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Human umbilical cord blood-derived mesenchymal stem cells and their effect on gliomas**SK Shankar**

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Glioblastoma in adults and pediatric brain tumors have become one of the favored vehicles for cancer stem cell hypothesis. There is compelling evidence that human glioblastoma is a heterogeneous tumor composed of lineage committed tumor cells and a subpopulation of cancer stem cells. These tumor-initiating stem cells have a high tumorigenic potential and low proliferation rate. [1],[2],[3],[4],[5] Glioma stem cells are found to be essentially similar to normal stem cells expressing CD133 stem cell marker. Cancer stem cells derived from human tumors and cell lines are capable of recapitulating original polyclonal tumor when transplanted into immunodeficient nude mice, indicating the synergistic influence of immune suppression on tumor implantation. It is well recognized that cancer stem cells can be enriched and harvested from many human tumor biopsy specimens using the CD133 (Prominin - 1) as a cell surface marker. Yet a subpopulation of CD133 negative stem cells exist with low turnover rate and tumorigenic propensity. [4],[6],[7] These cancer stem cells contribute to tumor radio/chemo resistance by an increase in DNA repair capacity through preferential activation of DNA damage response check points. [8] Bao et al, have shown that L1CAM (neural cell adhesion molecules - L1, CD 171, which regulates neural cell growth, survival, migration, axonal outgrowth and neurite outgrowth) is essential for growth and survival of CD133 positive glioma stem cells, both in vivo and in vitro, thus suggesting to be a possible therapeutic target to suppress the tumor growth. [9]

Prior to the discovery of replication competent neural progenitor/stem cells in the postnatal brain [10] mature astrocytes or committed astrocyte progenitors were thought to be the only cells capable of replication in the post natal brain and thus susceptible for malignant transformation. Although this concept is doubted, it is now shown that a genetic cocktail of a few transcription factors can convert normal mature skin cells to totipotent embryonic stem cells [11] and a tumor. Targeting the early cortical astrocytes with oncogenes or activated signal-generating proteins can produce tumors in animals. These transformation competent astrocytes can be generated from neonatal cortex, but not from the adult cortex. [12] Brain tumors formed from these stem cells not only form masses, but also infiltrate deep along fiber tracts and form small tumorlets detached from the main tumor body. Because of this wide unpredictable distribution of neoplastic cells, stem cell therapy needs to

seek these neoplastic cells and destroy them without damage to neighbouring normal cells. Scientists have shown that certain adult stem cells, neural, mesenchymal or endothelial cells have an uncanny ability to home to cancers, even traveling through distant areas of the body. [13]

Having shown the capacity of the stem cells to migrate far and home to tumor cells, the next logical approach was to deliver a payload of tumor-destroying molecules as adjuncts to chemotherapeutic agents. Cancer killing viruses, genes encoding antitumor cytokines like 1L-12, Interferon- β , 'pro-drug converting enzymes' have been engineered into engraftable neural stem cells. Having tested in animal models, neural stem cells engineered with TRAIL for proapoptotic effect or 1L-12 for antiangiogenic effect, they form potential therapeutic agents. [14]

Human mesenchymal stem cells (MSCs) are nonhemopoietic adult stem cells with multipotent capabilities. MSCs have the capacity to home to the site of tissue injury, easily transfectable and relatively non immunogenic [15],[16],[17] though the mechanism of immunogenic privilege is not well understood. [18] Some studies suggested that stromal cells surrounding epithelial tumors, far from being innocent bystanders promote the growth of adjacent transformed neoplastic cells. [19] Another study suggested that through their immune suppressive effect, they enhance tumor growth in vivo.[20] In studies on chronic limb ischemia models, the MSCs were found to produce proangiogenic cytokines enhancing angiogenesis. [21] Contrary to general expectation, when transplanted the MSCs were found to be antitumor and antiangiogenic even in angiomatous tumors like cutaneous Kaposi's sarcoma. These MSCs evaluated were derived from bone marrow of voluntary healthy young adults. [22] Human umbilical cord blood is a rich source of both hemopoietic stem cells and MSCs, with high proliferation and expansion potential than adult bone marrow-derived cells. [23]

Kang et al, have for the first time demonstrated cytotoxic ability of human umbilical cord-derived MSCs on human malignant glioma cells in vitro.[24] They also observed that human umbilical cord-derived MSCs when activated by 1L-15, granulocyte-macrophage stimulating factor and in combination, exerted greater cytotoxic effect. They ascribed the cytotoxic effect to immune response-related proteins secreted from the MSCs following activation. Ho et al, from National Cancer Centre, Singapore, have noticed interestingly different MSCs isolated from different sources displayed differential migration ability toward human glioma cells. Highly migrating MSCs cells had higher expression of genes regulating matrix metalloprotease [1] in contrast to the ones with low migrating potential. Functional abrogation of the transcription levels of MMP1 has aborted the migratory potential towards glioma cells. Conversely conditioned medium from the highly migrating MSCs or the presence of recombinant MMP1 can rescue the non migratory phenotype of MSCs to the functional activity. [25] Interestingly expression of MMP1 at remote areas also made the nonmigratory MSCs responsive to the signaling cues from the glioma cells. Blocking the interaction of the MMP1 and its receptor PAR1 effectively diminished the migratory potential. These observations strongly support the idea that matrix metalloproteases in the interstitium are critically involved in the migration of the MSCs [25] as well as the cancer cells.

Having realized the migrating and homing potential of MSCs and neural stem cells and not integrating into nonmalignant tissues, investigators started evaluating the therapeutic usefulness of various sources of these cells. Murphy, et al, realizing the pitfalls in using autologous bone marrow stem cells to induce angiogenesis in cases of 'critical limb ischemia' tried endometrial regenerative cells (mesenchymal-like stem cells) derived from menstrual blood, because of their angiogenic potential in the endometrium. [26] These mesenchymal-like endometrial stromal cells have high levels of matrix metalloproteases, and trophic factors, which can inhibit inflammation and manifest low immunogenicity and lack tumorigenicity. Having realized the potential of homing to the tumor and not to the normal parenchyma around, the search for suitable MSCs have been initiated to use these as therapeutic targets only to deliver tumor suppressor molecules, cytokines, genetic modulators and drugs. Serendipitously, to the utter surprise of the investigators, the angiogenic MSCs in critical limb ischemia were found to be of low angiogenic potential and yet cytotoxic to glioma cells in vivo and in vitro. This has transformed into a field of intense study for the treatment of brain tumors. Kang et al, showed significant cytotoxicity to U87MG human malignant glioma cell line in vitro, with or without activation by cytokines. [24] In this issue of Neurology India Yang et al, from have utilized human umbilical cord blood-derived MSCs to demonstrate the cytotoxic effect on highly malignant C 6 cell line implanted in the flank of mice, following intravenous or intratumoral injection of stromal cells. Thomas E Ichem from California on the other hand, injecting endometrial regenerative cells by intravenous and intratumoral route into intracerebrally implanted aggressive C 6 - glioma cells showed tumor regression and reduced angiogenesis and reduced number of

CD133 positive glioma tumor cells. [27] The important message of the studies is the ability to target the intracranial tumors by intravenous administration of MSCs derived from different sources without entering the cranium.

The mechanics of cytotoxicity of these MSCs appears to be divergent. In the case of Kaposi sarcoma, an angiogenic AIDS associated neoplastic lesion, inhibition of Akt pathway (which requires cell to cell contact between the neoplastic cells and the MSCs mediated through E-Cadherin is essential for antitumorogenic effect. [22] On the other hand, the cytotoxic effect of umbilical cord mesenchymal cells appears to be mediated by down regulation of Cyclin D 1 (as demonstrated in the article published in this issue) whose expression correlated with degree of malignancy, tumor progression and invasion. In addition enhanced production of immune response related proteins secreted by the MSCs following stimulation by cytokines indicate participation of autocrine and paracrine mechanisms in mediating cytotoxicity.

Although the potential of using MSCs derived from various sources to suppress and kill the glioma stem cells is encouraging, all the workers uniformly indicated that more work is needed to understand the basic biology and possible potential of adverse biological effects in the long term. Because of the homing property of MSCs to the site of injury, Andreef cautioned that "patients receiving the MSCs as a therapeutic modality, could not have recent surgery, pneumonia, catheters or wounds, [14] as the injected progenitor cells are found to share the tumor homing potential of MSCs. Labeling these endothelial cells with supermagnetic iron oxide nanoparticles and infusing them into mice and imaging by MRI, revealed the incorporation of the bone marrow-derived endothelial cells into areas of neovascularisation but not to quiescent vessels. This observation forms another potential drug delivery target and studying the progression of tumor by imaging.[29]

As a scientific study, various observations are exciting and have tremendous potential. However, it takes some more time before the MSC transfusion becomes a useful therapeutic strategy to human subjects.

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