Expression and clinical significance of S100 family genes in patients with melanoma

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Genes in the S100 family are abnormally expressed in a variety of tumor cells and are associated with clinical pathology, but their prognostic value in melanoma patients has not yet been fully elucidated. In this study, we extracted and profiled S100 family mRNA expression data and corresponding clinical data from the Gene Expression Omnibus database to analyze how expression of these genes correlates with clinical pathology. Compared with normal skin, *S100A1, S100A13*, and *S100B* were expressed at significantly higher levels in melanoma samples. *S100A2, S100A7, S100A8, S100A9, S100A10, S100A11*, and *S100P* were all highly expressed in primary melanoma samples but were expressed at low levels in metastatic melanoma, and all of these genes were strongly correlated with each other ($P < 0.001$). We found the expression of these S100 family genes to be significantly correlated with both lymphatic and distant melanoma metastasis, as well as with American Joint Committee on Cancer grade but not with Clark's grade, age, or sex. This suggests that expression of these genes may be related to the degree of tumor invasion. Although further validation through basic and clinical trials is needed, our results suggest that the S100 family genes have the potential to play an important role in the diagnosis of melanoma. S100 expression may be related to tumor invasion and may facilitate the early diagnosis of melanoma, allowing for a more accurate prognosis. Targeted S100 therapies are also potentially viable strategies in the context of melanoma. *Melanoma Res* 29:23–29 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Melanoma is a highly invasive malignant tumor of the skin associated with significant morbidity and mortality, the incidence of which has been increasing in recent years [1]. The 5-year survival rate of melanoma is high when the tumor does not metastasize; however, this 5-year survival rate declines dramatically if tumors metastasize [2]. Therefore, the ability to diagnose melanoma early in its progression and to differentiate between benign tissue and melanoma tumors is key to allowing for effective and rapid intervention and treatment of affected individuals [3]. Many molecular mechanisms are involved in the occurrence, development, and metastasis of cancer. One such family of proteins believed to be linked to the development and metastasis of cancer is the S100 proteins family. S100 proteins family plays important roles in multiple stages of tumor proliferation, migration, invasion, and apoptosis [4,5] and is closely related to the development and progression of various cancer types including lung, breast, and ovarian cancer [6–10]. The abnormal expression of S100 proteins has also been reported in melanoma. For example, *S100A4* interacts with *RAGE* to promote the metastasis of melanoma cells [11,12]. There is also a significant correlation between *S100A6* expression in metastatic melanoma and both duration of patient survival as well as the thickness of the associated primary tumor [13]. However, the biological roles played by *S100A* proteins in melanoma is not fully understood, nor has there been any systematic attempt to assess the expression of these genes in melanoma or to assess how their expression relates to the clinical progression of this cancer. In this study, we therefore used the Gene Expression Omnibus database maintained by the NCBI (American Center for Biotechnology Information) to study the expression of *S100A* family genes in skin and melanoma samples, with the goal of further understanding the pathogenic roles of *S100A* family genes in melanoma.

Materials and methods

Sources of data

We downloaded the gene expression profile data set with the accession number GSE46517 from the NCBI Gene Expression Omnibus database. This data set was submitted

and published by Kabbarah and colleagues using the Affymetrix HG-U133A gene chip [13]. This data set included 73 cases of metastatic melanoma and 31 cases of primary melanoma, as well as eight normal skin tissue controls. Of these samples, basic patient data were available for 52 cases of metastatic melanoma and 31 cases of primary melanoma. The S100 family mRNA expression values were extracted. Clinical and pathological data were also extracted where available, including patient sex, age, Clark's level, TNM grade, and New-American Joint Committee on Cancer (AJCC) grade.

The relationship between S100 family gene expression and clinical pathology

The gene expression data and clinicopathological data in 52 patients with metastatic melanoma and 31 patients with primary melanoma were analyzed. Wilcoxon signed rank tests were used to compare the data between the two groups. Log fold change values were used as a reference to generate a significance heatmap, with P value less than 0.01 serving as a significance threshold. The log fold change is equal to the logarithm of the average expression of the former gene divided by that of the latter gene.

Correlation analysis of S100 family genes

The S100 family gene expression values of 112 patients were correlated with each other.

Statistical analysis

Data were imported into Microsoft Excel 2016 (Microsoft Corp, Redmond, Washington, USA) for data preprocessing and matrix generation. *R* was used for all statistical analyses. Spearman's rank correlation was used for correlation analyses, with P value less than 0.05 indicating a significant correlation and P value less than 0.001 indicating a strong correlation. The χ^2-tests was used to compare the count data, and the Wilcoxon test was used to compare numerical data, with the significance threshold being set at P value less than 0.01. Measured data were expressed as mean ± SD. The Kruskal–Wallis test was used for comparison between groups, with the significance threshold being set at P value less than 0.01. *R* was used to generate box plots and related heatmaps, whereas Excel 2016 was used to draw a difference heatmap.

Results

Basic information

Expression values for a total of 17 S100 family gene members were obtained, including *S100A1–S100A14*, *S100B*, *S100G*, and *S100P*. For these genes, 104 samples yielded gene expression data and 83 cases yielded both gene expression data and clinicopathological data. The age range of these 83 patients at the time of tumor resection was 28–93 years (57.47 ± 16.11 years). N stage ($\chi^2 = 30.132$, $P < 0.001$), M stage ($\chi^2 = 31.176$, $P < 0.001$) and AJCC ($\chi^2 = 62.34$, $P < 0.001$) stage are more later in primary melanoma compared with metastatic melanoma (Table 1).

Table 1 Basic information of 83 patients with melanoma with clinical and pathological information

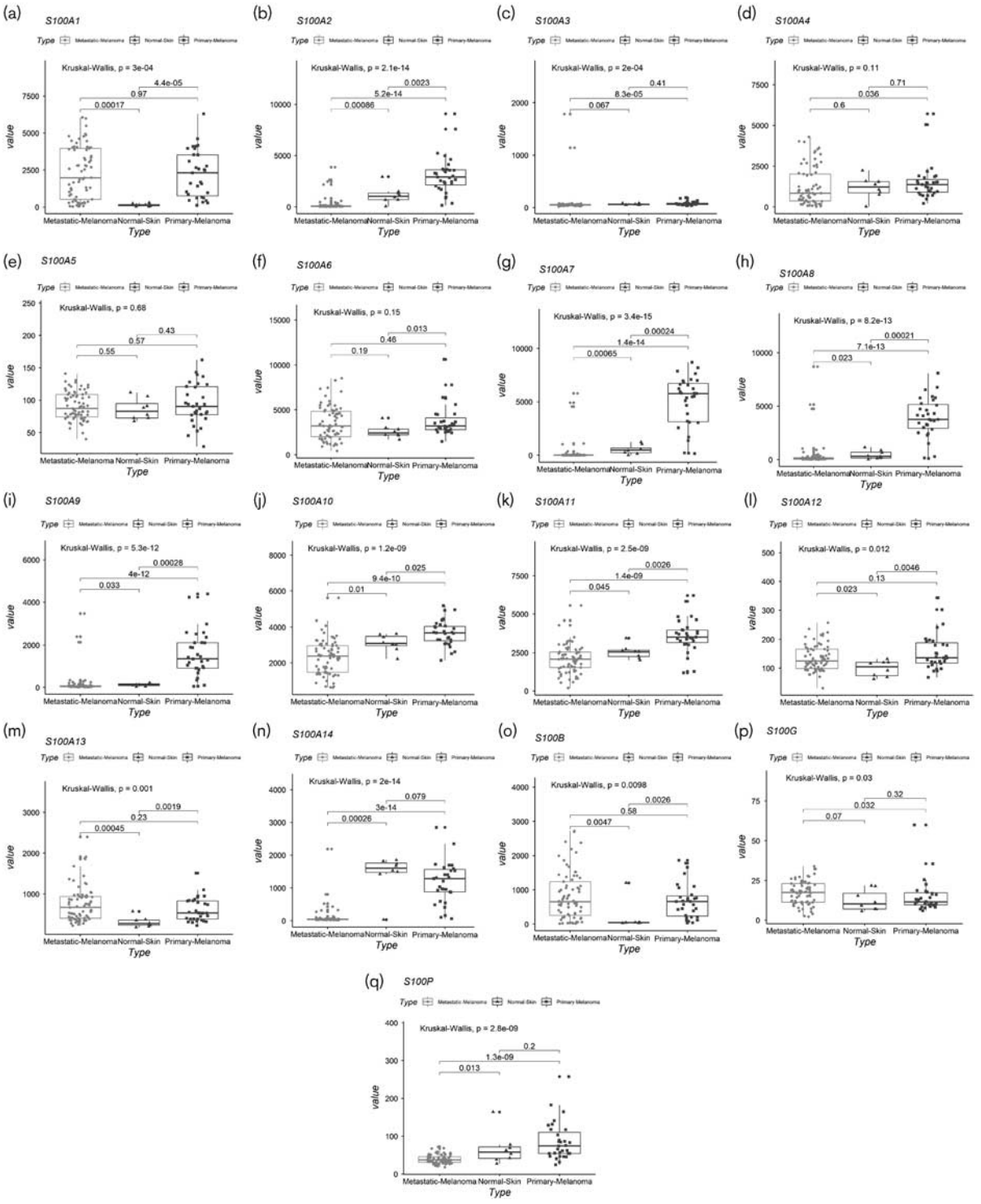
Parameters	Metastatic melanoma (52)	Primary melanoma (31)	χ^2	*P* value
Age (years)			0.18022	0.6712
≤60	29	15		
>60	23	16		
TNM T category			0.44642	0.504
T1–T2	16	13		
T3–T4	34	18		
Missing	2	0		
TNM N category			30.132	4.04E−08
N0–N1	16	30		
N2–N4	34	1		
Missing	2			
TNM M category			31.176	2.36E−08
M0	14	29		
M1	37	2		
Missing	1			
Clark's level			2.7539	0.09701
I–III	11	13		
IV–V	39	18		
Sex			2.1316	0.1443
Female	14	14		
Male	38	17		
AJCC			62.34	2.89E−15
1–2	0	27		
3–4	51	4		
Missing	1	0		
Site of primary tumor			4.533	0.1037
Extremity	16	15		
Head or neck	5	5		
Trunk	31	11		

AJCC, American Joint Committee on Cancer.

The expression level of S100 family genes in different tissues

For the available 104 patients, S100 gene expression was compared in 73 patients with metastatic melanoma, 31 patients with primary melanoma, and eight patients with normal skin who served as controls. *S100A1*, *S100A2*, *S100A3*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11*, *S100A13*, *S100A14*, *S100B*, and *S100P* mRNA were all differentially expressed among the skin, primary melanoma, and metastatic melanoma samples ($P < 0.01$). Genes were further divided into two classes. The first class of genes – *S00A1*, *S100A13*, and *S100B* – were all highly expressed in primary melanoma and in metastatic melanoma as compared within normal skin tissue ($P < 0.01$). The second class of genes – *S100A2*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11*, and *S100P* – were all highly expressed in primary melanoma and were expressed at lower levels in metastatic melanoma compared with normal skin tissue ($P < 0.01$). In addition, *S100A3* mRNA was expressed at lower levels in metastatic melanoma samples relative to primary melanoma samples. Compared with normal skin tissue, there was also reduced expression of *S100A14* mRNA in both primary melanoma and metastatic

Fig. 1



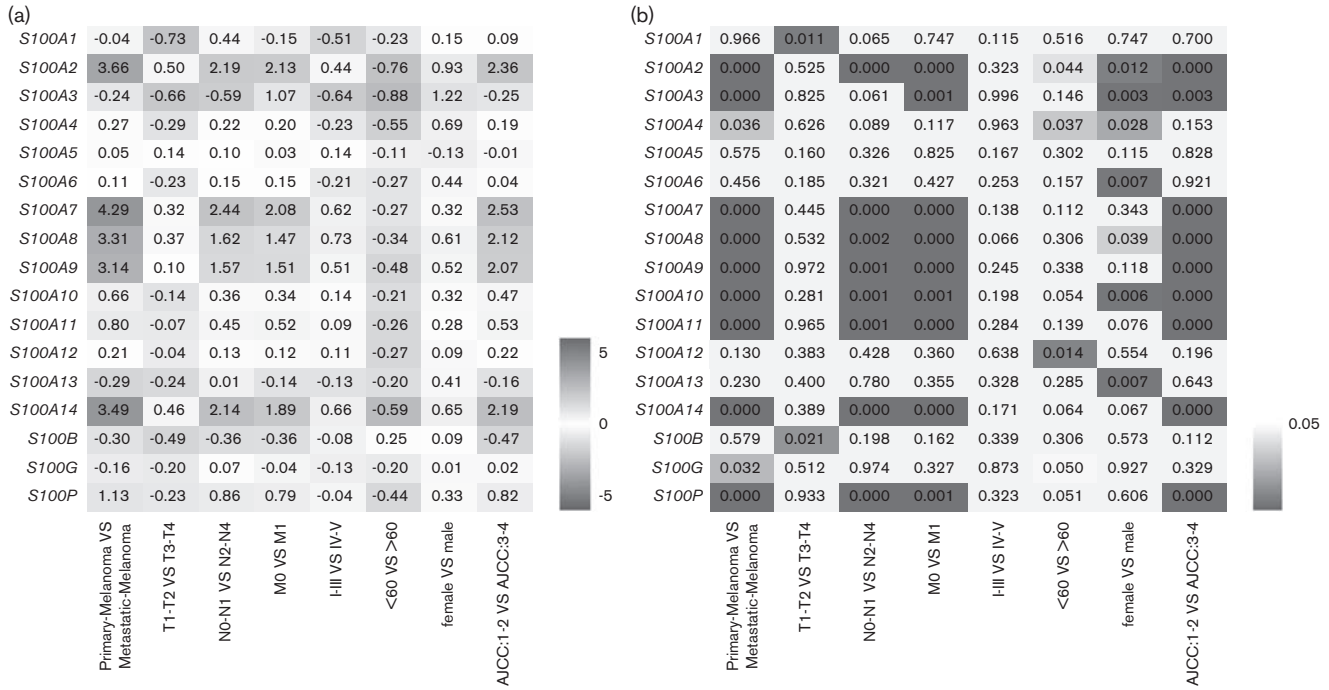
Expression levels of S100 family genes in different tissues. (a) S100A1 (b) S100A2, (c) S100A3, (d) S100A4, (e) S100A5, (f) S100A6, (g) S100A7, (h) S100A8, (i) S100A9, (j) S100A10, (k) S100A11, (l) S10012, (m) S10013, (n) S10014, (o) S100B, (p) S100G, and (q) S100P.

melanoma, with lower levels in metastatic melanoma relative to primary melanoma. No significant differences in the expression of *S100A4*, *S100A5*, *S100A6*, *S100A12*, or *S100G* mRNA were observed (Fig. 1).

The relationship between S100 family mRNA expression and clinical pathology

We found that eight genes – *S100A2*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11*, *S100A14*, and *S100P* – were

Fig. 2



Correlation between S100 family gene expression values and clinicopathological data, *P* value and log fold change, with FC being equal to the mean expression of the former gene divided by that of the latter gene. (a) A log fold change heatmap was generated, with positive value representing higher expression of the former gene in the two groups being compared, and negative value representing higher expression of the gene in the latter of the two groups compared. (b) A *P* value heatmap was generated, with grey indicating $P < 0.01$.

expressed at low levels in metastatic melanoma and were associated with the N and M categories of TNM staging ($P < 0.01$). There was no association with the T category. S100 mRNA expression was also associated with both lymphatic and distant site tumor metastasis, as well as with the AJCC stage ($P < 0.01$). Patients in the terminal stages of melanoma showed lower expression of these differentially expressed S100 family genes. No significant associations with Clark's rating, age, or sex were observed (Fig. 2).

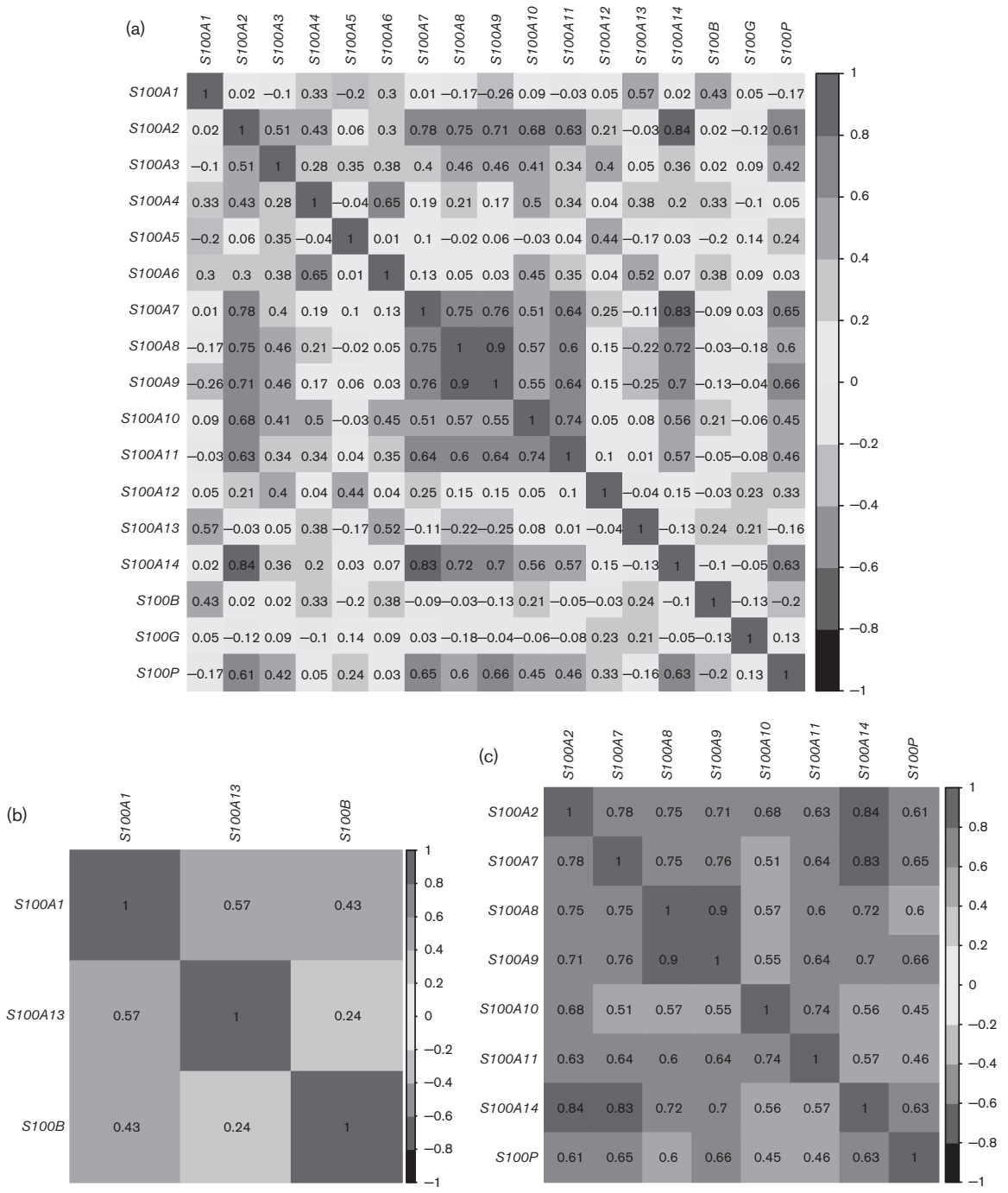
S100 family genes correlation analysis

Upon performing correlation analyses comparing S100 family gene expression with each other, we found that the first class type of each gene has a weak positive correlation ($P < 0.05$; Fig. 3b and Table 2). The genes in the second class of S100 family – *S100A2, S100A7, S100A8, S100A9, S100A10, S100A11, S100A14*, and *S100P* – were all strongly positively correlated with each other ($P < 0.001$; Fig. 3b and Table 2). *S100A14* mRNA expression correlated similarly with clinical pathology, as did S100 family genes in this second class, suggesting *S100A14* may itself be a member of this class. These results also showed that these genes were strongly correlated with each other ($P < 0.001$; Fig. 3c and Table 2). In addition, *S100A3* is positively correlated with the genes in this second class (Fig. 3a and Table 2), even though its expression is lower in metastatic melanoma than in primary melanoma.

Discussion

S100 was first discovered in the bovine brain by Moore [14], with two family members – *S100A1* and *S100B* – being initially identified. To date, more than 25 S100 family members have been found in humans, including *S100A1–S100A16, S100B, S100P, S100G*, and *S100Z* [6,15]. *S100A1-16* is located in the chromosome 1q21 region, *S100B* is located in the chromosome 21q22 region, *S100P* is located in the chromosome 4p16 region, *S100G* is located in the chromosome Xp22 region, and *S100Z* is located in the chromosome 5q13 region[4,16,17]. The S100 gene family is the largest subfamily of EF-hand calcium-binding proteins and is present only in vertebrates [15]. Gens of this family interact with different protein targets after undergoing calcium-dependent conformational changes, resulting in a wide range of intracellular and extracellular functions. Within a cell, a single S100 protein can modulate multiple targets, or multiple S100 proteins can co-regulate a single target, leading to a complex biology regulatory mechanism. These proteins have been shown to regulate the cell cycle, growth, migration, phosphorylation, cytoskeleton components, and many other cellular functions [4]. Extracellular S100 proteins can interact with multiple cell surface receptors including G protein-coupled receptors, Toll-like receptor 4, scavenger receptors, fibroblast growth factor receptor 1, and extracellular receptors such as matrix metalloproteinase inducer [18,19]. In the context of cancer, these proteins have also

Fig. 3



Heatmap of the S100 family genes. (a) A heatmap of all S100 family genes was generated. (b) The first class of S100 family genes is shown on an interrelation heatmap. (c) The second class of S100 family genes is shown on an interrelation heatmap.

been shown to be involved in cell proliferation, metastasis, angiogenesis, invasion, inflammation, and the differentiation of physiological functions [3]. In many cancers, expression of S100 family genes is significantly altered, implying that the S100 family is associated with tumor progression [4,20].

In this study, we studied the expression levels of each S100 family gene member in the context of melanoma. Our results revealed that there are two major classes of expression patterns for S100 family genes in this context. The first class of genes, *S100B*, *S100A1*, *S100A12* and

Table 2 Correlations between S100 family genes at the mRNA level

	S100A1	*S100A2*	*S100A3*	*S100A4*	*S100A5*	*S100A6*	*S100A7*	*S100A8*	*S100A9*	*S100A10*	*S100A11*	*S100A12*	*S100A13*	*S100A14*	*S100B*	*S100G*	*S100P*
S100A1	<0.001	0.845	0.300	0.001	0.039	0.002	0.896	0.083	0.008	0.379	0.771	0.632	<0.001	0.833	<0.001	0.600	0.087
S100A2	0.845	<0.001	<0.001	<0.001	0.563	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	0.032	0.763	<0.001	0.830	0.229	<0.001
S100A3	0.300	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.589	<0.001	0.805	0.349	<0.001
S100A4	0.001	<0.001	0.004	<0.001	0.692	<0.001	0.049	0.034	0.094	<0.001	<0.001	0.704	<0.001	0.038	0.001	0.301	0.639
S100A5	0.039	0.563	<0.001	0.692	<0.001	0.942	0.315	0.829	0.560	0.725	0.667	<0.001	0.078	0.750	0.043	0.163	0.014
S100A6	0.002	0.002	<0.001	<0.001	0.942	<0.001	0.194	0.639	0.745	<0.001	<0.001	0.711	<0.001	0.450	<0.001	0.364	0.772
S100A7	0.896	<0.001	<0.001	0.049	0.315	0.194	<0.001	<0.001	<0.001	<0.001	<0.001	0.011	0.277	<0.001	0.356	0.801	<0.001
S100A8	0.083	<0.001	<0.001	0.034	0.829	0.639	<0.001	<0.001	<0.001	<0.001	<0.001	0.126	0.028	<0.001	0.753	0.071	<0.001
S100A9	0.008	<0.001	<0.001	0.094	0.560	0.745	<0.001	<0.001	<0.001	<0.001	<0.001	0.127	0.010	<0.001	0.200	0.680	<0.001
S100A10	0.379	<0.001	<0.001	<0.001	0.725	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.599	0.406	<0.001	0.031	0.545	<0.001
S100A11	0.771	<0.001	0.001	<0.001	0.667	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.299	<0.001	<0.001	0.599	0.401	<0.001
S100A12	0.632	0.032	<0.001	0.704	<0.001	0.711	0.011	0.126	0.127	0.599	0.299	<0.001	0.668	0.123	0.738	0.020	0.001
S100A13	<0.001	0.763	0.589	<0.001	0.078	<0.001	0.277	0.028	0.010	0.406	0.904	0.668	<0.001	0.189	0.013	0.036	0.102
S100A14	0.833	<0.001	<0.001	0.038	0.750	0.450	<0.001	<0.001	<0.001	<0.001	<0.001	0.123	0.189	<0.001	0.289	0.630	<0.001
S100B	<0.001	0.830	0.805	0.001	0.043	<0.001	0.356	0.753	0.200	0.031	0.599	0.738	0.013	0.289	<0.001	0.193	0.041
S100G	0.600	0.229	0.349	0.301	0.163	0.364	0.801	0.071	0.680	0.545	0.401	0.020	0.036	0.630	0.193	<0.001	0.192
S100P	0.087	<0.001	<0.001	0.639	0.014	0.772	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.102	<0.001	0.041	0.192	<0.001

The correlations of gene mRNA expression in s100 families were tested using the Spearman's rank correlation.

S100A13, is highly expressed in the melanoma group compared with normal skin, which was consistent with previous reports. *S100B* is highly expressed in melanoma and plays a role in the treatment of melanoma as it can predict the efficacy of treatment [21]. High levels of *S100B* in melanoma are associated with a poor efficacy of the treatment, whereas low levels of *S100B* predict efficient response to the treatment and improved patient survival, and it is often associated with *LDH* expression [22] and can predict melanoma patient survival [23]. Overexpression of *S100A1* is associated with melanoma, breast cancer, ovarian cancer, and endometrial carcinoma [7,24,25]. In ovarian cancer, *S100A1* is highly expressed and is significantly associated with lymph node metastasis, tumor stage, and tumor grade [7]. *S100A12* mRNA expression is significantly upregulated in bladder cancer tissues, and *S100A13* is upregulated in astroglial gliomas and melanomas and is correlated with vascular endothelial growth factor-A expression, microvessel density, and tumor grade [26]. Cell lines with high expression of *S100A13* are more aggressive in lung cancer cell lines [27]. However, no association between expression of S100 family members in this first class gene expression and clinical pathology was observed. The second class of S100 genes was highly expressed in primary melanoma, but was expressed at low levels in metastatic melanoma. Genes in this class included *S100A2*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11* and *S100P*, and all of these genes were strongly correlated with one another. Expression of these genes was associated with AJCC grade and with both lymphatic and distant melanoma metastasis. We therefore speculate that these genes are likely to be associated with the degree of melanoma malignancy, consistent with the findings of earlier studies, wherein such genes are highly expressed in noninvasive tumors and are expressed at low levels in invasive tumors [6]. For example, *S100A11* is considered to be a tumor suppressor gene whose expression increases during the early stages of pancreatic cancer development and decreases upon subsequent cancer progression [28]. The expression of *S100A11* is suppressed during the development of bladder cancer, and the loss of its expression is associated with the poor survival of patients with bladder cancer [29]. Previous reports have found that the differential expression of S100 family members varies by tumor type. For example, *S100A8* and *S100A9* are upregulated in tumors including those of gastric, esophageal, and colonic origin but downregulated in head and neck squamous cell carcinoma, esophageal cancer , and cervical cancer [30,31]. *S100A10* is upregulated in renal cell carcinoma and gastric cancer but downregulated in breast cancer [32]. S100 family members may have different expression patterns at different stages of cancer progression. Many previous studies have not distinguished between noninvasive and invasive tumors, which may lead to some differences in results and will necessitate further verification. These

two groups of S100 genes thus yield two different progression-associated expression patterns, allowing for effective monitoring of cancer progression. If the expression of S100 family genes of the second class is low, this may be indicative of tumor metastasis. High expression of genes in the first class, meanwhile, predicts tumorigenesis.

Conclusion

In this study we have comprehensively examined the expression of S100 family genes as they relate to melanoma progression and clinicopathology. Our results show that S100 family genes may be divided into two classes of genes, one class is composed of *S100A1*, *S100A13*, and *S100B*, whereas the other is composed of *S100A2*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11*, and *S100A14*. We believe that the differential expression of these S100 genes is directly associated with the development and progression of melanoma. These gens can thus be used as an independent prognostic indicator in patients with melanoma, especially in the early stages of disease. These genes may also be effective markers allowing for differentiation between benign and malignant tumors. Further research and both basic and clinical experimentation will be needed to validate these findings. This study has greatly advanced the current understanding of the expression of S100 family genes in the context of melanoma, demonstrating that the S100 family may play a unique and important role in melanoma.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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