Immunochemistry & Immunopathology

Torensma, Immunochem Immunopathol 2016, 2:2
DOI:10.4172/2469-9756.1000123

Commentary Open Access

Immune Containment of Cancer Stem Cells

Ruurd Torensma*

Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

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.

References

1. Di J, Duiveman-de Boer T, Figdor CG, Torensma R (2011) Eradicating cancer cells: struggle with a chameleon. Oncotarget 2: 99-101.
2. Dolecek TA, Propp JM, Stroup NE, Kruchko C (2012) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 14 Suppl 5: v1-49.
3. Olson JJ, Kalkanis SN, Ryken TC (2015) Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J. Neurooncol. 125: 449-456.
4. Sherman JH, Moldovan K, Yeoh HK, Starke RM, Pouratian N, et al. (2011) Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. J. Neurosurg. 114: 1617-1621.
5. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, et al. (2014) Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science 343: 189-193.
6. Chen YH, McGowan LD, Cimino PJ, Dahiya S, Leonard JR, et al. (2015) Mouse low-grade gliomas contain cancer stem cells with unique molecular and functional properties. Cell Rep 10: 1899-1912.
7. Pouratian N, Schiff D (2010) Management of low-grade glioma. Curr Neurol Neurosci Rep 10: 224-231.
8. Pistollato F, Giampieri F, Battino M (2015) The use of plant-derived bioactive compounds to target cancer stem cells and modulate tumor microenvironment. Food Chem Toxicol 75: 58-70.

***Corresponding author:** Ruurd Torensma, Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands, E-mail: Ruurd.torensma@radboudumc.nl

Received May 12, 2016; **Accepted** December 19, 2016; **Published** December 23, 2016

Citation: Torensma R (2016) Immune Containment of Cancer Stem Cells. Immunochem Immunopathol 2: 123. doi: 10.4172/2469-9756.1000123

9. Norris L, Karmokar A, Howells L, Steward WP, Gescher A, et al. (2013) The role of cancer stem cells in the anti-carcinogenicity of curcumin. Mol Nutr Food Res 57: 1630-1637.

10. Miklossy G, Youn UJ, Yue P, Zhang M, Chen CH, et al. (2015) Hirsutinolide Series Inhibit Stat3 Activity, Alter GCN1, MAP1B, Hsp105, G6PD, Vimentin, TrxR1, and Importin alpha-2 Expression, and Induce Antitumor Effects against Human Glioma. J. Med. Chem. 58: 7734-7748.

11. Peng H, Jiang B, Zhao J, Chen B, Wang P (2015) Risperidone promotes differentiation of glioma stem-like cells through the Wnt signaling pathway. Tumor Biol. 36: 6677.

12. Zhao D, Yao C, Chen X, Xia H, Zhang L, et al. (2013) The fruits of Maclura pomifera extracts inhibits glioma stem-like cell growth and invasion. Neurochem Res 38: 2105-2113.

13. Senft C, Polacin M, Priester M, Seifert V, Kogel D, et al. (2010) The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas. BMC Cancer 10: 491.

14. Baharuddin P, Satar N, Fakiruddin KS, Zakaria N, Lim MN, et al. (2016) Curcumin improves the efficacy of cisplatin by targeting cancer stem-like cells through p21 and cyclin D1-mediated tumour cell inhibition in non-small cell lung cancer cell lines. Oncol. Rep. 35: 13-25.

15. Tu SP, Jin H, Shi JD, Zhu LM, Suo Y, et al. (2011) Curcumin Induces the Differentiation of Myeloid-Derived Suppressor Cells and Inhibits Their Interaction with Cancer Cells and Related Tumor Growth. Cancer Prev. Res. (Phila) 5: 205-215.

16. Sa G, Das T (2008) Anti cancer effects of curcumin: cycle of life and death. Cell Div 3: 14.

17. Naujokat C, Laufer S (2013) Targeting Cancer Stem Cells with Defined Compounds and Drugs. Journal of Cancer Research Updates 2: 36-67.

18. Shchors K, Massaras A, Hanahan D (2015) Dual Targeting of the Autophagic Regulatory Circuitry in Gliomas with Repurposed Drugs Elicits Cell-Lethal Autophagy and Therapeutic Benefit. Cancer Cell 28: 456-471.

19. Triscott J, Lee C, Hu K, Fotovati A, Berns R, et al. (2012) Disulfiram, a drug widely used to control alcoholism, suppresses the self-renewal of glioblastoma and over-rides resistance to temozolomide. Oncotarget 3: 1112-1123.

20. Triscott J, Rose PM, Dunn SE (2015) Concise review: bullseye: targeting cancer stem cells to improve the treatment of gliomas by repurposing disulfiram. Stem Cells 33: 1042-1046.

21. Liu P, Brown S, Goktug T, Channathodiyil P, Kannappan V, et al. (2012) Cytotoxic effect of disulfiram/copper on human glioblastoma cell lines and ALDH-positive cancer-stem-like cells. Br. J. Cancer 107: 1488-1497.

22. Han D, Wu G, Chang C, Zhu F, Xiao Y, et al. (2015) Disulfiram inhibits TGF-beta-induced epithelial-mesenchymal transition and stem-like features in breast cancer via ERK/NF-kappaB/Snail pathway. Oncotarget 6: 40907-40919.

23. Hothi P, Martins TJ, Chen L, Deleyrolle L, Yoon JG, et al. (2012) High-throughput chemical screens identify disulfiram as an inhibitor of human glioblastoma stem cells. Oncotarget 3: 1124-1136.

24. Wieland A, Trageser D, Gogolok S, Reinartz R, Höfer H, et al. (2013) Anticancer effects of niclosamide in human glioblastoma. Clin. Cancer Res. 19: 4124-4136.

25. Kim YS, Farrar W, Colburn NH, Milner JA (2012) Cancer stem cells: potential target for bioactive food components. J Nutr Biochem 23: 691-698.

26. Scarpa ES, Ninfali P (2015) Phytochemicals as Innovative Therapeutic Tools against Cancer Stem Cells. Int J Mol Sci 16: 15727-15742.

27. Lee CH, Yu CC (2016) Tumorsphere as an effective in vitro platform for screening anti-cancer stem cell drugs. Oncotarget 7: 1215-1226.

28. Martinez-Serrano MJ, Caballero-Banos M, Vilella R, Vidal L, Pahisa J, et al. (2015) Is sphere assay useful for the identification of cancer initiating cells of the ovary? Int. J. Gynecol. Cancer 25: 12-17.

29. Morrison BJ, Steel JC, Morris JC (2012) Sphere culture of murine lung cancer cell lines are enriched with cancer initiating cells. PLoS One 7: e49752.

30. Peng T, Qinghua M, Zhenning T, Kaifa W, Jun J (2011) Long-term sphere culture cannot maintain a high ratio of cancer stem cells: a mathematical model and experiment. PLoS ONE 6: e25518.

31. Silvestri I, Testa F, Zappasodi R, Cairo CW, Zhang Y, et al. (2014) Sialidase NEU4 is involved in glioblastoma stem cell survival. Cell Death Dis 5: e1381.

32. Schonberg DL, Miller TE, Wu Q, Flavahan WA, Das NK, et al. (2015) Preferential Iron Trafficking Characterizes Glioblastoma Stem-like Cells. Cancer Cell 28: 441-455.

33. Nakano I (2015) Stem cell signature in glioblastoma: therapeutic development for a moving target. J Neurosurg 122: 324-330.

34. Auffinger B, Tobias AL, Han Y, Lee G, Guo D, et al. (2014) Conversion of differentiated cancer cells into cancer stem-like cells in a glioblastoma model after primary chemotherapy. Cell Death Differ. 21: 1119-1131.

35. Jeter CR, Yang T, Wang J, Chao HP, Tang DG, et al. (2015) Concise Review: NANOG in Cancer Stem Cells and Tumor Development: An Update and Outstanding Questions. Stem Cells 33: 2381-2390.

36. Di J, Massuger LF, Duiveman-de Boer T, Zusterzeel PL, Figdor CG, et al. (2013) Functional OCT4-specific CD4 and CD8 T cells in healthy controls and ovarian cancer patients. Oncoimmunology 2: e24271.

37. Dhodapkar KM, Feldman D, Matthews P, Radfar S, Pickering R, et al. (2010) Natural immunity to pluripotency antigen OCT4 in humans. Proceedings of the National Academy of Sciences 107: 8718-8723.

38. Finocchiaro G, Pellegatta S (2015) Immunotherapy with dendritic cells loaded with glioblastoma stem cells: from preclinical to clinical studies. Cancer Immunol. Immunother 65: 101-109.