VISTA, PDL-L1, and BRAF—Markers in Prognosis of Melanoma

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Melanoma is currently known as one of the most aggressive malignant tumors. T cell Activation (VISTA) is a novel target that is considered to be highly important in determining the invasive potential and treatment response of a melanoma. Programmed death-ligand 1 (PD-L1) is a marker with whose importance has been revealed in multiple types of malignancies.

Keywords: melanoma ; VISTA ; PD-L1 ; BRAF ; prognosis

1. Introduction

Melanoma is a malignant tumor originating in melanocytic (melanin-producing) cells that has an increased potential for invasion and metastasis; therefore, its early diagnosis and treatment are very important for improving the prognosis of patients.

During embryonic life, melanocytes develop from the neural crest. At first, cells constitute a group of ectodermal cells, which originate from the external layer of the neural tube. In the next stages of embryo differentiation, and then during the formation of the fetus, these ectodermal cells migrate throughout the entire body and continue to differentiate into different components.

The precursor cells of melanocytes are called melanoblasts. These cells are derived from melanocytic precursors and will proliferate as they migrate toward the tegument.

The malignant transformation of melanocytes is the result of interactions between components related to the individual and the environment, elements that are generally found in the genesis of any type of cancer. Among the factors belonging to the environment, ultraviolet (UV) radiation is highlighted, which is considered the most important risk factor in the appearance of cutaneous melanoma. Genetic factors, as well as family history, are also considered to be important risk factors in melanoma genesis. The genes most heavily linked to the appearance of this cancer, according to the World Health Organization, are *BRAF* and *KRAS* [1][2].

1.1. Characteristics

In the presence of appropriate risk factors, melanoma can occur at any level of the skin. This tumor can arise de novo or originate from a melanocytic nevus. According to World Health Organization (WHO) guidelines, about 1 in 33,000 nevi will begin developing into melanoma. It is considered that cutaneous melanoma is responsible for more than 90% of the mortality involving all skin pathologies.

The gold standard for the diagnosis of melanoma is represented by the histological and immunohistochemical methods that are currently used in pathology laboratories, as well as new methods that are related to the genomic analysis of malignant tumors [3][4].

According to McGovern and Clark, there are two main stages in the development and progression of melanoma. The first is illustrated by the appearance of a pigmented area that extends radially (on the surface of the skin, along a horizontal axis). The second stage is characterized by growth that manifests the formation of a nodule [3][4][5].

1.2. Classification

The World Health Organization (WHO) classifies cutaneous melanoma from the perspective of its association with ultraviolet exposure, called cumulative solar damage. In this category, the types of melanoma associated with exposure to

sunlight are mentioned (such as superficial melanoma, lentigo maligna, desmoplastic melanoma). The second category includes the types of melanoma that are not considered to be associated with UV exposure and their effects on the skin (acral melanoma, melanoma of the mucous membranes, uveal melanoma). A special category is nodular melanoma, a tumor that occurs regardless of the way in which the malignant transformation of melanocytes takes place and, therefore, this type is found in and described for both classifications. The synonyms of the tumor are, according to WHO, “rapidly growing melanoma” and “primary melanoma without a radial phase”.

2. Inflammatory Cells—Tumor Infiltrating Lymphocytes

Inflammatory cells from the tumoral microenvironment present in primary melanocytic malignancies are always reported under the name of ‘brisk’ or ‘non-brisk’. The brisk infiltrate is defined by lymphocytes that are present in the entire invasive component of the tumor diffusely, or simply described as lymphocytes infiltrating across the entire base of the vertical growth phase. The non-brisk infiltrate is defined by lymphocytes that are distributed focally and it is not found along the base of the invasive component. Inflammatory infiltrate has an important prognostic significance. Its role was especially highlighted after the development and implementation of immunological therapy, demonstrating that these inflammatory cells not only determine the prognosis of survival for patients, but also of cancer therapy.

3. Immunohistochemistry

The use of immunohistochemistry in the diagnosis of melanoma is known and acknowledged worldwide. This analysis is an important tool which provides not only the diagnosis, but also can orientate the patients towards a certain prognosis. Immunohistochemistry staining has increased significantly in recent years, not only for melanoma, but for all types of neoplasms. A study conducted by Dinehart showed that a majority (95%) of surveyed dermatopathologists are using immunohistochemistry (IHC) in their practice [6]. Other studies highlight the increase in IHC use in up to 25% of melanoma cases. IHC analysis is shown to be highly valuable especially in cases of poorly differentiated neoplasms [7].

4. VISTA

The concept of immunological therapy in malignant neoplasia was mentioned and proposed for practice by Burnet, starting from the fact that the immune system has a role in detecting neoplastic cells and removing them from the body. VISTA (V domain Ig containing suppressor of T-cell activation) is considered a new therapeutic target for anticancer therapy. This molecule is part of the B7 family associated with checkpoint receptors and is the counterpart of PD-1 and PD-L1, also having ligand activity on APC and T lymphocytes or, as some research claims, has a suppressive effect on the mentioned inflammatory cells [8].

VISTA currently has a controversial role, the modulation of the tumor microenvironment remains an unsolved subject. Targeted studies on the molecule have shown that it is predominantly expressed by hematopoietic cells, especially granulocytes, but also by other cells of the myeloid line, the expression being lower than T lymphocytes. More precisely, VISTA is expressed by immature and mature myeloid line cells, CD4+ T lymphocytes, and CD8+ T lymphocytes. There are studies that have revealed that therapy with anti-VISTA agents have blocked the acute graft rejection against the host and had immunosuppressive effect due to their ability to remove cells that express VISTA [8][9][10].

The potential of VISTA in oncotherapy has been described and demonstrated for the first time in a case of a patient with fibrosarcoma. After a number of studies made on murine models for cancer, VISTA was exclusively identified on intratumoral leukocytes. A very important aspect about VISTA that is highlighted in the research up to now suggests the efficiency of VISTA blocking therapy, including in the presence of PD-L1. Therefore, VISTA and PD-L1 are considered to be independent pathways, and numerous important benefits can be obtained when both are targeted together in immunotherapy [10][11].

5. PD-L1

PD-1 is a molecule that was first discovered and described in 1992 as being associated with diseases such as glomerulonephritis or splenomegaly and having a role in cell apoptosis. In addition to these findings, it has been stated that PD-1 also has a role in gastritis and dilated cardiomyopathy, as demonstrated by experimental studies in mice.

The role of PD-1 and its ligand has also been studied in melanoma. Within the last decade, in 2014, the first drug was approved for immunotherapy against these molecules present in the tumor microenvironment. The results obtained from

the new treatment (nivolumab) were significantly better compared to those who followed the classical therapy, whether chemotherapy or based on *BRAF* inhibitors.

6. *BRAF*

BRAF mutations in melanoma are very well known and documented, being described to promote and sustain oncogenesis by inhibition of the apoptosis process and tumor suppressor inactivation. These mutations, especially *BRAF V600E*, are observed in approximately half of melanoma cases, and this specific mutation represents 90% of all known *BRAF* mutations [12]. Many studies have highlighted the fact that *BRAFV600E* is even more frequently encountered in melanomas that arise on a nevi. The activated mutation turns on the mitogen-activated protein kinase (MAPK) pathway. However, despite the fact that *BRAF* is very important in the development and progression of melanoma, studies have shown that it alone is not sufficient for tumor genesis [12][13]. Recent research studies previously mentioned, such as the one conducted by Rosenbaum, have attempted to compare the expression and the effect of *BRAF* in relation to the novel marker VISTA. It was confirmed that blockade of *BRAF* influences the levels of VISTA. Therefore, the combination of PLX4720 with the Mitogen-activated protein kinase kinase (MEK) inhibitor PD0325901 against *BRAF* lead to a decrease in VISTA expression. All the data collected from the study and Western blot analysis (used for the detection of VISTA) showed that *BRAF* inhibition upregulates *Forkhead Box D3*(*FOXD3*) (molecule involved in transcription processes in adult life) and suppresses the expression of VISTA [14][15][16].

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