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CEACAM1 - A PROMISING BIOMARKER FOR MELANOMA

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Abstract: *Malignant melanoma is the third most common skin cancer, but it also remains the most aggressive. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a promising diagnostic and prognostic biomarker for melanoma, because its expression is important for tumour development. This review aims at highlighting the most recent discoveries regarding CEACAM1 and its correlation to the diagnosis and prognosis of malignant melanoma. National Library of Medicine (NIH) PubMed was used for selecting articles published between 2004-2021, based on their relevance and novelty. With its multiple and somewhat contradictory effects, CEACAM1 seems to influence melanoma invasion, migration, immunomodulation and tumour suppression, serving as a useful diagnostic biomarker and target for therapy. While the incidence of malignant melanoma has been increasing over the last decades without signs of prognosis improvement, it is crucial that new biomarkers for diagnosis and detection of metastatic progression are discovered, and CEACAM1 might be a viable option.*

INTRODUCTION

Malignant melanoma is the third most common skin cancer (responsible for less than 5% of the cases), following basal cell carcinoma and squamous cell carcinoma.(1) It remains the most aggressive and treatment resistant among the ones previously mentioned, the main cause of death being represented by metastases.(2,3)

While its incidence has been increasing over the last decades, the diagnosis still remains a challenge due to the diversity of its morphogenic features (4) and the prognosis does not show significant signs of improvement (3), mainly due to the fact that treatment is only moderately successful.(5) Currently, the AJCC system takes the following prognostic factors into consideration for melanoma staging: Breslow depth, presence of ulceration, mitotic rate and lymph node involvement, but a great importance is also attributed to biomarkers. The only accepted blood-based biomarker that indicates the presence of melanoma is lactate dehydrogenase (LDH), which is unfortunately highly nonspecific.(6)

As for tissue-based biomarkers, there are two categories: the differentiation markers (e.g. S100, gp100 / HMB-45, tyrosinase, MART-1 / Melan-A, HMW-MAA) and the progression markers (e.g. Ki67, PCNA, cyclin D1, p1, p53, b3-integrin) (7), but none of the previously mentioned could be used exclusively due to their variable sensitivity and specificity; therefore, the current approach implies detecting and measuring combinations of multiple biomarkers (multiplex assays).(8)

This review aims at highlighting the most recent discoveries and studies regarding CEACAM1 and its correlation to malignant melanoma, since such an aggressive type of cancer requires attention and finding new ways of diagnosis and treatment.

LITERATURE REVIEW

National Library of Medicine (NIH) PubMed was used for gathering original articles and reviews published between 2004 and 2021, based on keywords first (malignant melanoma, CEACAM1, immunohistochemistry, prognosis, biomarker, immunotherapy). Secondly, the articles which were not free were excluded, and the remaining ones have been selected by their relevance (their impact factor) and novelty (starting from the current year).

Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1), previously known as biliary glycoprotein I or CD66a7 and member of the carcinoembryonic antigen (CEA) family (9) is a promising diagnostic and prognostic biomarker for melanoma, as it has been demonstrated that its expression is important in tumour development.(3) There are certain types of cancer in which CEACAM1 levels are reduced (colorectal, prostate, mammary gland, bladder), but in the case of malignant melanoma (along with non-small-cell lung carcinoma, pancreas, thyroid and squamous cell carcinoma) it is overexpressed. CEACAM1 is not present on normal melanocytes, but its expression is increased on melanocytic nevi (either acquired or congenital, but not on blue nevi) and in 89% of the lesions found in metastatic melanoma.(10) While it is not exclusively expressed on melanoma cells (it can also be detected on some epithelial and immune cells), its role in metastatic progression in this particular form of cancer is certain.(9) Apart from its presence on the surface of different types of cells, elevated levels of CEACAM1 were detected in serum from patients with melanoma and they indicate worse survival (in mice, they were present at a tumour volume of 14 mm^3, proving themselves useful for early melanoma diagnosis).(11,12) There are at least three secreted CEACAM1 isoforms (sCEACAM1)

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created by alternative splicing of the CEACAM1 transcript and requiring protein synthesis and functional vesicular transport, which are found in many bodily fluids (human serum, bile, saliva, seminal fluid, breast milk).(12) Still, there are cells that express CEACAM1 and are not responsible for elevating the soluble fractions (e.g. CEACAM1+ lymphocytes).(13)

CEACAM1 can mediate homophilic (CEACAM1-CEACAM1) and heterophilic interactions (CEACAM1-CEACAM5) (9) and it is present in two isoforms, a short one (CEACAM1, 10 to 12 amino acids) and a long one (CEACAM1, 71 to 73 amino acids).(14) The isoforms are known to have diverse, and in some aspects contradictory effects in different types of cancer, including malignant melanoma. Their functions will be discussed separately.

CEACAM1-L

CEACAM1-L has two phosphorylatable tyrosine residues which allow regulation of the signaling pathways by responding to receptor tyrosine kinases (RTKs) activation.(12) Among its isoforms, CEACAM1-4L is most expressed even during early disease progression (starting from stage I/II to stage III), either alone or along with others, located intracellularly around the nucleus (CEACAM1-3L) or extracellularly at cell-cell contact (CEACAM1-4L).(15) Essentially, CEACAM1-4L is known for enhancing invasive behaviour and migration, but its effects on immune cells are also important in the evolution of malignant melanoma. It is responsible for inhibition of T cell activation which contributes to reducing the signaling through MAPK (Mitogen-activated protein kinase) pathway and it also decreases the levels of interferon, IL-2 and IL4. In opposition, CEACAM1-3L promotes MAPK pathway signaling and the production of cytokines (similar to the effects of the short isoform CEACAM1-3S). CEACAM1-L is also known to increase granulocytes' survival.(12) Another immunological effect of CEACAM1-4L is that it mediates the escape of NK (natural killer) cell mediated killing by lowering the expression of several cell ligands (MICA, CD155, CD112, ULBP2).(1)

CEACAM1-S

CEACAM1-3S is considered a potential biomarker for disease progression in malignant melanoma because its level increases in late stages (stage III, IV) and, similar to CEACAM1-L, it can be located intracellularly (CEACAM1-3S) or extracellularly (CEACAM1-4S).(15) Expression of CEACAM1-3S was proved to be beneficial for melanoma patients as it can increase overall survival due to its effects on NK cell mediated killing – it tends to increase expression of ligands (MICA, CD155, ULBP2) which promotes cytolysis – and its influence on T cells – increased MAPK signaling and cytokine production – (1,15).

OTHER ROLES OF CEACAM1

Apart from those previously mentioned, which include invasion, migration, immunomodulation, but also tumour suppression and increasing survival, CEACAM1 has a wide variety of effects.(1) These effects are obtained mostly, but not exclusively, by the ability of CEACAMs to act as adhesion molecules either to one another or with extracellular ligands.(16)

CEACAM1 is an angiogenic growth factor, being the only member of the CEA family that has an endothelial cytoplasmic tail and it is found in small blood vessels. During early stages of angiogenesis, angiogenic stimuli upregulate CEACAM1 which acts as a chemoattractant; later on, the usefulness of CEACAM1 consists of its abilities to recruit accessory cells and to form cell-cell junctions. It is a key factor in the capillary-like tube formation in vitro and cell differentiation; moreover, endothelial cells which express CEACAM1 tend to switch to an angiogenic phenotype.(16,17) An important observation is that the angiogenic effect does not depend on the VEGF/VEGFR-1/2 system, therefore anti-VEGF/VEGFR system medication is ineffective against CEA-induced angiogenesis and the vascularization of the tumour continues to strengthen under treatment. However, it appears that by interfering with CEA-receptors (by immunologically targeting them, for instance) the tumour growth is reduced and the VEGF induced luminal formation is stopped, thus this new direction of treating malignant melanoma should be further studied as CEACAM1 might interfere with VEGF in the formation of microvessels.(18,19)

CEACAM1 represents a substrate for the insulin receptor (IR) and it is responsible for downregulating the mitogenic effects of insulin.(1) This occurs due to the ability of insulin to promote phosphorylation after it binds to IR, therefore CEACAM1-L is phosphorylated at Tyr-488 and it can downregulate the signaling of insulin by endocytosis of the IR-insulin complex.(19) It is also known for causing hyperglycemia, defective glucose tolerance and insulin resistance.(12)

CEACAM1 represents a substrate for the epidermal growth factor receptor (EGFR), which is responsible for phosphorylation at Tyr-488. This causes inactivation of EGF-stimulated Ras/MAPK pathway. (19) However, the connection between CEACAM1 and the MAPK pathway is more complex, seeing that the first one is regulated by the second one via ETS1. ETS1 is a major transcription factor, for which there are four binding sites on the promoter of CEACAM1 and it was demonstrated that the deletion of those sites cancels the outcome of MAPK pathway inhibition.(20,21)

CEACAM1 is present on the surface of circulating NK cells and CD8+ lymphocytes of melanoma patients, as well as on tumour-infiltrating lymphocytes (TILs). This facilitates the homophilic interactions between melanoma cells and TILs which tend to have an inhibitory effect on the latter, hence the limited efficacy of the new form of treatment represented by TIL adoptive cell therapy (only 40% of complete regressions when it is associated with lymphodepleting chemotherapy).(10,22) The adoptive cell therapy implies in vitro expansion of TILs from resected tumours and transferring them back to the patients, taking into consideration that these immune cells can also destroy normal melanocytes.(22)

CEACAM1 serves as receptor for certain pathogens. Some bacteria express specific proteins (Opa expressed by Neisseria, UspA1 expressed by Moraxella, HopQ expressed by Helicobacter pylori) which bind heterophilically and with high affinity to CEACAM1. This results in transcytosis, followed by severe side effects due to reducing the inflammatory response and colonization of the human mucosae.(1,19) A few enterobacteria, such as Escherichia coli and Salmonella, are able to recognize high-mannose residues displayed by CEACAM1, which is also important for the process of colonization of the commensal flora.(16,19)

CONCLUSIONS

While the incidence of malignant melanoma has been increasing over the last decades, there are not many signs of improvement regarding its prognosis. This is the reason why finding new biomarkers with increased sensitivity and specificity that can be used for diagnosis (as early as possible in the progression of the disease) and prognosis (which implies early detection of distant metastases) is crucial. With its diverse and somewhat contradictory effects in some cases, CEACAM1 seems to influence melanoma progression, migration, immunomodulation, but also tumour suppression and improvement of prognosis (depending on the isoform), while also being easy to measure in serum and readily identified by immunohistochemistry on biopsies. Its elevated levels in the blood of melanoma patients are correlated with poor prognosis,

therefore it could be used as a substitute for LDH which is highly unspecific. Taking all things into consideration, CEACAM1 represents a promising diagnostic and prognostic marker, while also being a potential target for therapy.

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