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mRNA EXPRESSIONS MMP-2 AND MMP-9 AS POTENTIAL MOLECULAR MARKERS FOR DISTINGUISHING THE BOUNDARY BETWEEN TUMOUR AND NORMAL TISSUE IN BASAL CELL CARCINOMA

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Abstract

Introduction: Non-melanoma skin cancers (NMSC) are the most common malignant neoplasms, the number of which continues to increase. BCC is characterized by slow growth, its main clinical feature being that it infiltrates adjacent tissues and destroys adjacent structures.
Material and methods: The expression of mRNA transcripts for collagen types I, IV and MMP-2 and MMP-9 were compared in skin biopsies from patients with BCC of the skin and in the biopsies of healthy skin from the tumour margin. The study involved seventy patients diagnosed with BCC.
Results: The differences between mRNA expressions for MMP-2 and MMP-9, type I collagen and type IV collagen were investigated in nodular and infiltrative BCC both in tumour tissue samples and normal tissue samples taken from the tumour margins of the same patients.
Conclusions: Significantly higher levels of mRNA expressions for type I collagen, MMP-2 and MMP-9, as well as consistently lower levels of mRNA expression for type IV collagen in tumour tissue compared to tumour margin tissue obtained from the same patients, were identified in both types of BCC. These differences indicate a different role for collagen I and collagen IV in the pathomechanism of BCC.
Key words: BCC, MMPs, molecular markers, collagen type I and IV

Introduction

Non-melanoma skin cancers (NMSC) are the most common malignant neoplasms, the number of which continues to increase [1,2]. Between 75% and 80% of all NMSCs are basal cell carcinoma (BCC) [3,4]. The incidence of this cancer is increasing by 10% annually [5,6]. In Europe, the United States and Australia, the frequency of BCC diagnoses has grown dynamically in recent years, particularly among white people [7]. Despite the fact that BCC occurs most often in old age, the average age of BCC onset continues to fall and even occurs in adolescents [8].

According to the BCC classification system, which is based on an analysis of its clinical features, the course of the disease and a histopathological assessment, BCC can be nodular, infiltrative, superficial, pigmented, morphoeic, ulcerative and major ulcerative [9].

The important risk factors for the development of BCC are ultraviolet radiation, a positive family history of BCC, male sex, old age and skin phototypes I and II on the Fitzpatrick scale [10–12]. At the genetic level, the important factors in the pathogenesis of BCC are the activation of the Hedgehog (Hh) pathway, involvement of the MYCN, PPP6C, STK19, LATS1, ERBB2, PIK23C, N-RAS, K-RAS and H-RAS genes, the loss of function in PTPN14, RB1 and FBXW7, as well as P53 dysfunction in the formation of BCC [9].

BCC is characterized by slow growth, its main clinical feature being that it infiltrates adjacent tissues and destroys adjacent structures. In most cases, this cancer shows a low degree of local malignancy and the frequency of metastases is minimal. So far, only 400 cases of BCC metastases to other organs have been

described, including to the lymph nodes, lungs, liver and bones [3,9], but recurrences are frequent (40% to 50%) [5]. BCC very rarely metastasizes and is also rarely life-threatening, yet over the several-year course of the disease, significant local advancement of the tumor may lead to the involvement of adjacent tissues, which is particularly visible in the area of the face [11,13,14]. The number of recorded cases and the location of the tumor, primarily on the face, neck and trunk, mean that BCC is a significant problem. A wide excision of a neglected lesion may lead to significant anatomical deformations [2,3,9]. For this reason, particularly when located on the face, BCC causes serious aesthetic defects that have a significant impact on the quality of life of patients [3,15].

The diagnosis of BCC is important. When detected in the early stages, this cancer is curable. A BCC is likely to be diagnosed while examining a patient [12,16]. The macroscopic evaluation of the tumor most often allows for an accurate diagnosis. However, in case of doubt, the diagnosis can be confirmed by histopathological analysis [2,5,9,12]. Taking a biopsy from the lesion makes it easier to make the right decision about further treatment methods and, above all, makes it possible to choose the appropriate surgical technique for removal of the lesion. Treatment methods include conventional surgery, Mohs micrographic surgery, laser therapy, cryosurgery, curettage and radiotherapy, and, in certain cases, pharmacotherapy with Imiquimod, 5-fluorouracil or Vismodegib, or Sonidegib – an inhibitor of the Hh pathway [3,4,17–19].

Surgical methods with a 4 mm margin are most commonly used in treatment. Due to the difficulties in assessing the margin, the tumor is often not completely removed, leading to recurrence of the disease [2,20]. The development of molecular biology has enabled the introduction of a new approach for both the diagnosis and treatment of neoplasms [12]. Taking a biopsy makes it possible to implement molecular biology techniques to assess the advancement of the neoplastic lesion and to determine the normal tissue boundaries.

Metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases capable of remodeling and degrading extracellular matrix (ECM) proteins and the basal membrane (BM) of the vessels [21]. MMPs are responsible for the decomposition of the ECM and, therefore, their synthesis must be precisely regulated on many levels to ensure the ECM components are synthesized and proteolyzed in the correct proportions [22].

MMPs degrade ECM components and are responsible for the selective proteolysis of cell receptors, adhesion factors, growth factors and cytokines, and for the maintenance of the normal functions of connective tissue cells [23,24]. Thanks to this, MMPs regulate the structure of the ECM. MMPs are the only enzymes capable of degrading type IV collagen, which is the basic component of the BM of blood vessels. Metalloproteinase 2 (MMP-2) and metalloproteinase 9 (MMP-9) are the main enzymes that catalyze the hydrolysis of type IV collagen. This is possible due to the presence of a fibronectin type II domain in

the molecules of these enzymes [25–27]. The additional MMP-2 also degrades type I collagen, which accounts for 80% of the total skin collagen mass. The role of MMPs in initiating the development of skin neoplasms, such as malignant melanoma, BCC, squamous cell carcinoma, as well as in glioblastomas, lung, stomach, uterine and breast neoplasms, has also been emphasized [28–33]. The presence of increased levels of MMPs correlates with the stage of the tumor [34]. It is presumed that increased local expression of MMPs may be considered a new, significant prognostic factor that may influence the decision to implement adjuvant treatment [34,35].

The main role in the progression of BCC is played by the gelatinases MMP-2 and MMP-9, as well as their inhibitors – TIMPs [36,37]. In the catalytic domain of these enzymes, there is a fragment of repeating amino acid sequences, which allows the MMP-2 and MMP-9 molecules to bind to collagen and elastin [38,39]. As these MMPs can degrade type IV collagen, neoplastic cells can migrate beyond the tumor tissue and create distant metastases [40]. A key role in this process is attributed to MMP-9, which acts as a promoter of tumor invasion [41]. Increased MMP-9 expression correlates with the BCC stage and is responsible for the more severe course of this disease [40,42,43].

There are also reports on the role of MMP-9 in the process of neoangiogenesis, as it is involved in the growth of endothelial cells and the activation of pro-angiogenic factors [40].

Our study investigated the expressions of mRNA transcripts for the metalloproteinases MMP-2 and MMP-9 and their substrates of type IV and I collagens in BCC. A quantitative evaluation of the mature mRNA transcripts was conducted. This allows for proper evaluation of protein expression, since the biosynthesis of these proteins is regulated primarily when transcription and post-transcriptional modification takes place. The presence of mRNA in these tissues confirms the expression of the gene. Examining the mRNA transcripts makes it possible to assess the quality of gene expression after post-transcriptional modification. It is possible to evaluate the expression of this gene at the RNA level using many methods of molecular biology. In this study, the RT-PCR technique was used.

The main goal of this study was to demonstrate and compare the expression of mRNA transcripts for collagen types I, IV and metalloproteinases MMP-2 and MMP-9 in skin biopsies from patients with BCC of the skin and in the biopsies of healthy skin from the tumour margin of the same patients.

Material and methods

Agreements KBET/74/B/11 were obtained from the Bioethics Committee of the Jagiellonian University regarding the use of the skin biopsy samples collected for the purposes of this study. The material for the study included biopsy samples

of neoplastic tissue obtained from BCC patients. The control group consisted of healthy tissue biopsy samples taken from the tumor margins of the same patients. The material was surgically collected during the tumor removal procedure.

The study involved seventy patients – twenty women and fifty men – diagnosed with BCC. It included biopsy samples collected from patients with primary BCC lesions only, with no coexisting neoplasms. Patients were divided into age groups. There were twenty individuals under the age of 68, thirty-two aged between 69 and 78 years, and eighteen aged 79+. The mean age of the patients was 72.7 ± 6.2 years.

The nodular type of BCC was diagnosed in forty patients and the infiltrative BCC variant in thirty. In each case, the patient's skin phototype was determined according to Fitzpatrick's classification and the location of the neoplastic lesion on the patient's skin was recorded. Phototype II was determined in fifteen individuals and phototype III in fifty-five. Neoplastic lesions were located on the head in fifty-six patients, and on the torso in fourteen. The presence of the tumor and its type were diagnosed by clinical examination and confirmed by histopathological examination.

mRNA expression for the genes of MMP-2, MMP-9, collagen I (COL1A1), collagen IV (COL4A4), and a reporter gene for beta-actin (ACTB) was identified in the skin biopsy samples collected from BCC patients. This expression was identified on both tumor tissues designated T (tumor) and normal tissues designated NT (normal tissue) derived from the tumor margins of the same patients.

The total RNA was isolated from cells with TRIzol (Invitrogen, USA). The concentration of the RNA extracted was determined on the basis of its absorbance at a wavelength of 260 nm in a UV photometer (Photometer UV GeneRay, Biometra). RNA samples (1 mg) were reversely transcribed to cDNA using a RevertAid™ H Minus First Strand cDNA Synthesis Kit (Fermentas, Lithuania) with beta-actin as a reporter gene.

RT-PCR was performed in a Mastercycler gradient EP 5331 thermocycler (Eppendorf, Germany) using Opti Taq hot-start polymerase (Eurx, Poland) and the following primers (DNA Gdansk, Poland): HU MMP-2 F 5'-CACTTTCCTGGGCAACAAAT-3', HU MMP-2 R 5'-CTCCTCAATGCCCTTGATGT-3' (10 μM primer solution); HU MMP-9 F 5'-TCCCTGGAGACC TGAGAACC-3' HU MMP-9 R 5'-GTCGTCGGTGTCGTAGTTGG-3'(10 μM primer solution); HU COL1A1 F 5'- ACGCATGAGCGGACGCTAACC -3' HU COL1A1 R 5'- AGTGTCTCCCTTGGGTCCCTCG -3'(10 μM primer solution); HU COL4A4 F 5'-CCC CTC AGG ACC AGG GTG CAA-3', HU COL4A4 R 5'-AGG GGC GGATCGCCTCTTCCA-3'(4 μM primer solution); and HU ACTB F5'-GGACTTCG AGCAAGAGATGG-3'HU ACTB R 5'-AGCACTGTGTTGGCGTACAG-3'(6 μM primer solution). The reaction products, MMP-2 (271 kbp), MMP-9 (659 kbp), type I collagen (414 kbp), type IV collagen (482 kbp) and β-actin (234 kbp), were separated via agarose gel electrophoresis.

The electrophoretograms were visualized with a UV transilluminator (Vilber Lourmat, France) and photographed with a digital camera (Olympus, USA) with the aid of a PolyDoc system for electrophoretic gel documentation and analysis (Vilber Lourmat, France). The digital recordings of the electrophoretograms underwent densitometric analysis with the software Quantity One 4.2.1 (Bio-Rad, USA) to determine the densities of the RT-PCR products, which were assumed to be the equivalents of mRNA expressions for MMP-2, MMP-7, MMP-9 and type IV collagen.

Statistical analysis was conducted using the package SPSS 18 (IBM, USA). The parametric paired samples *t*-test was used to compare the measurements and the independent samples *t*-test to compare the groups in terms of the values of the parameters tested. The power and direction of the correlations between pairs of variables were determined on the basis of Pearson's coefficients of linear correlation (r) and the correlation between two variables using Spearman's rank correlation coefficient. The statistical significance of all the tests was assumed to be $p \leq 0.05$.

Results

Biopsy samples were collected for analysis from the tumor foci of nodular and infiltrative BCC as well as from the healthy tissue margin of the same patients. Based on the results obtained, a normal distribution was found and therefore the parametric Student's *t*-test was used. This cancer is more common in men, which was confirmed by this study, where the group of seventy patients included fifty men and only twenty women, although those who met the inclusion criteria had been randomly selected. BCC are classified as NMSC, which most often occurs in people with skin phototypes I, II or III. The incidence of this type of neoplasm is nineteen times higher in the white population than black [44]. Most often, BCC occurs in people with phototypes II and III, which was also confirmed by this study, where phototype II occurred in fifteen individuals and phototype III in fifty-five. Due to the constantly increasing number of cases of NMSC, numerous studies are being conducted to understand the pathogenesis of these neoplasms and to develop effective therapeutic methods.

Differences between the mRNA expressions for MMP-2 and MMP-9, type I collagen and type IV collagen were investigated in nodular and infiltrative BCC in tumor tissue samples and normal tissue samples taken from the tumor margins of the same patients (Table 1).

Differences between the mRNA expressions for MMP-2, MMP-9, type I collagen and type IV collagen depending on the BCC type (nodular, infiltrative) in the T and NT groups are presented in Table 2.

Table 1. Differences between the mRNA expressions for MMP-2 and MMP-9, type I collagen and type IV collagen in tumour (T) and normal tissue (NT) biopsy samples in nodular and infiltrative BCC

Group	Mean	Differences in paired samples					t	Significance (two-sided)
		Standard deviation	Standard error of the mean	95% confidence interval for the difference between means				
				Lower limit	Upper limit			
NODULAR	MMP-2 T – MMP-2 NT	0.55	0.12	0.02	0.51	0.58	**31.26**	**< 0.001**
	MMP-9 T – MMP-9 NT	0.27	0.16	0.02	0.22	0.32	**11.64**	**< 0.001**
	COL IV T – COL IV NT	5.87	3.27	0.49	4.89	6.85	**12.05**	**< 0.001**
	COL I T – COL I NT	1.06	0.27	0.04	0.98	1.14	**26.58**	**< 0.001**
INFILTRATIVE	MMP-2 T – MMP-2 NT	0.71	0.31	0.05	0.61	0.81	**14.42**	**< 0.001**
	MMP-9 T – MMP-9 NT	0.45	0.16	0.03	0.40	0.51	**17.84**	**< 0.001**
	COL IV T – COL IV NT	27.71	12.83	2.03	23.61	31.82	**13.66**	**< 0.001**
	COL I T – COL I NT	0.39	0.20	0.03	0.33	0.45	**12.60**	**< 0.001**

Table 2. Differences between the mRNA expressions for MMP-2, MMP-9, type I collagen and type IV collagen depending on the BCC type (nodular, infiltrative) in the T and NT groups

Parameter (nodular to infiltrative)	t	Significance (two-sided)	Mean difference	Standard error of the difference	95% confidence interval for the difference between means	
					Lower limit	Upper limit
MMP-2 T	**-2.06**	**0.043**	-0.09	0.05	-0.19	0.00
MMP-2 NT	**3.61**	**0.001**	0.07	0.02	0.03	0.10
MMP-9 T	**-5.05**	**0.000**	-0.18	0.04	-0.25	-0.11
MMP-9 NT	1.49	0.139	0.01	0.01	0.00	0.02
COL IV T	**-11.52**	**0.000**	-22.60	1.96	-26.51	-18.70
COL IV NT	-1.32	0.191	-0.76	0.58	-1.91	0.39
COL I T	**12.06**	**0.000**	0.62	0.05	0.52	0.72
COL I NT	-1.22	0.224	-0.04	0.04	-0.12	0.03

Differences between the mRNA expressions for MMP-2 and MMP-9, type I collagen and type IV collagen in nodular and infiltrative BCC depending on the phototype of the patients' skin were also examined. The results are presented in Tables 3 and 4.

The correlation between an increase in mRNA expression for MMP-2 and an increase in mRNA expression for type IV collagen in nodular and infiltrative BCC was investigated. The results are presented in Table 5.

The correlation between an increase in mRNA expression for MMP-9 and a decrease in mRNA expression for type IV collagen in nodular and infiltrative BCC was investigated. The results are presented in Table 6.

The correlation between an increase in mRNA expression for MMP-9 and an increase in mRNA expression for type I collagen in nodular and infiltrative BCC was investigated. The results are presented in Table 7.

Table 3. Differences between the mRNA expressions for MMP-2 and MMP-9, type I collagen and type IV collagen depending on skin phototype in the T and NT groups

Parameter	Phototype II	Phototype III	Phototype II	Phototype III
	Nodular		Infiltrative	
MMP2 T	0.88	0.86	0.93	0.88
MMP2 NT	0.32	0.29	0.26	0.22
MMP9 T	0.31	0.38	0.53	0.55
MMP9 NT	0.07	0.07	0.07	0.06
COL IV T	17.79	20.28	44.80	43.39
COL IV NT	12.84	14.46	14.49	13.86
COL I T	1.47	1.51	0.88	0.85
COL I NT	0.47	0.41	0.44	0.43

Table 4. Correlation between the skin phototype and the levels of mRNA expression for MMP-2 and MMP-9, type I collagen and type IV collagen in the T and NT groups

	Mean Group 1	Mean Group 2	t-value	df	p	Std. Dev. phototype II	Std. Dev. phototype III	F-ratio Variances	p Variances
				Nodular type					
PHOTOTYPE vs. MMP2 T	2.82	0.84	32.69	88	0	0.39	0.12	9.65	0
PHOTOTYPE vs. MMP2 NT	2.82	0.29	43.01	88	0	0.39	0.07	25.14	0
PHOTOTYPE vs. MMP9 T	2.82	0.34	39.74	88	0	0.39	0.16	5.74	0
PHOTOTYPE vs. MMP9 NT	2.82	0.06	47.62	88	0	0.39	0.03	175.21	0
PHOTOTYPE vs. COL IV T	2.82	19.51	-27.07	88	0	0.39	4.12	113.38	0
PHOTOTYPE vs. COL IV NT	2.82	13.63	-27.89	88	0	0.39	2.57	44.25	0
PHOTOTYPE vs. COL I T	2.82	1.47	19.78	88	0	0.39	0.25	2.47	0
PHOTOTYPE vs. COL I NT	2.82	0.41	39.78	88	0	0.39	0.12	9.78	0

	Mean Group 1	Mean Group 2	t-value	df	p	Std. Dev. phototype II	Std. Dev. phototype III	F-ratio Variances	p Variances
	Infiltrative type								
PHOTOTYPE vs. MMP2 T	2.82	0.94	25.12	78	0	0.38	0.27	1.90	0
PHOTOTYPE vs. MMP2 NT	2.82	0.23	41.53	78	0	0.38	0.09	18.09	0
PHOTOTYPE vs. MMP9 T	2.82	0.52	34.99	78	0	0.38	0.16	5.72	0
PHOTOTYPE vs. MMP9 NT	2.82	0.06	45.38	78	0	0.38	0.01	716.56	0
PHOTOTYPE vs. COL IV T	2.82	42.11	-19.98	78	0	0.38	12.43	1043.14	0
PHOTOTYPE vs. COL IV NT	2.82	14.41	-26.31	78	0	0.38	2.75	51.25	0
PHOTOTYPE vs. COL I T	2.82	0.85	28.00	78	0	0.38	0.23	2.92	0
PHOTOTYPE vs. COL I NT	2.82	0.46	34.30	78	0	0.38	0.21	3.51	0

Table 5. Correlation between an increase in mRNA expression for MMP-2 and an increase in mRNA expression for type IV collagen in nodular and infiltrative BCC

Group			COL IV T	COL IV NT
NODULAR	MMP-2 T	Pearson's correlation	0.08	0.10
		Significance (two-sided)	0.62	0.50
	MMP-2 NT	Pearson's correlation	0.06	**0.41****
		Significance (two-sided)	0.69	**0.01**
INFILTRATIVE	MMP-2 T	Pearson's correlation	-0.04	0.07
		Significance (two-sided)	0.79	0.68
	MMP-2 NT	Pearson's correlation	**-0.35***	0.06
		Significance (two-sided)	**0.03**	0.72

* The correlation is significant at a level of 0.05 (two-sided)

** The correlation is significant at a level of 0.01 (two-sided)

Table 6. Correlation between an increase in mRNA expression for MMP-9 and a decrease in mRNA expression for type IV collagen in nodular and infiltrative BCC

Group			COL IV T	COL IV NT
NODULAR	MMP-9 T	Pearson's correlation	0.10	-
		Significance (two-sided)	0.51	-
	MMP-9 NT	Pearson's correlation	-	0.19
		Significance (two-sided)	-	0.21
INFILTRATIVE	MMP-9 T	Pearson's correlation	-0.10	-
		Significance (two-sided)	0.53	-
	MMP-9 NT	Pearson's correlation	-	0.17
		Significance (two-sided)	-	0.29

Table 7. Correlation between an increase in mRNA expression for MMP-9 and an increase in mRNA expression for type I collagen

Group			COL I T	COL I NT
NODULAR	MMP2 T	Pearson's correlation	-0.05	-0.07
		Significance (two-sided)	0.75	0.65
	MMP2 NT	Pearson's correlation	-0.14	0.20
		Significance (two-sided)	0.35	0.18
INFILTRATIVE	MMP2 T	Pearson's correlation	-0.13	-0.08
		Significance (two-sided)	0.43	0.61
	MMP2 NT	Pearson's correlation	-0.16	0.00
		Significance (two-sided)	0.31	0.98

Discussion

In both groups, nodular and infiltrative BCC patients, mRNA expressions for MMP-2, MMP-9 and type I collagen were always significantly higher in the tumor tissue than in the normal tissue collected from the tumor margin of the same patients. In contrast, the level of mRNA expression for type IV collagen was significantly lower in the tumor tissue than in the tumor margin tissue from the same patients.

The data obtained result from the fact that type IV collagen forms a barrier between the epidermal cells and the structure of the dermis. This barrier protects subsequent layers of the skin against the infiltration of cancer cells and against the spread of cancer cells in the body. In both nodular and infiltrative BCC, the developing tumor destroys the structure of the BM, including, primarily, type IV collagen. Type IV collagen is known to be a component of connective tissue, builds basal membranes and plaques in tissues, creates network structures in the BM of the epidermis, and is also found around nerve and muscle fibres in the skin. The greatest amounts of this protein are found in the skin and the endothelium of blood vessels.

Metalloproteinases MMP-2 and MMP-9 are enzymes that catalyze the proteolysis of type IV collagen and thus destroy the BM barrier. Neoplastic cells, particularly of malignant neoplasms, can secrete MMPs or stimulate normal cells to produce them, for example, through the EMMPRIN protein [45]. Moreover, the transformed cells themselves have the ability to synthesise MMPs [26]. Increased proteolysis of the components of the ECM allows the tumor to grow and also conditions the passage of the neoplastic cells. Degradation of type IV collagen, which is the main component of the BM, determines the migration of the neoplastic cells to the blood vessels and then to distant tissues and organs, which is rare in the case of BCC [3,7]. Moreover, the hydrolysis of ECM proteins, including

adhesion proteins such as E-cadherin, reduces the adherence of the neoplastic cells to the BM [46]. Changes in the cell genotype, which determine the different phenotype of the neoplastic cells, can be assessed by determining the molecular markers of neoplasms.

The structure of the extracellular space undergoes constant changes conditioned by the activity of proteolytic enzymes, including MMPs.

In this study, it was found that mRNA expression for MMP-2 and MMP-9 was always significantly higher in the tumor tissues of nodular and infiltrative BCC than in healthy tissues collected from the tumor margins of the same patients, which clearly suggests the participation of MMPs in the process of tumor formation. The above changes in the expression of metalloproteinases MMP-2 and MMP-9 (reflected in the mRNA expression for these enzymes) cause disturbances in the balance of the BM and the ECM [47], due to which endothelial cells can freely migrate, and their accumulation in the tumor is reflected in the formation of new blood vessels. The components necessary for its growth are delivered through the vessels to the tumor that form.

Nodular and infiltrative BCC

This study also explored the differences between mRNA expressions for type I collagen, type IV collagen, MMP-2 and MMP-9, determined in neoplastic tissue collected from tumor foci in nodular BCC compared to the infiltrative variant and the same parameters determined in healthy tissue taken from the margins of the nodular tumor compared to infiltrative BCC.

On the basis of a statistical analysis of the results obtained, it was found that in the group of nodular BCC patients, the level of mRNA expression for type I collagen in tissues collected from tumor foci was significantly higher than in patients with the infiltrative variant. This results from the fact that nodular BCC is isolated from the rest of the tissues by a collagen sheath, which limits the malignancy of this tumor and translates into the level of mRNA synthesis for this type of collagen. Type I collagen is the most abundant in the skin, accounting for 80% of the total skin collagen.

In the case of the expression of mRNA for type IV collagen, nodular BCC patients had a slightly lower expression in neoplastic tissue than those with the infiltrative variant in samples collected from tumor foci. This proves that the expression of IV collagen is balanced due to the significantly greater invasiveness of infiltrative BCC, compared to nodular BCC, which is isolated from the surrounding tissues by type I and III collagen sheaths and thus does not have as high an invasive potential as infiltrative BCC. Our study showed a significantly lower level of mRNA expression for type IV collagen in samples taken from the tumor margin in nodular BCC compared to the infiltrative one, which may suggest that in infiltrative BCC, healthy cells adjacent to the

neoplastic tissue increase mRNA expression for type IV collagen to protect against the infiltration of cancer cells.

mRNA expression for MMP-2 in nodular BCC tumor foci showed significantly lower levels than mRNA expression for MMP-2 determined in tumor foci in the infiltrative variant. This confirms the invasive nature of infiltrative BCC because MMPs catalyze the proteolysis of the basal membranes and allow cancer cells to infiltrate adjacent tissues. On the other hand, mRNA expression for MMP-2 in samples taken from the tumor margin of nodular BCC patients was significantly higher than mRNA expression for MMP-2 in the tumor margin of infiltrative BCC, which suggests a significant silencing of mRNA expression in cells adjacent to an infiltrative BCC. The increase in mRNA expression for MMP-2 in tissues adjacent to a nodular BCC may suggest a counterbalancing mechanism triggered by the carcinoma cells of the collagen-surrounded tumor by stimulating healthy cells surrounding the tumor to produce MMP-2 through the EMMPRIN protein [48].

Our study shows that patients with nodular BCC had significantly lower levels of mRNA expression for MMP-9 in tumor foci than patients with the infiltrative variant. This is confirmed by numerous observations that the invasive potential of the infiltrative type depends on MMP-9 expression.

According to El-Bahrawy et al. [49], the lack of membrane expression of β-catenin with its simultaneous expression in the cell nucleus is responsible for the greater invasiveness of infiltrative BCC, which is considered to be more aggressive than the nodular type. The β-catenin complex together with E-cadherin is properly located in the membrane and is responsible for the regulation of cell signal transmission. Damage to this complex may contribute to the greater invasiveness and metastasis of the tumor [50,51].

Skin phototype

The differences between mRNA expressions for type I collagen, type IV collagen, MMP-2 and MMP-9 in nodular and infiltrative BCC in the neoplastic tissue and the healthy tissue collected from the tumor margin in patients according to their phototypes determined on the Fitzpatrick scale were investigated (phototype II, phototype III).

mRNA expression levels for type I collagen and metalloproteinases MMP-2 and MMP-9 were always higher in both neoplastic and normal tissues in patients with phototype II than in those with phototype III, and the mRNA values for type IV collagen were lower. The differences were statistically significant for all these parameters.

An increase in mRNA expression for MMP-2 and a decrease in mRNA expression for type IV collagen

The correlation between the increase in mRNA expression for MMP-2 and the decrease in mRNA expression of type IV collagen in nodular and infiltrative BCC was investigated.

Pearson's correlation analysis showed that in nodular BCC there was no relationship between the level of mRNA expression for MMP-2 and the level of mRNA expression for type IV collagen in both neoplastic and healthy tissues. In the case of infiltrative BCC, the analysis showed no correlation between mRNA expression for MMP-2 and mRNA expression type IV collagen in neoplastic tissues. However, a relationship was found between mRNA expression for MMP-2 and mRNA expression for type IV collagen in normal tissues. As the level of mRNA expression for type IV collagen decreased, the level of mRNA expression for MMP-2 increased in healthy tissues surrounding the tumor. The strength of this correlation was moderate.

In the protein-protein system, type IV collagen is a substrate for MMP-2 and therefore it is necessary to understand the correlation between the mRNA expression levels for type IV collagen and MMP-2. It was particularly interesting to find a significant correlation between the increase in mRNA expression for MMP-2 and the concomitant decrease in mRNA expression for type IV collagen in tissue treated as healthy in a histopathological examination. This proves a visible disturbance in the structure of the ECM and the BM, which may indicate that the initial development of the neoplastic process is already taking place at the molecular level, despite the tissue being classified as normal in a histopathological examination.

An increase in mRNA expression for MMP-9 and a decrease in mRNA expression for type IV collagen

The Pearson's correlation test did not show a statistical significance between the increase in mRNA expression for MMP-9 and the decrease in mRNA expression for type IV collagen in nodular and infiltrative BCC.

The relationship between the enzyme, MMP-9, and the substrate, type IV collagen, is not reflected in the mRNA level in the tissues examined.

An increase in mRNA expression for MMP-2 and an increase in mRNA expression for type IV collagen

The Pearson's correlation test did not show a statistical significance between the increase in mRNA expression for MMP-2 and the increase in mRNA expression for type I collagen in nodular and infiltrative BCC, although it is assumed that

collagen I synthesis may be compensated in response to an increase in the level of MMP-2 expression.

Molecular markers of the tumor formation process

It is known that the proteolysis of the ECM is the result of the action of not only individual MMPs produced by different types of cells, both neoplastic and normal. The participation of numerous hormones, cytokines and growth factors that induce the synthesis of proteolytic enzymes or their inhibitors is also important [26,52].

Malignant tumors contain cells that exhibit the features of an invasive phenotype, which is characterized by the presence of factors that determine the tumor's ability to grow, migrate and its tendency for pathological angiogenesis. Determining the markers attesting that a cell has acquired an invasive phenotype is particularly important in order to differentiate between tumor tissue and normal tissue correctly. Currently, cancer is diagnosed using histopathological examinations. Identifying cells with an invasive phenotype allows the boundary between neoplastic and healthy tissues to be determined at the molecular level. As the tumor margin is sometimes misdiagnosed in histopathological analysis, BCC lesions are not always completely removed. Diagnosing neoplastic cells on the basis of their phenotype features enables radical removal of a neoplastic lesion. This avoids leaving cells which have been classified as normal in the histopathological examination and in which the process of carcinogenesis has, in fact, already begun, and so these cells are the cause of the recurrence of the disease.

In the event of BCC, extending the diagnostics of neoplastic lesions to include tests comparing mRNA expressions and/or MMPs proteins in a neoplastic lesion to normal tissue could significantly increase the accuracy of the assessment of the margin of the lesion, and thus increase the usefulness of tests confirming or excluding the development of the neoplastic process at very early stages [3]. As regards therapeutic measures, the lesion is most often removed surgically in patients with BCC. Hence, molecular markers are constantly sought to distinguish between neoplastic tissue and the healthy tissue margin. Metalloproteinases MMP-2 and MMP-9 may be considered such markers. The results obtained for mRNA expressions for MMP-2 and MMP-9 confirm the usefulness of these assays in diagnosing molecular neoplastic lesions in BCC.

Conclusions

1. Significantly higher levels of mRNA expressions for type I collagen, MMP-2 and MMP-9, as well as consistently lower levels of mRNA expression for type IV collagen in tumor tissue compared to tumor margin tissue obtained from

the same patients were demonstrated in both types of BCC. These differences indicate a different role for collagens I and IV in the pathomechanism of BCC.
2. In infiltrative BCC, mRNA expression is significantly higher for MMP-2 and MMP-9, which proves the more invasive nature of this form of tumor.
3. In nodular BCC, mRNA expression is significantly higher for type I collagen because the tumor is surrounded by collagen proteins, which ensure a lower invasive potential of nodular BCC compared to the infiltrative variant.
4. Patients with skin phototype II have significantly higher mRNA expression levels for MMP-2, MMP-9 and type IV collagen and significantly lower mRNA expression for type I collagen.
5. Metalloproteinases MMP-2 and MMP-9 can be used as molecular markers of the ongoing neoplastic process in the course of BCC.

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mRNA dla MMP-2 i MMP-9 jako potencjalne markery molekularne pozwalające na rozróżnienie granicy między guzem a tkanką prawidłową w przypadku raka BCC

Streszczenie

Wprowadzenie: Nieczerniakowe nowotwory skóry (NMSC) są najczęstszymi nowotworami złośliwymi, których liczba stale rośnie. BCC charakteryzuje się powolnym wzrostem, a główną cechą kliniczną tego guza jest naciekanie okolicznych tkanek i niszczenie sąsiadujących struktur.
Materiał i metody: Ekspresję transkryptów mRNA dla kolagenu typu I i IV oraz MMP-2 i MMP-9 porównano w biopsjach skóry od pacjentów z BCC skóry oraz w biopsjach zdrowej skóry z marginesu guza. W badaniu wzięło udział 70 pacjentów, u których zdiagnozowano BCC.
Wyniki: Stwierdzono różnice między ekspresją mRNA dla MMP-2 i MMP-9, kolagenu typu I i IV w BCC guzkowym i naciekowym w próbkach tkanek nowotworowych i tkanek prawidłowych pobranych z marginesów guza tych samych pacjentów.
Wnioski: Istotnie wyższe poziomy ekspresji mRNA dla kolagenu typu I, MMP-2 i MMP-9, a także zawsze niższe poziomy ekspresji mRNA dla kolagenu typu IV w tkance nowotworowej w porównaniu z tkanką marginesu guza uzyskaną od tych samych pacjentów wykazano w obu typach BCC. Postrzegane różnice wskazują na inną rolę kolagenu I i kolagenu IV w patomechanizmie BCC.
Słowa kluczowe: BCC, MMP, markery molekularne, kolagen typu I i IV