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Advances in NKT cell Immunotherapy for Glioblastoma

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Abstract

Type I or invariant natural killer T cells belong to a unique lineage of innate T cells, which express markers of both T lymphocytes and NK cells, namely T cell receptor (TCR) and NK1.1 (CD161C), respectively. Thus, apart from direct killing of target cells like NK cells, and they also produce a myriad of cytokines which modulate the adaptive immune responses. Unlike traditional T cells which carry a conventional αβ TCR, NKT cells express semi-invariant TCR – Vα14-Jα18, coupled with Vβ8, Vβ7 and Vβ2 in mice. In humans, the invariant TCR is composed of Vα24-Jα18, coupled with Vβ11.

Keywords

NKT cell immunotherapy; Glioblastoma; T-cell receptor; T-lymphocyte; Cancer immunity; Brain tumor cells; Solid tumors

Introduction to NKT Cell Biology

NKT cell development occurs in the thymus, where they acquire effector functions as they mature [1-4]. In mice, NKT cells are quite enriched within the T lymphocyte compartments of liver and adipose tissues while lower percentages are found in spleen, blood and bone marrow. In humans however, fewer NKT cells are detectable in blood and liver. Promyelocytic leukemia zinc finger (PLZF), the master transcription factor for innate lineage is indispensable for NKT cell development and effector functions [5,6]. Mice deficient of PLZF are almost devoid of NKT cells while the CD4 T cells in T cell-specific PLZF transgenic mice show memory and effector program similar to NKT cells [5,6]. NKT cells are CD1d-restricted in that they recognize lipid antigens presented by CD1d, an MHC-I-like antigen-presenting molecule [2]. NKT cells are known to particularly recognize and react to a glycosphingolipid α-galactoceramide (αGalCer), presented by CD1d, as such, CD1d- αGalCer tetramers are used to stain and recognize NKT cells. Upon activation, either

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through antigen-recognition or via cytokines (IL-12, IL-18, IL-33), NKT cells have the peculiar ability to rapidly secrete explosive amounts of both Th1 and Th2 cytokines IFNγ and IL-4, apart from other cytokines including IL-17, GM-CSF, IL-2, IL-10, IL-13, TNF-α, etc [7,8]. Recent studies indicate that NKT cells function as effector subsets dedicated to producing Th1, Th2 and Th17 cytokines and are labelled NKT1, NKT2 and NKT17, respectively [7,9].

Literature Review

NKT cells residing in adipose tissues are unique in that they lack PLZF and are more anti-inflammatory in function, being able to produce IL-10 and IL-4 [7,10]. Their number was found to decrease in expanded adipose tissues from obese mice. NKT1 cells are enriched in spleen and liver, NKT2 in lungs and gut while NKT17 cells are more abundant in lymph nodes, skin, intestine and lung tissues, indicating that tissue-resident NKT cells tailor their functions and roles based in the tissues they reside in. A very recent study reported a newer NKT subset, memory follicular helper iNKT ($iNKT_{FH}$) cells, which are able to generate in the absence of follicular helper T cells by presentation of lipid antigens by dendritic cells and can elicit B cell memory responses [11].

Owing to their ability to produce a myriad of cytokines and chemokines, NKT cells play a role in various diseases, infections and pathological conditions, either protective or pathogenic [12,13]. NKT cell-derived cytokines and chemokines modulate the immune responses of several different cell types, including, but not limited to, conventional CD4 T and CD8 T cells, macrophages, neutrophils, B-cells, NK-cells and dendritic cells [14,15]. Not surprisingly thus, NKT cells have been shown to play protective role in immunity against bacterial and viral pathogens, tumors, and autoimmune diseases [16,17] while being able to promote graft tolerance [18]. On the other hand, NKT cells have been described to play pathogenic roles in atherosclerosis, allergy and metabolic disorders.

NKT cells in cancer immunity

Increasing evidence from recent research indicates that innate-like T cells have significant and important role in cancers making them potential candidates for immunotherapies [19,20]. It is well-accepted that NKT cells aid in tumor immunity. Several studies in different tumor models of mice depicted NKT cell-mediated tumor surveillance [16,21,22]. In humans, reduced numbers of circulating NKT cells, lower proliferation and cytokine expression of NKT cells were demonstrated in patients suffering from different kinds of cancers [23-25]. Further, a positive correlation was reported between the number of tumor-infiltrating NKT cells and a better prognosis [24-27]. Mostly, correlative, these studies in humans corroborated the findings from mice models, pointing towards NKT cells as targets for immunotherapies.

NKT cells target tumors by means of two effective strategies. Firstly, they can kill tumor cells by direct cytolysis using perforin and granzyme B [28,29]. However, with only a few solid tumors expressing CD1d, tumors escape being recognized by NKT cells [29,30]. In fact, down-regulation of CD1d by some tumors was seen, which correlated with the disease

progression [31-33]. Secondly, by modulating the recruitment and the function of other immune cells by means of secreted cytokines, NKT cells play an indirect role [20,28]. In this scenario, NKT cells may be activated by CD1d-expressing antigen presenting cells or by antigen-independent activation by means of cytokines in the tumor microenvironment. NKT cells can recruit and/or activate other effector cells like T cells, B cells, NK cells as well as DCs. Alternatively, NKT cells can act by altering the immune-suppression in the tumor microenvironment [34]. Several studies have shown that NKT cells negatively regulate or reverse the immunosuppression by myeloid-derived suppressor cells (MSDCs) and tumor-associated macrophages [34,35].

Because of the varied targets of NKT cells and the ability to boost and amplify adaptive immune responses, NKT cells are believed to be good candidates for anti-tumor therapies. Several pre-clinical and a few clinical studies support this notion of NKT-cell based immune therapies for targeting tumors [36].

NKT cells in glioblastoma

Glioblastoma multiforme (GBM) is the most common and aggressive type of primary brain tumor in adults. Median survival in these patients is less than two years, particularly low in those with high grade gliomas [37]. Despite new approaches to surgery, radiotherapy and chemotherapy, survival has increased only modestly over the last 30-50 years. This poor prognosis for GBM has been attributed to extensive cellular and genetic heterogeneity existing not only between the four major subtypes (classical, neural, pro-neural and mesenchymal) but also at intra-tumoral level [38-40].

Although brain was initially considered as an immune-privileged organ, several studies eventually demonstrated ample amount of infiltration of immune cells in patients with malignant glioma [41,42]. However, endogenous immune responses against brain tumor cells are unable to control the tumor growth [43]. Several preclinical studies have tried to utilize anti-tumor immune responses generated by innate and adoptive immune cells including NK and T cells [44,45]. In most of these cases, immune responses of NK and T cells were suppressed by glioma tumor cells. Another challenge to the development of therapies is the glioma cell-mediated immune regulation at the tumor microenvironment, which depends on several factors and on recruitment of several immune suppressive cells a like Tregs, tumor-associated macrophages and MSDCs [45].

Given the molecular heterogeneity in GBM tumors, and their profound immunosuppression, an effective immunotherapy is a big challenge. Additionally, Gliomas are poorly immunogenic. Thus, multitarget approaches and combinatorial therapies might hold a therapeutic value in fighting gliomas. Recent years have seen a surge in the number of immunotherapeutic studies and strategies against gliomas which show promise [46]. Here we outline the role of NKT-cells in gliomas and the NKT-cell mediated therapies reported thus far.

Discussion

NKT cell numbers and their functional status in glioma patients is the first and most important thing to be considered in order to evaluate the role of these cells in glioma tumor protection. As stated earlier, the NKT cell numbers and the functional responses of NKT cells were reported to be altered in patients with solid tumors [22]. In contrast, the abundance of circulating NKT cells were reported to be comparable between GBM patients and age-matched controls [47,48]. Additionally, the same study showed that NKT cells from GBM patients were equally capable of expanding *in vitro* in the presence of mature autologous DCs loaded with α-GalCer and were able to kill glioma target cells in a CD1d-depen dent manner. NKT cell-mediated direct tumor lysis is dependent on the expression of CD1d on these cells. However, very few non-hematopoietic solid tumors express CD1d on their surface and gliomas are one of them [31,47,49-51]. Glioma cells from adult patients with both low and high-grade gliomas were found to express CD1d on their surface. What is not yet clear is the extent of NKT cell infiltration into the glioma tumor microenvironment. Also, the *in vivo* role of NKT cells in glioma patients is yet to be determined.

Medulloblastoma is another type of brain cancer expressing CD1d and not surprisingly thus, medulloblastoma cell lines were effectively killed by NKT cells activated with α-GalCer [51]. Interestingly, injection of NKT cells directly at tumor site significantly extended the survival of NOS/SCID mice implanted with human medulloblastoma cell line. As promising as these results are, it would be interesting to see if the strategy can be applied for treating glioma tumors. In a preclinical model of glioblastoma, irradiated whole tumor cells pulsed with α-GalCer increased the median survival of tumor-bearing mice in a CD1d-dependent manner by prompting T cell adaptive responses [48,52]. They also showed that the irradiated whole tumor cells pulsed with α-GalCer were capable of activating NKT cells *in vitro* and eliciting T cell responses.

CD1d is expressed by antigen presenting cells including dendritic cells (DCs) at high levels. DCs efficiently present ligands like α-GalCer to NKT cells and activate them to in turn enhance innate and adaptive immune responses [52,53]. Ligands specific to NKT cells (α-GalCer) have been evaluated as adjuvants for dendritic cells (DC)-based vaccine immune therapy in treating breast cancer and melanoma [54,55]. DCs are also the most efficient of APCs and as such they have been tested for vaccine immune therapy by loading with tumor lysates as antigens. A few DC-based vaccines have shown some effectiveness against glioblastoma although only to a limited extent [29,56,57]. Immunization by co-delivery of a-galCer loaded DCs and tumor antigens has proved to be an effective strategy for providing NKT cell-mediated tumor-immunity [48,58-62]. In a recent study, Liu et al. reported an effective method of NKT cell based immune therapy [63]. They used exosomes, small vesicles secreted by tumor cells as antigens. The tumor-derived exosomes were co-delivered with α-GalCer in a DC-based vaccine intravenously to orthotopic glioblastoma rat models to generate a more effective therapeutic response as measured by prolonged survival rate, decreased rate of glioma growth, increased antigen-specific CTL response and strong immune-modulatory effects [63].

Conclusion

Tumor tolerance in glioma depends upon the local production of cytokines and cytokines from tumor cells and recruitment of immunosuppressive cells in tumor microenvironment. It is well established that NKT cells act by modulating the immune responses either by boosting immune responses or by suppressing immune-regulation. However, it is also reported that NKT cells play a role in immune tolerance in a few graft models [64,65]. Involvement of NKT cells in tumor tolerance is not clearly established but one study showed the presence of immune tolerant IL-10^{+}IL-6^{+} NKT cells in the glioma tissues from patients and micro RNA 92a (miR-92a) secreted from glioma cells was found was found to play a critical role in the generation of these regulatory NKT cells [66]. IL-10 and IL-6 play central role in maintaining the immune suppressive microenvironment in gliomas. IL-10^{+}IL-6^{+}NKT cells, which were induced by co-culture of NKT and glioma cells *in vitro*, expressed significantly lower levels of cytokines IFN-γ, perforin and FasL and were found to suppress proliferation of $CD8^{+}$ T cells.

Pending Questions and Future Perspectives

Despite the recent developments which increase our understanding about NKT cell biology and functions [28,67-69], their role in the different types of tumors is not completely understood. The studies on the role of NKT cells in gliomas is very limited. A few studies described here do show good promise for the use of NKT cells as potent immune therapy for treating glioma patients. As glioma tumors are very heterogeneous in nature, more studies are warranted in order to completely understand the role of NKT cells in gliomas. Firstly, expression and functional status of CD1d need to be screened between different grades of gliomas. Localization and activation status of NKT cells in glioma microenvironment are other aspects that may govern the efficacy of NKT cells immune therapy but not much is known. It would be interesting to see if and how NKT cells migrate to glioma tumor site. Signaling pathways involved in the migration of NKT cells to the tumor site can then be meddled with for therapeutic purposes. It is known that gliomas are hypoxic in nature. Recent study shows that the activation and function of NKT cells changes with redox state of these cells and thus it would be interesting to probe if the immune functions of the brain-resident NKT cells are modulated in the glioma microenvironment to favor the glioma growth [68,69]. MDSCs, which are potent immuno-suppressive cells express CD1d and NKT cells have been shown to negatively regulate or reverse their immunosuppression [70-72]. Any role of NKT cells in the regulation of immune suppressive activity of MDSCs in glioma models needs to be investigated. This interaction may enhance the outcome of anti-glioma immune therapy if targeted as combined therapy.

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