expression of FKBP51, compared with thymus samples, used as a control tissue for normal lymphocytes, normal skin and cutaneous inflammatory dermatoses with highest values found in cases with more aggressive biological behaviour. TRAF2 expression levels appeared to be consistent with those of FKBP51.

Materials and methods

Study population

Formalin-fixed, paraffin-embedded (FFPE) tissue blocks of 44 MF, representative of different stages of the disease, diagnosed from January 1994 to January 2015 were retrieved from the archives of the Department of Advanced Biomedical Sciences, Pathology Unit, University Federico II of Naples. The diagnosis was based on a combination of clinical and histological data and confirmed by an expert panel of dermatologists and pathologists, according to the criteria of the WHO-EORTC Classification of Cutaneous Lymphoma.[1] Only cases with an available clinical and pathological follow-up of at least 24 months were recruited. As controls, 10 benign inflammatory dermatoses, including four psoriasis, three chronic atopic eczema and three lichen planus, were selected too. Normal skin (nine cases) and thymus (five cases) were used as external controls. The study was performed according to the guidelines of the Institutional Ethic Committee, which, in agreement with the Italian law, with reference to the topics of the current research, do not ask for the Ethical Committee approval, and, according to the Declaration of Helsinki require, for studies based only on retrospective analyses on routine archival FFPE-tissue a written informed consent from the living patient, following the indication of Italian DLgs no. 196/03 (Codex on Privacy) at the time of surgery for the CL.

Histochemistry

Immunohistochemistry was carried out as previously described.[43–47] The polyclonal anti-FKBP51 (clone H-100, sc-13983 Santa Cruz Biotechnology, Santa Cruz, CA, USA; 1 : 200 dilution) and anti-TRAF2 (clone C-20, sc-876 rabbit polyclonal antibody, Santa Cruz Biotechnology; 1 : 200 dilution) were applied. For each session of staining, positive and negative controls were put on. For negative controls, non-immune serum (1 : 500) in Tris-buffered saline (TBS) buffer was used instead of the primary antibodies. Three pathologists (MM, SS and GDR) scored synchronously the sections until consensus was reached. The cells were judged positive for FKBP51 when a red signal predominantly nuclear or also cytoplasmic was observed. The cells were judged positive for TRAF2 when a red signal predominantly cytoplasmic was observed. In all cases, five fields (×40 magnification) were assessed, evaluating a minimum of 50 cells in the representative areas.

qPCR

RNA extraction from FFPE tissues for qPCR analysis was carried out as described.[38] Gene expression was performed using the SsoAdvancedTM SYBR Green Supermix (Bio-Rad, Hercules, CA, USA), and specific qPCR primers to analyse each transcript, particularly, to detect FKBP51, X-linked inhibitor of apoptosis protein (XIAP) and BCL-2 validated QuantiTec primers from Qiagen (Valencia, CA, USA) were used, along with co-amplified ribosomal 18S and β-Actin as internal controls for normalization.[28,48] For the comparison between thymus, skin cases and MF groups, quantitative gene expression for FKBP51 was performed with the $2^{-\Delta CT}$ comparative method. Quantitative gene expression for FKBP51, XIAP and BCL-2 in MF cases was performed as relative expression change fold using normal thymus as reference sample.

Table 1 Clinical and pathological features of the study population

Age	Min	29	
	Max	96	
	Mean (95% CI)	62.2 (57.9–66.5)	
	Median (95% CI)	64 (59–67)	
Sex	M	30	68.2%
	F	14	31.8%
MF lesion type	Patch	11	25%
	Plaque	15	34.1%
	Tumour	18	40.9%
Stage	IA	11	25%
	IB	9	20.5%
	IIA	6	13.6%
	IIB	4	9.1%
	III	4	9.1%
	IIIA	5	11.4%
	IVA	4	9.1%
	IVB	1	2.3%

Statistical analysis

The statistical significance of differences of FKBP51 or TRAF2 expressions between groups was determined by one-way analysis of variance (ANOVA). When the ANOVA test resulted positive ($P < 0.05$), we performed a *post hoc* Student–Newman–Keuls' test, for pairwise comparison of subgroups. Correlation analysis between FKBP51 and TRAF2 IHC expression scores was carried out with a Spearman rank correlation test and drawing a scatter plot graph. The statistical analysis was performed using the R statistical package v. 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).[49,50]

Results

Clinical and pathological parameters

The clinical data and pathological features of the disease are collected and listed in Table 1. The study population was composed of 44 patients (30 males and 14 females), with an average age of 62.2 years (range 29–96 years), of which 11 with patch MF (11 stage IA), 15 with plaque MF (nine stage IB and six IIA) and 18 with tumour MF (four stage IIB, nine stage III, five stage IV). All MF is characterized by an infiltrate of T-helper memory lymphocytes.

FKBP51 in thymus

In thymus, FKBP51 expression was very low (score 1; Fig. 1g,h). Only one patient with hyperplastic thymus-expressed FKBP51 in <30% of the T lymphocytes (score 3).

FKBP51 in normal skin

In normal skin specimen, <10% of lymphocytes (score 1) expressed FKBP51.

FKBP51 in inflammatory dermatoses

All the inflammatory dermatoses evaluated showed nuclear positivity for FKBP51. The protein was expressed in less than 20% of lymphocytes (score of 1–2; Fig. 1e,f) in most of evaluated cases

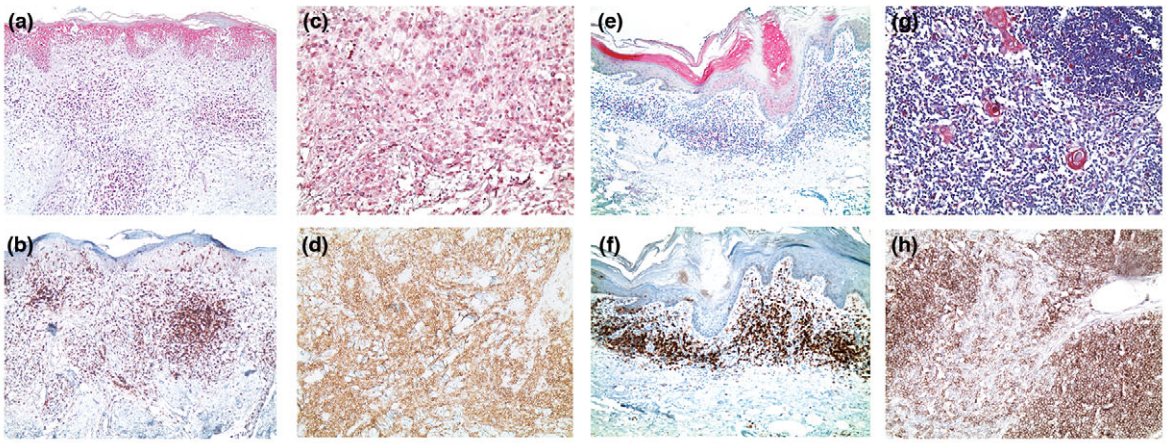

Figure 1 FKBP51 immunostaining in a representative case of patch- and nodular MF compared to a cutaneous benign dermatosis and thymus. (a,b) Patch MF: positivity of neoplastic cells for FKBP51 (original magnification, a: anti-FKBP51 ×10; b: anti-CD4 ×10); (c,d) Nodular MF: FKBP51 is diffusely expressed in MF lymphocytes (original magnification, c: anti-FKBP51 ×10; d: anti-CD4 ×10); (e,f) Benign dermatosis: staining for FKBP51 demonstrates positivity of lymphocytes in some small clusters in chronic dermatitis (original magnification, e: anti-FKBP51 ×10; f: anti-CD4 ×10); (g,h) Thymus: scattered lymphocytes are positive for FKBP51 in thymus (original magnification, g: anti-FKBP51 ×10; h: anti-CD4 ×10).

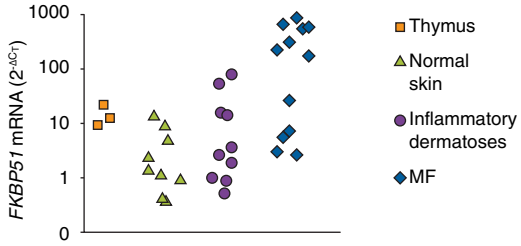

Figure 2 FKBP51 expression in deparaffinized tissues. Transcript levels of FKBP51 in RNA extracted by deparaffinized tumours from three thymus, nine normal skin samples, 10 inflammatory dermatoses and 12 MF cases (four patch, four plaque and four tumour MF; for details, see Materials and methods).

(eight of 10); the remaining two cases (a chronic atopic eczema and a lichen planus) expressed FKBP51 in 30–40% of inflammatory lymphocytes (score of 3–4).

FKBP51 in Mycosis fungoides

All the cases of MF showed nuclear and/or cytoplasmic expression of FKBP51 in cells of both the epithelial (single or aggregated) and dermal infiltrate.

The strongest level of expression was observed in nodular MF (stages IIB, III and IV; Fig 1c,d), with the highest level of positivity in the dermal neoplastic lymphocytes (>70% of MF lymphocytes expressed FKBP51; score of 7–10 in all cases; Fig. 1c,d) of MF with large-cell transformation (LCT) (11 of 18 patients).

In patch MF (stage IA; Fig. 1a,b), FKBP51 was expressed by 20–50% of epidermotropic lymphocytes (scores of 2–5) and by 20–40% of dermal neoplastic cells. In plaque MF (stages IIA and IB), FKBP51 was expressed by 20–70% of epidermotropic neoplastic T cells (score of 2–7) and by 20–60% of dermal tumoral lymphocytes (score of 2–7).

To strengthen FKBP51 immunohistochemical data, transcript levels of FKBP51 were analysed by qPCR in deparaffinized samples from three cases of thymus, 19 skin samples, including

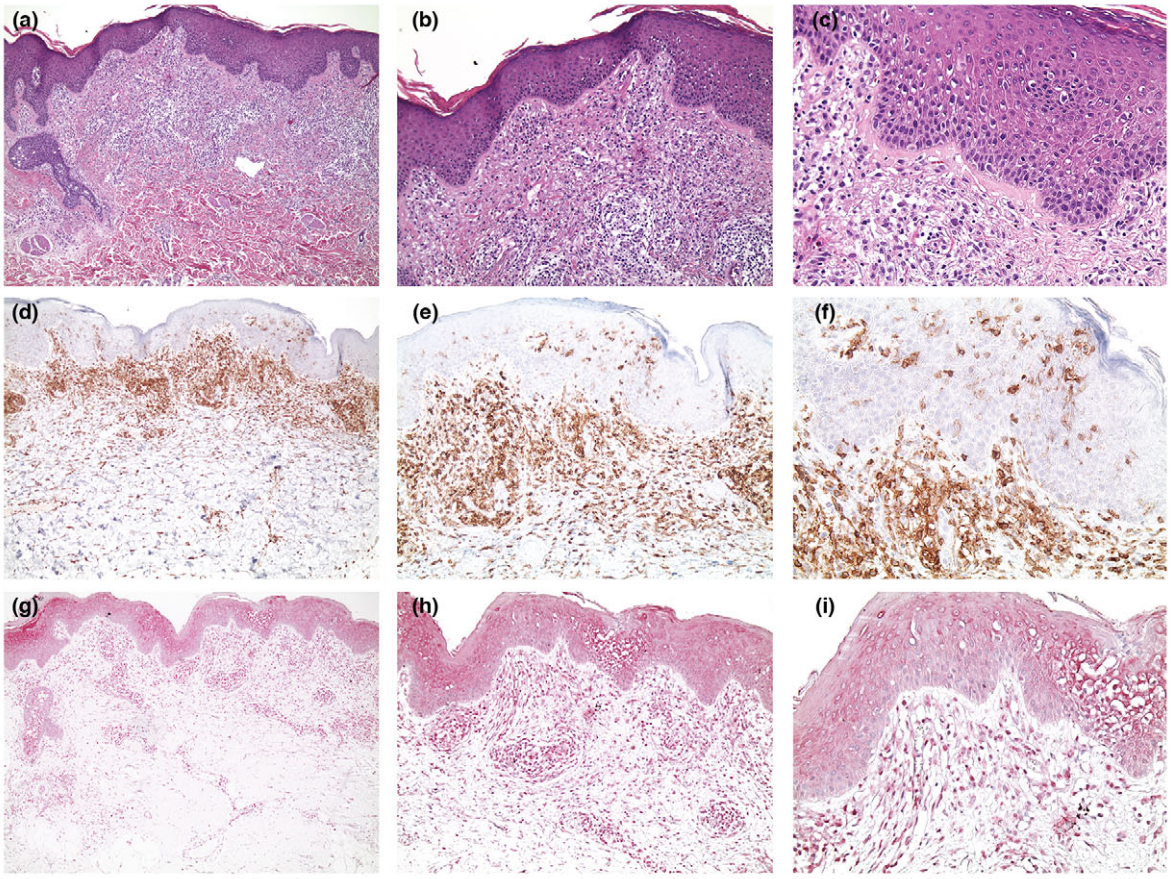

Figure 3 Representative case of plaque MF (IIA) with aggressive biological behaviour. (a–c) Plaque MF (original magnification, haematoxylin and eosin ×5, ×10, ×20); (d–f) Diffuse positivity of neoplastic cells for CD4 (original magnification, ×5, ×10, ×20); (g–i) FKBP51 is diffusely and strongly expressed (original magnification, ×5, ×10, ×20).

normal skin (nine cases) and inflammatory dermatoses (10 cases) and 12 cases of MF (four patch-, four plaque- and four nodular cases; Fig. 2). FKBP51 was expressed in all cases of MF evaluated. According to immunohistochemical data, FKBP51 was expressed in all evaluated MF cases with the highest level of expression in nodular MF. Results of mRNA quantitation by RT-PCR were in line with those of IHC. Indeed, in nodular MF (stage III; advanced MF, cases 9–12), the $2^{-\Delta CT}$ values were ≥305, while in patch/plaque stage MF (cases 1–4), the $2^{-\Delta CT}$ values were ≤6.9. Analysis of inflammatory dermatoses (N = 10) revealed a heterogeneity in expression with a median value of $2^{-\Delta CT}$ = 1.8. In two of 10 cases, $2^{-\Delta CT}$ values were higher than those of patch/plaque stage MF (51.9 and 77.4). In these two dermatoses, the immunohistochemical signal was, however, lower than that of patch/plaque MF, suggesting an increased protein translation rate in the tumour. The nine normal skin cases showed mRNA levels ≤to those of thymus samples. Interestingly, a case of plaque MF (case 8) (stage IIA; early MF; Fig. 3a–i) that progressed to advanced stage during the follow-up also showed a remarkable level of FKBP51 transcript ($2^{-\Delta CT}$ = 652), thus supporting the hypothesis that FKBP51 may have a prognostic and predictive value in MF.

For each sample, FKBP51 expression was evaluated as percentage of FKBP51-positive tumour cells in five high power fields (HPF). The scores are, then, summarized in Table 2. FKBP51 positivity expression score ranged between 2 and 10, mean value 5.6 (95% confidence interval CI for the mean 4.8–6.3), median value 5 (95% CI for the median 4–7). We analysed FKBP51 expression score distribution over MF lesion type and clinical stages (Fig. 4a,b). Table 3 summarizes the mean, SD and median FKBP51 IHC score along with group comparison statistical analysis results. FKBP51 IHC expression was significantly higher in tumour MF compared to plaque and patch MF; IHC expression of FKBP51 protein also directly correlated with clinical stage (Table 3).

TRAF2 in Mycosis fungoides

TRAF2 is a NF-κB-regulated gene[23] and it also mediates activation of this transcription factor. All the cases of MF showed cytoplasmic expression of TRAF2 in cells of both the epithelial (single or aggregated) and dermal infiltrate.

The strongest level of TRAF2 expression was observed in nodular MF, with the highest level of expression (>70% of MF lymphocytes expressed TRAF2; score of 6–10 in all cases) in patients with LCT (11 of 18).

In patch MF (stage IA), TRAF2 was expressed by 20–60% (score of 2–6) of neoplastic T cells. In plaque MF (stages IB and IIA), TRAF2 was expressed by 20–70% of neoplastic T cells (score of 2–7). In nodular MF (stages IIB, III and IV), TRAF2 was expressed by 60% to 100% (score of 6 to 10) of neoplastic T-cells.

The percentage of neoplastic cells positive for TRAF2 was counted in five HPF and summarized in Table 2. TRAF2

Table 2 Conversion table with percentage of IHC-positive neoplastic cells and corresponding score

Score	% positive neoplastic cells
1	≤10%
2	>10 ≤ 20%
3	>20 ≤ 30%
4	>30 ≤ 40%
5	>40 ≤ 50%
6	>50 ≤ 60%
7	>60 ≤ 70%
8	>70 ≤ 80%
9	>80 ≤ 90%
10	>90 ≤ 100%

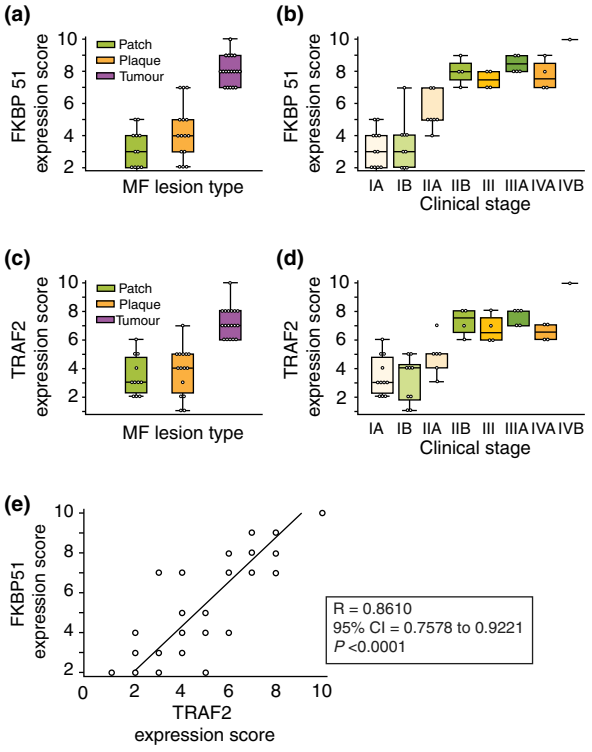

Figure 4 FKBP51 IHC score distribution across the three MF lesion types (a) and across the clinical stages (b). Panels (c) and (d) show TRAF2 IHC score distribution across, respectively, MF lesion types and stages. (e) Scatter plot showing the high concordance between FKBP51 and TRAF2 scores in the study population.

positivity expression score ranged between 1 and 10, mean value 5.1 (95% confidence interval CI for the mean 4.4–5.8), median value 5 (95% CI for the median 4–6). We analysed TRAF2 expression score distribution over MF lesion type and clinical stages (Fig. 4c,d). Table 3 summarizes the mean, SD and median TRAF2 IHC score along with group comparison statistical

Table 3 FKBP51 expression score distribution over MF lesion type and clinical stage. Comparison between groups was assessed by ANOVA test resulted statistical significant ($P < 0.001$). Significant pair comparison ($P < 0.05$) has been assessed by Student–Newman–Keuls test; all significantly different pairwise comparisons are reported

Variable: FKBP51 Factor: MF lesion type					ANOVA	**Different ($P < 0.05$) from**
Factor	***n***	**Mean**	**SD**	**Median**	***P* value**	**factor nr**
Patch	11	3.3	1.2	3.0	<0.001	3
Plaque	15	4.3	1.8	4.0		3
Tumour	18	8.1	0.9	8.0		1–2
Variable: FKBP51 Factor: Clinical stage					ANOVA	**Different ($P < 0.05$) from**
Factor	***n***	**Mean**	**SD**	**Median**	***P* value**	**factor nr**
IA	11	3.3	1.2	3	<0.001	3–4–5–6–7–8
IB	9	3.4	1.6	3		3–4–5–6–7–8
IIA	6	5.5	1.2	5		1–2–4–5–6–7–8
IIB	4	8	0.8	8		1–2–3
III	4	7.5	0.6	7.5		1–2–3
IIIA	5	8.4	0.6	8		1–2–3
IVA	4	7.8	0.9	7.8		1–2–3
IVB	1	10		10		1–2–3
Variable: TRAF2 Factor: MF lesion type					ANOVA	**Different ($P < 0.05$) from**
Factor	***n***	**Mean**	**SD**	**Median**	***P* value**	**factor nr**
Patch	11	3.5	1.4	3	<0.001	3
Plaque	15	3.8	1.7	4		3
Tumour	18	7.2	1.1	7		1–2
Variable: TRAF2 Factor: Clinical stage					ANOVA	**Different ($P < 0.05$) from**
Factor	***n***	**Mean**	**SD**	**Median**	***P* value**	**factor nr**
IA	11	3.5	1.4	3	<0.001	3–4–5–6–7–8
IB	9	3.1	1.6	4		3–4–5–6–7–8
IIA	6	4.8	1.3	5		1–2–4–6–7–8
IIB	4	7.3	1	7.5		1–2–3
III	4	6.8	1	6.5		1–2
IIIA	5	7.6	0.6	8		1–2–3
IVA	4	6.5	0.6	6.5		1–2–3
IVB	1	10		10		1–2–3

analysis results. TRAF2 IHC expression was significantly higher in tumour MF compared to plaque and patch MF; IHC expression of TRAF2 protein also directly correlated with clinical stage (Table 3).

Association of TRAF2 and FKBP51 in Mycosis fungoides

All the nodular MF showed the simultaneous expression of FKBP51 and TRAF2 in more than 60% of neoplastic cells (Fig. 5). More interestingly, the only case of IIA stage MF, which resulted in progression to advanced disease during the follow-up, showed this simultaneous overexpression. Conversely, the two cases (stages IIA and IB) with the expression of only one of the two markers with score >6 showed no evidence of progression.

The observation that the strongest reactivity occurred in advanced stages suggested a strict relationship between TRAF2 and FKBP51, as it has been previously suggested for melanoma.[28] Because FKBP51 promotes NF-κB activation, we analysed FKBP51 mRNA expression in MF samples from patients along with two NF-κB-regulated genes, namely the anti-apoptotic B-cell lymphoma 2 (Bcl-2) and XIAP, by qPCR. As shown in Fig. 6, the transcript levels of such NF-κB-target genes resulted increased in advanced stage MF and were consistent with FKBP51 levels, in line with the concept that FKBP51 sustains NF-κB activation.[28]

Furthermore, we observed a significant correlation between FKBP51 and TRAF2 IHC expression scores, as shown by the scatter plot in Fig. 4e. Correlation coefficient between FKBP51 and TRAF2 was 0.8610 (95% CI 0.7578 to 0.9221). Spearman rank correlation test also resulted statistically significant ($P < 0.0001$) (Fig. 7).

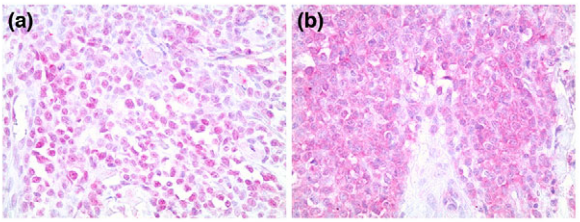

Figure 5 FKBP51 and TRAF2 expression in a representative case of nodular MF. (a) Nuclear and cytoplasmic staining for FKBP51 was observed in most neoplastic cells (original magnification, anti-FKBP51 × 40); (b) TRAF2 diffusely stains the cytoplasm of the same atypical cells (original magnification, anti-TRAF2 ×40).

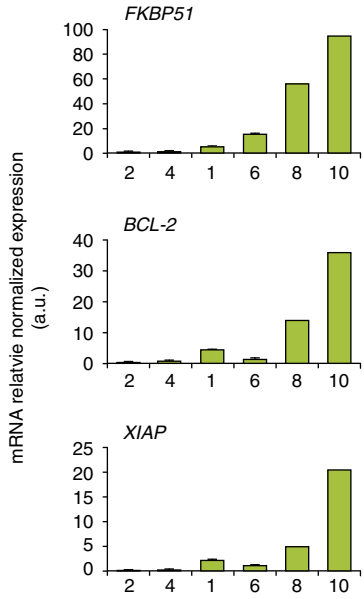

Figure 6 FKBP51 mRNA levels are associated with NF-κB-target genes expression in MF cases. Transcript levels of FKBP51 (top), BCL-2 (middle) and XIAP (bottom) in RNA extracted by deparaffinized tumours from six MF cases (case number is reported). Expression was normalized to 18S RNA and expressed as fold increase, considering a normal thymus as the reference sample (expression = 1). Histograms show the average values and standard deviations from expression values of two different experiments.

Discussion

FKBP51 is an immunophilin engaged in the control of a growing number of essential biological processes, both in normal and in neoplastic cells.[51–53] Firstly reported by Baughman and colleagues[54] as constitutively expressed in normal human T lymphocytes, FKBP51 expression was found in many different normal tissues,[55] with sometimes increased levels in the corresponding malignancies.[39] FKBP51 works by two distinct functional domains: a TPR (tetratricopeptide repeats tandem) domain that interacts with the heat shock proteins (HSP90 and HSP70) and a N-terminal domain that exert the peptidyl-prolyl isomerase activity.[56–59] During the past decade, a growing number of studies have highlighted a relevant role for FKBP51 in regulation of proliferation,[33,60–62] apoptosis,[33,34,36,37,63] tumour cell invasion,[64] metastasis[64] and resistance to treatment.[33,34,36,63] For most of these functions, a NF-κB-mediated mechanism of action has been demonstrated.[33,34,36,37,61] NF-kB transcription factor has a well-established role in regulating the expression of distinct target genes that are related to angiogenesis, anti-apoptosis and metastases.[65–67] Giraudier *et al.*,[61] in 2002, were the first to identify the role of FKBP51 in the control of NF-κB pathway in idiopathic myelofibrosis, a myeloproliferative syndrome characterized by abnormal proliferation of megakaryocytes and bone marrow fibrosis. Two years later, Bouwmeester *et al.*[27] confirmed the involvement of FKBP51 in the NF-κB-signalling network and suggested a role for this protein as a cochaperone of IKKα, IKKε, TAK1 and MEKK1. In 2004, another study identified FKBP51 as a crucial element in the chemotherapy-induced activation of NF-κB in melanoma.[36] The relevance of FKBP51 in NF-κB-mediated therapy resistance and aggressive behaviour has been extensively studied in melanoma,[28,34,36,64] leukaemia[37] and gliomas.[33] FKBP51 expression in reactive and neoplastic T cells and its biological significance are as yet unexplored. In the current work, FKBP51 expression was investigated for the first time in a selected population of CTCL, more specifically in 44 cases of MF, representative of the different stages of the disease. Normal skin, chronic dermatitis and thymus were simultaneously analysed, for comparison, as sources of normal T lymphocytes. The lowest levels of expression were found in normal skin and thymus. Expression of FKBP51 was observed in all assessed MF cases, with highest levels in tumour skin biopsies from patients with LCT associated with more aggressive disease and poor prognosis. In addition, we noted that LCT-MF showed a predominantly cytoplasmic localization for FKBP51 in comparison with patch and plaque MF and with the chronic dermatitis, in which the staining is almost exclusively nuclear. More interestingly, we found that cases, which showed a stronger and diffuse cytoplasmic expression of FKBP51, were also characterized by a strong cytoplasmic staining for TRAF2. The observation that FKBP51 and TRAF2 resulted significantly co-expressed in the cytoplasm of the tumour cells is extremely intriguing and in line with the function of FKBP51 within IKK kinase complex and the regulation of NF-κB-signalling activation. FKBP51 expression, indeed, appeared to be associated with that of NF-κB-regulated genes, namely TRAF2, BCL-2 and XIAP. Proteins encoded by such genes have a relevant role in protecting cells from apoptosis and, reasonably, may be responsible for therapy resistance of advanced MF. The suggested causative role of FKBP51 in MF resistance is in

agreement with several studies showing the sensitivity to rapamycin of some CTCL.[68,69]

Conclusions

In conclusion, our study shows that FKBP51 expression could help to better define a subgroup of MF patients with the most aggressive biological course because progressively increased from benign inflammatory dermatoses that express FKBP51 less strongly and in lower percentage through patch/plaque MF to tumour MF, being involved in deregulated NF-κB pathway.

We suggest a relationship between FKBP51 overexpression, NF-κB activation and the biological aggressiveness of MF and propose the phenotypic and molecular analysis of this protein as an adjunctive biomarker, in addition to clinical and histological data. Furthermore, considering that NF-κB inhibition increasingly attracts special interest as a possible strategy for treatment of CTCL, in combination therapies, targeting of FKBP51 may provide a promising therapeutic tool in this direction.[70,71]

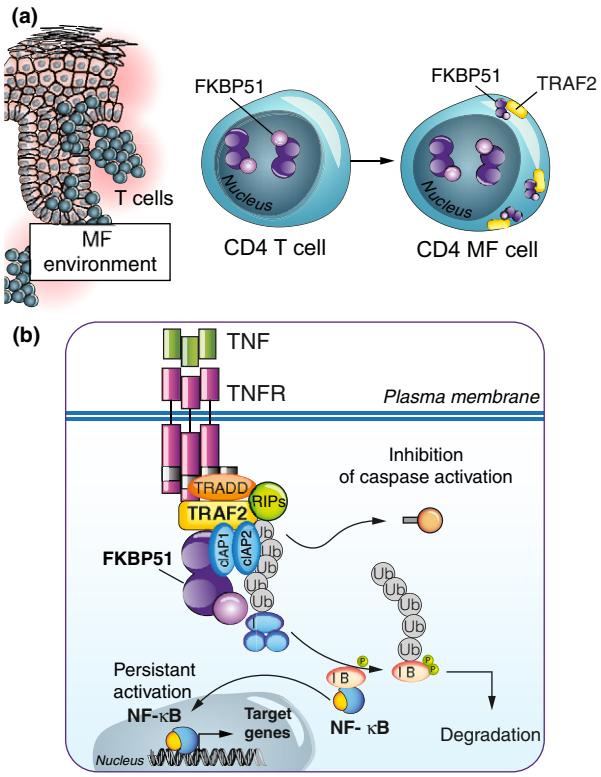

Figure 7 FKBP51 sustains NF-κB activation in CD4 MF cells. (a) Increased expression of FKBP51 in CD4 MF cells, compared to normal CD4 T lymphocytes. In MF cells, increased FKBP51 interacts with TRAF2. (b) Schematic representation of the TNFR signalling complex that leads to NF-κB activation. FKBP51 serves as a scaffold and isomerase for the correct assembly and function of IKK kinase complex.

Further investigations on larger series of patients will better disclose interplay between FKBP51 and NF-κB pathway in lymphomagenesis.

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