Correlation between the WT1 suppressor gene and skin lesions: an alternative diagnostic-differential factor

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The WT1 gene is located on the 11p13 chromosome. This transcription factor is expressed with a dynamic pattern during human development, has either oncogenic or suppressor tumour properties [1]. Its mutations or an increase in expression lead to the development of diseases such as Wilms' tumour, leukaemia, Frasier's syndrome or Denys-Drash syndrome [2, 3]. There are a few reports in the literature which confirm the role of this gene in the pathogenesis of skin diseases.

In 1994, Rodeck *et al.* proved that WT1 can be found in melanoma cells. Its presence was confirmed in seven out of nine cell lines tested. However, its overexpression in normal human melanocytes in any of the five strains was not observed [4]. Perry *et al.* reached similar conclusions in 2006. They found that overexpression of WT1 is more prominent in vertical growth melanoma than radial growth melanoma. Overall, the presence of WT1 was estimated to be approximately 50–80%, and out of all 49 samples, as many as 25 showed features of over 75% of suppressor gene overexpression. On the other hand, in the case of benign lesions, this range was about 7–30% [5].

Wagner *et al.* found in 2007 that the WT1 gene is present in over 80% of melanoma neoplastic cells. The attempt to inhibit WT1 resulted in a decrease in the activity of proteins such as zyxin and nestin. This led to a reduction in skin cancer proliferation [6]. Authors also analysed the presence of the WT1 gene in benign melanocytic nevi. Six out of the nine Spitz nevi showed WT1 expression in more than half of the affected cells. Three out of nine samples taken of melanotic nevi showed signs of WT1 in approximately 20% of the cells. Four out of nine dysplastic nevi were WT1 positive in about half of the cells, the rest in about 20%. However, its presence in the area of unaffected skin has not been confirmed. This study proves that the presence of WT1 may be an effective method for differentiating between skin lesions [6].

An analysis of the diagnostic effectiveness of melanoma based on the WT1 gene was carried out in 2017 by Kim *et al.* 35 samples of melanoma were used for the study, including 28 in the invasive stage and 50 melanotic nevi. Gene expression in invasive malignant melanoma reached the level of approx. 66%, while in other groups it reached a maximum of approx. 26%, which is a wide range that allows for obtaining relatively reliable results. Interestingly, in situ melanoma showed only about 6% of WT1. The III, IV, and T4 stages of this skin cancer had approx. 80% presence of the WT1 gene [7].

Garrido-Ruiz *et al.* investigated 163 melanomas and 108 benign nevi samples. Vertical growth melanomas showed WT1 overexpression in 46.5%, while radial growth melanomas only in 16%. This overexpression also increased in direct proportion to the level of Clark invasion, reaching almost 60% in stages IV and V, while approx. 30% in stages I–III. There was also a correlation between the level of overexpression and the thickness of the neoplastic lesion. The deeper proliferating lesions showed a higher percentage of WT1 – at the cutoff point of 1 mm, the difference between the groups was about 20%. Unlike other studies, researchers found that the suppressor gene was more abundant in benign nevi (51.5%, which included, among others, approx. 70% of the group referred to as "compound/intradermal nevi" and approx. 62.5% of Spitz nevi) than in melanomas (approx. 40%) [8].

Conner *et al.* also analysed the diagnostic value of the WT1 gene in neoplasms, including malignant melanoma. They collected material from the exudates and then looked for the presence of WT1 and the AE1/AE3 complex. The same result was obtained in all 17 cases

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of melanoma: the presence of a suppressor gene in the cytoplasm and no AE1/AE3 complex [9].

Al Dhaybi *et al.* in 2010 investigated the relationship between the presence of the WT1 suppressor gene and the development of vascular lesions. They analysed 126 cases and found that the expression of WT1 occurs in all 64 cases of "vascular tumours", which included, among others, 25 cases of infantile haemangioma, 11-non-involuting congenital haemangioma or 10-pyogenic granuloma. On the other hand, out of 61 vascular malformations, only three were characterized by the presence of this gene: 1 case in the group described by the researchers as "angiokeratoma/verrucous haemangioma" (out of 30 analysed) and 2 cases of targetoid hemosiderotic haemangioma. One can conclude that also in the case of vascular lesions, the presence of the WT1 suppressor gene may be an effective diagnostic method [10].

Trindade *et al*. analysed WT1 overexpression in vascular lesions in a group of 167 cases. 117 were diagnosed as vascular neoplasm, 87 of which were childhood haemangiomas and 50 were malformations. All neoplasms tested positive for WT1. In the case of the malformation group, only arteriovenous one showed the presence of the suppressor gene. The others did not show signs of overexpression of WT1 [11].

Increased gene activity also occurs in psoriasis. Wu *et al*. in 2018 proved that an increased expression of the WT1 gene is caused by pro-inflammatory cytokines, e.g. interleukin 22 or interferon-g, moreover, skin damage additionally enhances the activity of the suppressor. This results in the induction of cell proliferation with the simultaneous inhibition of apoptosis within the keratinocytes. On the other hand, by blocking the WT1 gene, these processes were reversed: proliferation slowed down, while the intensity of apoptosis increased [12].

In conclusion, nowadays molecular analysis complement clinical parameters of various dermatologic conditions and it could serve as a marker of disease severity as well as a marker of therapeutic potential of drugs used [13]. According to quite recent and promising reports, WT1 together with other molecules could be used as part of the panel with the most sensitive and specific combination of immunostains available for the diagnosis of desmoplastic melanoma [14] and in confirming the diagnosis or better evaluation of the residual/recurrent tumour component in dermatofibrosarcoma protuberans [15].

Conflict of interest

The authors declare no conflict of interest.

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