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Editorial Open Access

N-Glycolyl GM3 Ganglioside as a Relevant Tumor Antigen in Humans

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Editorial

It is known, human cells are incapable of synthesizing the N-glycolyl neuraminic acid (NeuGc) due to the inactivation of the cytidine monophospho-N-acetyl-neuraminic acid hydroxylase, the enzyme responsible for the synthesis of this sialic acid [1]. Conversely, the aberrant expression of NeuGc-sialoconjugates has been detected in humans, although preferentially in malignant tissues [2,3]. The more accepted hypothesis for the presence of NeuGc in human malignancies is associated with its incorporation from dietary sources to the altered metabolism of malignant cells [4] which is also favored by the hypoxic conditions of tumors [5]. However, the significance of NeuGc-containing conjugates in tumor biology as well as its clinical implications is still under investigation. One of these molecules is N-glycolyl GM3 ganglioside (NeuGcGM3).

The expression of NeuGcGM3 in normal adult tissues is limited. The overall pattern of expression of this ganglioside is summarized as cytoplasmatic and mainly located in epithelial cells and associated secretions [3,6-11]. Rarely, an incomplete plasmatic membrane pattern in these cells can be observed. By the contrary, in a variety of human tumors the over-expression of NeuGcGM3 is commonly detected in the surface of malignant cells, although diffusion to cytoplasm is also evidenced [3,6-11]. This fact converts NeuGcGM3 in an attractive target for the immunotherapy of these tumors, minimizing the risk of potential damage of healthy tissues. Moreover, the localization of NeuGcGM3 in the plasmatic membrane seems to be a mechanism misused by malignant cells to generate immunosuppression and promote tumor progression.

The occurrence of NeuGcGM3 containing shorter-chain fatty acid has been detected in breast cancer [12]. This is an alteration in the ceramide portion that affects the anchors of the ganglioside molecule to the cell membrane. Consequently, NeuGcGM3 could be actively shed from the plasmatic membrane of malignant cells and take up by other cells (e.g. peritumoral lymphocytes of lymph node metastasis) [11] by insertion of their lipid anchors into the membrane. The incorporation of NeuGcGM3 into the plasmatic membrane of T lymphocytes down-modulate the CD4 expression and interfere in the functions of both CD4+CD25- T lymphocytes and dendritic cells (DCs) [13,14]. The inhibition of DCs differentiation, maturation and migration were also evidenced in non-small cell lung cancer (NSCLC) [15]. All these factors together could lead to tumor-induced suppression limiting the possibility of a specific immune response.

On the other hand, it has been hypothesized that inflammation caused by anti-NeuGc immune response could facilitate tumor progression [16]. Nevertheless, in human healthy donors occur naturally antibodies against NeuGcGM3 that are able to recognize and kill tumor cells expressing this antigen [17]. Interestingly, in the sera of NSCLC patients decreased levels of these natural anti-NeuGcGM3 antibodies were evidenced [18]. This fact suggests a reduction in the capacity of these patients to effectively fight against malignant cells expressing NeuGcGM3, facilitating the development of tumors. In line with this, the contribution of NeuGcGM3 to primary tumor growth was previously demonstrated using different murine models [13,19]. Moreover, an increased expression of this ganglioside from primary tumors to metastatic lesions was reported, similar to what has been observed in breast cancer samples [20].

The association of NeuGcGM3 with the aggressiveness of tumors seems to be also linked with the capacity of this ganglioside to increase the proliferation of malignant cells. It is well recognized that uncontrolled division rate is a hallmark of malignant tumor growth. In this sense, NeuGcGM3 is capable to binds to the extracellular domain of the epidermal growth factor receptor (EGFR), diminishing the role of the N-acetyl GM3 in the inhibition of the EGFR tyrosine kinase [21]. This binding could favor an uncontrolled EGFR system activation mediated by the epidermal growth factor ligand (EGF). In line with this, the triple expression of NeuGcGM3, EGFR and EGF constitutes an immunophenotype of NSCLC with the highest index of cell proliferation. As a result, patients displaying this phenotype showed more probabilities to develop both recidive of primary tumor and disease recurrence [22].

In breast cancer, urinary bladder tumors and malignant gliomas, the expression of NeuGcGM3 was associated with more aggressive forms of the disease. Interestingly, the accumulation of this ganglioside increased progressively with the histological grade of bladder tumors and malignant astrocitomas [23]. The histological grading is considered among the most noticeable prognostic factors in these patients. In addition, the expression of NeuGcGM3 in colon adenocarcinoma correlated with more advantaged stage of the disease [24]. Furthermore, the aberrant expression of NeuGcGM3 was related with both poor overall survival and/or disease-free survivals in colon adenocarcinoma [24] and NSCLC [21,22]. However, in NSCLC opposite results were also found [15], potentially related with differences in the immunohistochemical analysis, the scoring system and the histological type proportion.

Finally, the *in vivo* localization of NeuGcGM3 using radio-immunoscintigrafic studies with the 14F7 monoclonal antibody labeled with 99mTc permitted to detect breast [25], lung and colon tumors (unpublished data). Interestingly, in breast cancer the results of the radio-immunodiagnostic correlated with those from the immunohistochemical analysis. This finding supports the utility of NeuGcGM3 detection by immunohistochemistry in the selection of patients for cancer immunotherapy. Preliminary results in breast tumors, melanoma and NSCLC suggested that racotumomab and NGcGM3/VSSP molecular vaccines improve the survival of patients with immune response to NeuGcGM3 antigen [26-28]. Nonetheless, the assessment of the potential predictive value of NeuGcGM3

expression for efficacy outcomes in response to these specific therapies would be subject of further investigations.

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