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Immune Containment of Cancer Stem Cells

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The role in the control of pathogenic microorganisms is well known. Most of the population will survive the attack from the microorganisms. The patients that succumb from the disease have less armamentarium to fight the microorganism. Herpes virusses like Epstein Barr virus live livelong with the infected patient. The immune system and the virus are communicating vessels that keep each other into control.

The immune system is also capable to wipe out tumor cells with the same efficiency when mutated antigens are present in the tumor. Releasing the full power of the immune system by checkpoint antibodies has shown the capabilities of the system.

Unlike microorganisms cancer cells comprise a large array of cells each with its own function to maintain the tumor. Cancer stem cells have emerged as drivers of tumor maintenance after eradication of the proliferative tumor cells by cytostatic drugs or irradiation. Cancer stem cells are quiescent and therefor less vulnerable for the classical cancer drugs. However, more mature cancer cells and cancer stem cells are also connecting vessels [1].

Like Herpes virus the control of the immune system of cancer stem cells can be studied by low-grade tumors. Low Grade gliomas (LGG) are rare tumors. There are classified as astrocytoma, oligodendroglioma or mixed oligoastrocytoma. Their incidence is low, estimated rates are in the US 0.58, 0.27, and 0.21 per 100,000, respectively, based on data from 2005-2009 [2]. Since those tumors do not proliferate very fast they are less vulnerable for DNA synthesis inhibiting procedures like chemotherapeutic drugs and irradiation [3]. Seizures can be controlled by anti epileptic drugs with or without temozolomide [4]. However, these treatments induce mutations, which aggravate the situation and leads to an untreatable recurrence of the tumor [5]. They resemble cancer stem cells [6] sharing the same low proliferation characteristics.

Treatment of these uncommon tumors is needed to prevent seizures, changes in mental status and severe focal neurologic deficits depending on the location of the brain involved [7]. However, new treatment modalities are eagerly awaited for. Based on their similarity with cancer stem cells it is expected that those treatments developed to eradicate cancer stem cells will be of benefit for LGG and their derailment to high-grade tumors that are virtually untreatable.

Several groups studied compounds that killed putative cancer stem cells. Remarkably there are several food components that make agents that kill cancer stem cell [8-17]. Also several old medicines are in focus again that kill cancer stem cells [18-24]. These natural compounds disturb important signaling pathways in cancer stem cells [25,26]. Those pathways, Wnt, Hedgehog and NOTCH are also indispensable for normal stem cell maintenance. Also no valid *in vitro* culture method is available to study pure stem cells. Xenotransplantation is the best *in vivo* method to study cancer stem cells. The sphere culture is approaching at least stem cell maintenance [27-30]. However, these compounds work excellent *in vitro* but because those pathways are also needed *in vivo* by normal cells introduction of these compounds is problematic.

Several aberrancies were described for glioblastoma (GBM) stem cells. For example the survival of cancer stem cells was dependent on an overexpressed sialidase that removes sialic acid from membrane bound proteins [31]. Blocking the NEU4 sialidase and thus maintaining sialic acid expressing cells, blocked the survival of GBM stem cells. Apparently sialic acid blocks the outgrowth of glioblastoma stem cells. Other studies focus on the different metabolic properties of glioma cancer stem cells like a different iron metabolism [32].

But blocking cancer stem cells is only one side of the medal. The plasticity of cancer stem cells is high leading to dedifferentiation of more mature cancer cells to cancer stem cells when the latter are removed from the population [33,34].

Such a scenario is perfect for the immune system to cope with if we know the antigens that makes them stem cells. Cancer stem cells (over) express the stem cell proteins OCT4a, SOX2 and NANOG [35]. Immunity against those proteins was demonstrated [36,37]. Indeed loading high grade GBM lysates into dendritic cell, the initiator and booster of an immune response, showed an antitumor response but loading the dendritic cells with cancer stem cell lysates proved even to be better [38]. These approached are hopeful for cancer patients to keep the cancer stem cells under control but several hurdles need to be taken. The tumor induced down regulation of the immune response is just one of them and at least partially counteracted by so called checkpoint antibodies.

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