Targeting Cancer Stem Cells, The Major Leap Toward a Cure

Fatehi M[1], Fatehi A[2]

1. Department of Molecular Genetics, University of Toronto, Canada
2. Department of Medical Biophysics, University of Toronto, Canada

Corresponding Author:
Mostafa Fatehi, BSc, Master of Science student
Tel: (+1) 416 94 67 490
Email: m.fatehi@utoronto.ca

Received: 20 May 2010
Accepted: 20 Jun. 2010
Iran J Cancer Prev; 2010; 3: 109-10

The concept of stem cells, cells that can self-renew and differentiate, was initially postulated by Pappenheim in 1917 and their existence has since been shown in many different tissues [1]. The original ideas for cancer stem cells came in remarkable papers by Southham et al and Hamburger et al which showed that cancer cells had varying tumor-initiating capacities [2, 3]. Later, John Dick's lab isolated acute myeloid leukemia stem cells in 1994 and acute lymphocytic leukemia stem cells soon thereafter [4, 5]. Since then, cancer stem cells have been isolated in many solid tumors; in brain, head and neck, breast and prostate cancer [6-15].

The cancer stem cell model represents a paradigm shift in our understanding of carcinogenesis and tumor cell biology. In this model, tumors originate in either tissue stem cells or their immediate progeny through dysregulation of the normally tightly regulated process of self-renewal. Consequently, tumors contain a cellular subcomponent that retains key stem cell-like properties. These properties include self-renewal, tumor regeneration, and differentiation [16].

Despite the mounting evidence in support of the CSC model, there is some controversy regarding the similarities and differences between cancer and somatic stem cells [17]. Significantly, some recent reports have claimed that unlike somatic stem cells, CSCs may not be rare subpopulations within tumors in some cancers [17]. In response, Weinberg comprehensively argues that the CSC model rests on solid experimental foundations and that the differences in the observed frequencies of CSCs within tumors reflects the various cancer types and hosts used to assay these cells and .

The existence of CSCs has fundamental implications for cancer risk assessment, early detection, prognostication, and prevention. Control of many stem cell phenotypes depends on epigenetic reprogramming; thus epigenetic transformation of CSCs has become a very promising area of basic and preclinical molecular-targeted prevention science. An important characteristic of these cells is their ability to restrict DNA damage sustained during radiation or chemotherapy [18, 19] and their ability to effectively pump out chemotoxic agents through a wide range of active membrane transporters. As a result, many current therapeutic agents are only able to reduce the bulk of the cancer cells while residual CSCs are able to regenerate the cancer. In addition, cancer stem cells are implicated in developing drug resistant progeny in some cancers such as chronic myeloid leukemia (CML) [20].

Thus, it is imperative that any truly curative treatment of cancer specifically target CSCs. Successful stem cell therapy will have to avoid targeting normal stem cells with phenotype and cell signalling pathways similar to CSCs. There is not enough literature in this field yet but an effective way to contrast somatic and cancer stem cells may be in evaluating protein expression levels and looking for mutant proteins specific to cancerous cells. In addition, prospective therapies like epigenetic modifications using interfering RNA and therapies based on synthetic lethality may achieve exquisite selectivity when aimed at CSCs and represent major improvements in cancer treatment. Effective eradication of CSCs will be the major breakthrough required in the road to finding cures for various cancer types.

Please cite this article as: Fatehi M, Fatehi A. Targeting Cancer Stem Cells, The Major Leap Toward a Cure. Iran J Cancer Prev. 2010; Vol3, No3, p.109-10.

References

1. Pappenheim A:Prinzipien der neuen morphologischen Haematologie nach zytogenetischer Grundlage. Folia Haematol. 1917. 21:91-101.
2. Southam C, Brunschwig A: Quantitative studies of autotransplantation of human cancer. Cancer. 1961. 14:461-3.
3. Hamburger AW, Salmon SE: Primary bioassay of human tumor stem cells. Science. 1977. 197:461-3.
4. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M, Paterson B, Caligiuri MA, Dick JE. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994. 367: 645–8.
5. Bonnet D, Dick JE Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997. 3:730–7.
6. Sullivan, J.P., Minna, J.D., Shay, J.W. Evidence for self-renewing lung cancer stem cells and their implications in tumor initiation, progression, and targeted therapy. Cancer Metastasis Rev. 2010. 29:61–72.
7. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA. 2003. 100: 3983–8.
8. Dome B, Timar J, Dobos J, Meszaros L, Raso E, Paku S, et al. Identification and clinical significance of circulating endothelial progenitor cells in human non-small cell lung cancer. Cancer Res. 2006. 66:7341-7.
9. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. Nature. 2004. 432:396–401.
10. Chiba T, Kita K, Zheng YW, Yokosuka O, Saisho H, Iwama A, et al. Side population purified from hepatocellular carcinoma cells harbors cancer stem cell-like properties. Hepatology. 2006. 44:240–51.
11. Grichnik JM, Burch JA, Schulteis RD, Shan S, Liu J, Darrow TL, et al. Melanoma, a tumor based on a mutant stem cell? J Invest Dermatol. 2006. 126:142–53.
12. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, et al. Identification and expansion of human coloncancer-initiating cells. Nature. 2007. 445:111–5.
13. Patrawala L, Calhoun T, Schneider-Broussard R, Li H, Bhatia B, Tang S, et al. Highly purified CD44+ prostate cancer cells from xenograft human tumors are enriched in tumorigenic and metastatic progenitor cells. Oncogene. 2006. 25:1696–708.
14. Szotek PP, Pieretti-Vanmarcke R, Masiakos PT, Dinulescu DM, Connolly D, Foster R, et al. Ovarian cancer side population defines cells with stem cell-like characteristics and Müllerian Inhibiting Substance responsiveness. Proc Natl Acad Sci U S A. 2006. 103:11154–9.
15. Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, et al. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell. 2007. 1:313–23
16. Wicha, M.S., Liu, S., Dontu, G., Cancer Stem Cells: An Old Idea—A Paradigm Shift. Cancer Res. 2006. 66: (4). 1883-90.
17. 17. Gupta, P., Chaffer, C.L., Weinberg, R.A., Cancer stem cells: mirage or reality? Nat Med. 2009. 15(9), 1010-12.
18. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006. 444: 756–60.
19. Diehn M, Cho RW, Lobo NA, Kalisky T, Dorie MJ, Kulp A.N., et al. Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature. 2009. 458: 780–3.
20. Michor, F., Mathematical Models of Cancer Stem Cells. Journal of Clinical Oncology. 2008. 26(17), 2854-61.