editorial

Cancer Stem Cell Immunotherapy: the Right Bullet for the Right Target

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Glioblastoma multiforme (GBM) is the most aggressive form of primary central nervous system (CNS) tumors that arise from glial cells. This type of cancer presents a rapid evolution and relapse within the first year of diagnosis even after surgery and radiotherapy treatments.[1,2] The maximum survival time after first relapse and with surgery plus temozolomide is about 8 months.[1,2] Relapse of patients with GBM is attributed to the recurrence and persistence of tumor stem cells (TSC) which migrate to healthy brain tissues. Although, this population of cancer cells represent a small fraction of the malignant cells, they are exclusively responsible for propagating the disease.[3] TSCs proliferate, differentiate, and uniquely maintain the tumor growth while keeping their ability to self-renew.[4] Brain TSCs are characterized by their expression of high levels of CD133 in addition to other normal neural stem cell markers such as nestin, but they lack differentiated neural lineage markers.[5] TSCs were shown recently to resist radiation therapy and lead to tumor recurrence after treatment.[6] Therefore, alternative therapies that target TSCs are crucially needed.

GBM is characterized with a local and systemic immune suppression manifested with decreased cellular and humoral immunity. This immune deficiency is believed to be due to several factors including secreted transforming growth factor (TGF),[7] tumor cells lacking the major histocompatibility complex (MHC) molecules,[8] co-stimulatory molecules and/or up-regulation of co-inhibitory molecules like B7-H1.[9] In this issue Moviglia et al carried out a vaccine trial in a small number of patients with GBM to enhance the patients' immune response to the disease. Two vaccine preparations were tested: mixed leukocyte culture (MLC) and tumor B-cell hybridoma (TBH). MLC is a mononuclear cell preparation (MNC) collected from an unrelated-unmatched donor that is stimulated for 3 days against the cancer patient's irradiated-inactivated MNC. The stimulated cells are then implanted in the tumor lodge after neurosurgery.[10] In this mode of therapy, cytokine production by the stimulated MNC, placed beside the tumor cells, might induce its regression by host anti-tumor effector mechanisms. The rationale for such therapy is based on previous favorable data obtained by the same group in patients with pancreatic cancer.[10] The TBH vaccine was prepared from B cells obtained from the patients' mononuclear cells, after in vitro culturing and expansion with IL-4 and IL-6, and subsequent fusion with TSCs obtained by mechanical dissociation of the tumor biopsy and culturing in vitro.[11]

Three different treatment combinations were given to 3 groups of GBM patients after first relapse of debulking surgery (DS) + radiotherapy (Rx): Group 1 received DS + MLC; Group 2 received DS + MLC + TBH and Group 3 received DS + TBH. It was demonstrated that patients in Group 3 who underwent the TBH treatment had a long-lasting median survival of 25 months after the first immunization compared to those in Group 1 (MLC) who had a shorter median survival of 4.5 months. Group 2 (MLC + TBH) had a relatively higher median survival of 9.5 months. Although both treatments in Group 1 and 2 had a strong and rapid therapeutic effect compared to Group 3, treatments in Group 1 and 2 resulted also in brain inflammation provoking encephalitic autoimmune reactions which were absent in Group 3 treated with the TBH alone. It seems that the MLC reaction was the responsible for such brain inflammation. Another important observation in this study is the involvement of TSC and B cells in the generation of the TBH hybridoma. TCS will be an important source for provision of tumor antigens, while B cells expressing both stimulatory (HLA class I/II) and costimulatory molecules (B7.1, B7.2, CD40) and will act as professional antigen presenting cells. TBH may activate CD4+ T helper cells which in turn help in the generation, activation and expansion of tumor antigen-specific CD8+ cytotoxic T lymphocytes (CTL). On the other hand, TBH may help in the activation and

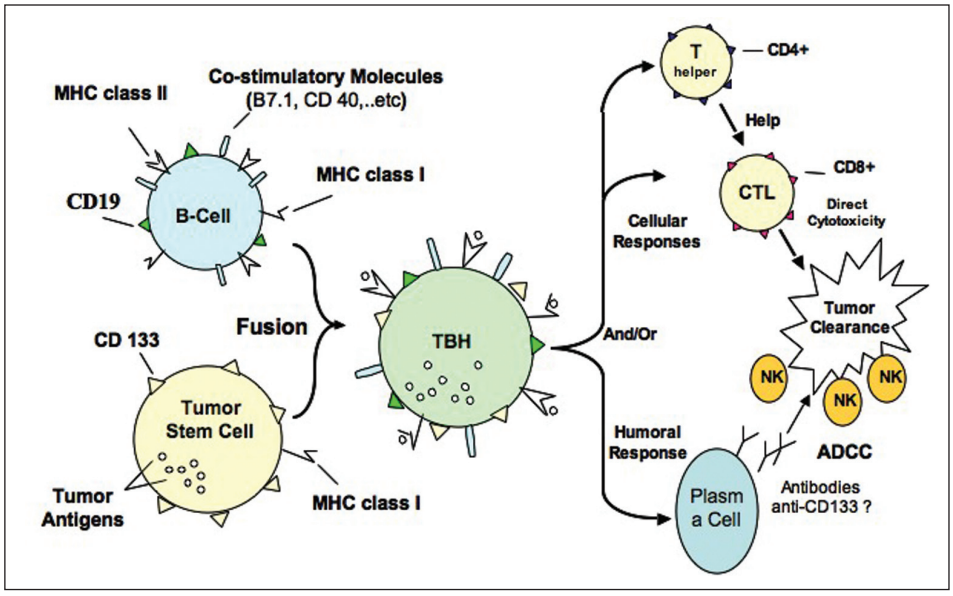

Figure 1. Possible humoral and cellular immune responses generated by TBH and their contribution to a better survival rate in brain cancer patients.

ADCC= Antibody dependent cytotoxicity, CTL= Cytotoxic T lymphocytes, TBH= Tumor B-cell hybrid, NK= Natural killer cells

generation of plasma cells that can secrete antibodies directed against tumor surface antigens expressed by TSCs such as CD133. This can lead to antibody dependent cytotoxicity (ADCC) that can kill tumor cells by natural killer cells (NK). Figure 1 illustrates possible humoral and cellular immune responses generated by TBH and their contribution to a better survival rate in brain cancer patients. Another practical advantage of using B cells, over other antigen presenting cells, in the generation of the TBH hybrid, is attributed to their expansion and long-term in vitro culture allowing vaccination of patients with the same cell preparation in sufficient amounts for the whole vaccination program.

It seems that the immune response generated against TSC antigens will prevent tumor escape of immune surveillance by eliminating tumor recurrence after relapse.

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