

Could Cancer Initiate From Bone Marrow Progenitors?

Hmed Ben Nasr¹, Serria Turkey Hammami¹, Khaled Zeghal¹

Abstract

Background: Defining cancer stem cells and their origins is of much controversy, and constitutes a challenged knockout for cell targeting- anticancer drugs. Herein, we put forward a hypothetic model for cancer stem cells initiation from bone marrow stem cells. These later, will differentiate into an ancestral progenitor that activates a memorial program – the black box cassette- that is responsible of abnormal neo-organogenesis in the form of tumors and metastases. To approve this model, we assume that characterizing and investigating the most primitive forms of the bone marrow progenitors is required; both inside their niche and in circulation of cancer patients.

Keywords: Bone marrow; Progenitors; Neoplasm; Origin

Please cite this article as: Ben Nasr H, Hammami ST, Zeghal Kh. Could Cancer Initiate From Bone Marrow Progenitors? *Iran J Cancer Prev.* 2013; 6(2):108-12.

1. Dept. of Pharmacology, Medicine Faculty, Sfax University, Rue Magida Boulila, Sfax, Tunisia

Corresponding Author:
Hmed Ben Nasr, PhD
Phone: (+216) 74 24 70 36
Email: hmedbnasr@gmail.com

Received: 11 Feb. 2013
Accepted: 9 Apr. 2013
Iran J Cancer Prev 2013;2:108-12

Introduction

Cancer diseases consist of unexpected evolutionary life- forms that threaten human beings [1]. Even as tremendous inventions had have ameliorated anticancer therapeutic practices, these pathologies' developmental and progressive mechanisms are still disputed; and inclined a chiefly limiting factor in front of drugs' efficiency. Consequently, several opinions and hypotheses have been formulated to define tumorigenesis and metastasis origins. Johannes Muller (1838) and her student Rudolph Virchow (1821-1902) were the first pathologists describing the cellular origin of cancer [2]. This finding opened new skylight for specific cells targeting-drugs' discovery. Huge plethora of studies has depicted, one by one, cascades of cancer development, to finally draw the cancer stemness theory which is reinforced by several molecular and genomic scrutinies [3].

Because of the important heterogeneity of the characterized Cancer Stem Cells (CSCs), which are harbored within different kinds of tumors; it was stubborn to accurately demarcate their origins. In regard of the copious common patterns shared with CSCs, we hope to highlight relevant opinions dealing with the possibility that bone marrow progenitors did initiate the cancerous transformation.

From Normalcy to Malignancy

The cell transformation and progression, from normalcy to malignancy, could be simulated to a honey-bees' colonial development and reproduction. This insect's queen gives naissance to numerous and

various individuals, amongst which only rare genetically defined mature females (future queens) will generate new outposts, when and where conditions are favorable. Thus, in certain circumstances, normal cell will transform to a CSC through several mechanisms, and acquire a genomic program enabling it to get patterns of "honey- bees' queen". Thereafter, CSC enters the miscellaneous sequential life-cycle from tumorigenesis to metastasis. Several works impressively assembled and described the cellular, molecular and genetic circuitry that is ensued by the transformed cell to result into metastases [4, 5]. They commonly stippled for a repeated cascade of events that permit various capabilities for tumoral cells: self- sufficiency in growth signals, insensitivity to antigrowth signals, escaping to apoptosis, unlimited replicative potential, sustained angiogenesis, tissue invasion, migration and metastasis. Nonetheless, these events are physiological alterations, eroding the multi-cellular organism homeostasis, that are guaranteed by both the CSC (intrinsic factors) and the surrounding microenvironment (extrinsic factors). The genetic and epigenetic alterations constitute the major intrinsic factors leading to the disease's development and progression [6]; while extrinsic factors assemble various elements such as immune surveillance depletion [7]; aging [8] and inflammation [9]. These two factors constitute the basic trait for Paget' hypothesis: the seed and soil [10]. Seemingly, the reliability between intrinsic and extrinsic elements outlines a rate of knot for CSC evolutionary scenario. Thus, it is conceivable that each genomic modification might, reciprocally, match with an adequate

environmental variation point [11]. Whether these two sequential events fit one to other, is still an important inquiry to enlighten. It was assumed that, at least, two or more mutational events (genomic modifications) should occur to initiate the primary cancerous transformation [4]; but to raise into metastasis in distant organs several passive and/ or active modifications are required, in both CSCs' daughters and their surrounding microenvironment. Garraway and Sellers (2006) have developed a model of aberrant lineage ontogeny and somatic genetics, in order to explain the chronological evolving of the disease. They proposed that tumorigenesis and metastasis arose from the activation of an inborn "backward" developmental program of lineage progenitors and their survival genetic programs [12]. Such system might generate an ancestral form of stem cells that aberrantly grow and invade into the body [13], like as it occurred during organogenesis. Herein, we describe this program as a "black box cassette". Hold inactive in normal cells' memory, this black box cassette is unexpectedly reactivated under some defined conditions, and will turn on a fastidious machinery of organogenesis leading to tumor development and metastases. In conjunction to the cancer stemness theory, this conception could bring simple explanations in oncology.

Bone Marrow Stem Cells, as Origin of Cancer

Bone marrow constitute the primarily reservoir of stem cells (BMSCs) in the body. A BMSC did normally replicate and differentiate into several progenitors and somatic cells [14]. When BMSCs are in contact with other tissues, they give raise to tissues' neo-genesis. Also, it has been revealed that BMSCs acquire tissue morphology and landmarks, by spontaneous fusion with normal cells [15, 16]. Thus, it is plausible to seek for BMSCs as the origin of various cancer diseases. Some experimental models of BMSCs transplantations into nude or immune-compromised animals prompted relative improving for their transformation into solid tumors [17-19]. This pathologic deviation of BMSCs could be mediated by the accumulated chromosomal instability, as observed in murine model [20]. Using similar experimental model, Zheng and Liang (2008), showed that the donating-males' BMSCs did not contribute to the induced hepatocellular carcinoma into receptive females [21]. Such debate might be caused by the important conditioning, like the immune system depletion that permits not only tumorigenesis but also any introduced pathogen's growth. So,

clinical investigations are likely much relevant to improve our knowledge on the pragmatic release of tumorigenic cells from BMSCs. Beyond, the great assays examining the genetic and cluster designating landmarks of cells, BMSCs have been identified in the core of tumor, in cancer patients [22]. Reciprocally, cancerous cells were found to circulate and to home into the bone marrow niche [23]. This mutual relocation of both tumorigenic cells and BMSCs derived ones rappels the circulatory loops of immune cells.

Interestingly, osteosarcomas that could directly originate inside the bone marrow niche, is the most frequent metastasis in childhood [24]. Furthermore, in myeloma patients, there are several chromosomal translocations that occur into osteoclasts' nuclei. According to the authors, these genetic aberrations are hybrids of osteoclasts with myeloma cells [25]. Instead, they could instigate from an aberrant BM progenitors; too [17]. Tumoral cells have been characterized into bone marrow aspirates from non-metastatic, and disease- free breast cancer patients, after systemic recovery; and in earlier stages (I and II) of the disease [23, 26]. These observations bring relative approval to our opinion. This view of point have been discussed by Dawson et al. (2011), who summarized that the tumor progression is firmly dependent on bone marrow stromal cells' lineages [27].

The most primitive form of BMSCs, the innate BMSC, will replicate and self-renew to generate various normal progenitor lineages (HSCs: Hematopoietic Stem Cells, and BMDSCs: somatic Bone Marrow Derived Stem Cells), in order to ensure homeostasis and damaged tissues' repair [14]. Under the influence of various extrinsic and eventually intrinsic factors, these progenitors will systematically lead to different kinds of the known myeloma; diffuse and follicular lymphomas; and distant sarcomas (yellow panels) [28]. Pfaff et al. (2012) showed that a pluripotent stem cell derived from BMSCs could re-differentiate into hematopoietic cells [29]. This prompted the possibility that BMSCs produces an ancestral form of progenitors that exhibit an active engine dotted for organogenesis [13]: the black box cassette (green panels). These ancestral cells exhibit embryonic-like stem cells properties and could be found both into bone marrow niche and the blood circulation [30]. Ultimately, they will easily enter sequential and spontaneous differentiations to any kind of stromal cells progenitors and migrate to a definite organ where they clone and contribute to tumorigenesis. Perhaps, there will be swaying and switching

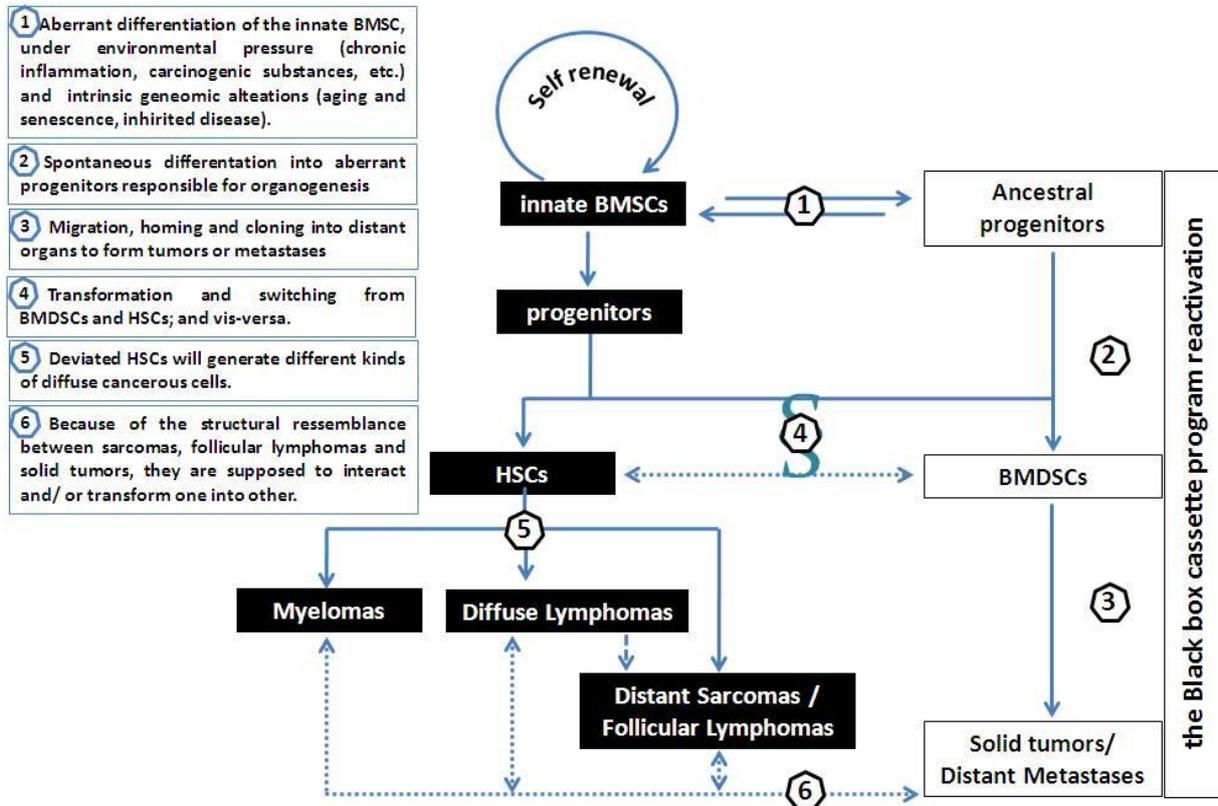


Figure 1. Schematic representation of the hypothetical mechanisms of the release of CSCs from Bone Marrow Stem Cells (BMSCs). BMSCs will generate aberrant Bone Marrow Derived Stromal Cells (BMDSCs) that contribute to tumorigenesis and metastasis.

between the yellow and green pathways, dependently on lineages' nature and the surrounding microenvironment (dotted lines). Pragmatically, interacting and switching between two forms of cancers have been observed [31]. Perhaps, this might explain the possible reversibility of the metastatic neuro-blastoma observed in childhood [10]. Furthermore, this theoretical scenario of tumor development and metastasis could reveal the mystery of cancers without defined origins [32]. The awakened black box cassette program might stand in memory of the normal cell. Several investigations evidenced the existence of such memorial program, in various stromal cells, which was expected to be under epigenetic factors' control [33, 34]. So, the consecutive spatio-temporal variation in derived progenitor cells [35] would be subsequent to DNA methylation dynamic that is supposed to guide memory in stem cells [36]. Since that, the epigenetic alterations in BMSCs will prompt the black box cassette program to viaduct an erroneous

organogenesis (Figure 1). Instead, this program remains tightly controlled by the blastocyst [37].

Concluding Remarks and Perspectives

Our opinion outlines that cancer initiating- cells could derive from bone marrow progenitors. To do so, BMSCs are firstly pushed to generate an ancestral form of progenitors that have an activated memorial program – the black box cassette- leading to fastidious tissular neo-genesis. This scenario, did involve few genomic modifications that are needed for the ancestral cell release; whereas tumorigenesis and metastases progression are spontaneously mediated without requirement of further genetic interventions. In this way of thinking, the intra and inter- tumoral cells' heterogeneity and diversity are quietly acquired during both the colonization or at the first transformations leading to various ancestral progenies of stem cells. Conventionally, this is challenged by huge designating markers that are extremely variable. However, it could be envisaged that they are temporarily expressed by the

progenitors as they have instable genomes. To get better comprehension concerning this hypothesis, we suggest that fine-tuning of cells' depicting techniques toward the characterization and isolation of the most primitive forms of cancer patients' BMSCs, into both bone marrow niche (aspirates) and the circulation (blood and lymph), is necessary. Thereafter, accurate experimental models will be helpful to find the relationships between these cells and tumorigenesis and metastasis.

Acknowledgment

The authors greatly thank Dr Zoheir Sahnoun and Dr Kamilya Ksouda, from the Laboratory of Pharmacology, Medicine Faculty of Sfax, Sfax University, Rue Magida Boulila, Sfax; Tunisia, for their assistance and help in penning and revising the manuscript.

Conflict of Interest

The present work did not present any conflict of interest.

Authors' Contribution

Hmed Ben Nasr contributed in designating the subject, data collection and synthesis and penning. Serria Turkey Hammami contributed in data collection and revision of the paper.

Khaled Zeghal participated in designating the subject and synthesis and revised the paper.

References

1. Davies PCW, Lineweaver CH. cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors. *Physiol Biol.* 2011; (doi:10.1088/1478-3975/8/1/015001).
2. The history of cancer. American Cancer Society. 2011; www.cancer.org
3. Dalerba P, Cho RW, Clarke MF. Cancer stem cells: models and concepts. *Annu Rev Med.* 2007; 58: 267-84.
4. Bertram JS. the molecular biology of cancer. *Mol Aspects of Med.* 2001; 21: 167-223.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000; 100: 57- 70.
6. Nguyen DX, Massague J. genetic determinants of cancer metastasis. *Nat Rev Genetics.* 2007; 8: 341- 52.
7. Mapara MY, Sykes M. Tolerance and cancer: mechanisms of tumor evasion and strategies for breaking tolerance. *J Clin Oncol.* 2004; 22: 1136-51.
8. Hoeijmakers JHJ. DNA damage, aging, and cancer. *N Engl J Med.* 2009; 361: 1475-85.
9. Arias JI, Aller MA, Arias J. Cancer cell: using inflammation to invade the host. *Mol Cancer.* 2007; 6: 29.
10. Paget S. the distribution of secondary growths in cancer of the breast. *Lancet.* 1989, 1: 571-3.
11. Stafford LJ, Vaidya KS, Welch DR. metastasis suppressors genes in cancer. *Int J Biochem Cell Biol.* 2008; 40: 874- 91.

12. Garraway LA, Sellers WR. Lineage dependency and lineage –survival oncogenes in human cancer. *Nature Rev Cancer.* 2006; 6: 593-602.
13. Stuger J. Cancer is the reactivation of abort mechanisms from embryogenesis in later stages of life. *Med Hypotheses Res.* 2011, 7: 57-69.
14. Ergen AV, Goodell MA. Mechanisms of hematopoietic stem cell aging. *Exper Gerontol.* 2010; 45: 286-90.
15. Terada N, Hamazaki T, Oka M, Mastalerz DM, Nakano Y, Meyer EM, et al. bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature.* 2002; 416: 542-5.
16. Werbowetski-Ogilvie TE, Schnerch A, Rampalli S, Mills CE, Lee JB, Hong SH, et al. evidence for the transmission of neoplastic properties from transformed to normal human stem cells. *Oncogene.* 2011; 30(46):4632-44.
17. Basky SH. the bone marrow stem cell origin of Human breast cancer using transgenic mouse models. *Standard Form 298 (Rev. 8-98) ANSI Std. Z39.18.* 2008.
18. Liu C, Chen Z, Chen Z, Zhang T, Lu Y. multiple tumor types may originate from bone marrow-derived cells. *Neoplasia.* 2006; 8: 716-24.
19. Yilmaz Y, Lazova R, Qumsiyeh M, Cooper D, Pawelek J. Donor Y chromosome in renal carcinoma cells of a female BMT recipient: visualization of putative BMT-tumor hybrids by FISH. *Bone Marrow Transplant.* 2005; 35: 183- 6.
20. Miura M, Miura Y, Padilia-Nash HD, Molinolo AA, Fu B, Patl V, et al. accumulated chromosomal instability in murine bone marrow mesenchymal stem cells leads to malignant transformation. *Stem Cells.* 2006; 24: 1095-1103.
21. Zheng J-F, Liang L-J. Transplanted bone marrow stromal cells are not cellular origin of hepatocellular carcinomas in a mouse model of carcinogenesis. *World J Gastroenterol.* 2008; 14: 3015-20.
22. Zhau HE, He H, Wang CY, Zayafon M, Morrissey C, Vessella RL, et al. human prostate cancer harbors the stem cell properties of bone marrow mesenchymal stem cells. *Clin Cancer Res.* 2011; 17: 2159- 69.
23. Wiedswang G, Borgen E, Karesen R, Avist H, Jqnbu J, Kvalheim G, et al. Isolated tumor cells in bone marrow three years after diagnosis in disease-free breast cancer patients predict unfavorable clinical outcome. *Clin Cancer Res.* 2004; 10:5342-8.
24. Flores RJ, Li Y, Yu A, Shen J, Rao PH, Lau SS, et al. a systems biology approach reveals common metastatic pathways in osteosarcoma. *BMC Sys Biol.* 2012; 6:50.
25. Andersen TL, Boissy P, Sondergaard TE, Kupisiewicz K, Plesner T, Rasmussen T, et al. Osteoclast nuclei of myeloma patients show chromosome translocations specific for the myeloma cell clone: a new type of cancer-host partnership? *J Pathol.* 2007; 211:10-17.
26. Tjensvoll K, Oltedal S, Kvaloy JT, Gilje B, Reubenn JM, Smaaland R, et al. persistent tumor cells in bone marrow of non-metastatic breast cancer patient after primary surgery are associated with inferior outcome. *BMC Cancer.* 2012; 12: 190.

27. Dawson MR, Chae SS, Jain RK, Duda DG. direct evidence for lineage-dependent effects of bone marrow stromal cells on tumor progression. *Am J Cancer Res.* 2011; 1: 144-54.

28. Hjelmstrom P. Lymphoid neogenesis: de novo formation of lymphoid tissue in chronic inflammation through expression of homing chemokines. *J Leukocyte Biol.* 2001; 69: 331-9.

29. Pfaff N, Lachmann N, Kohlscheen S, Sgodda M, Araúzo-Bravo MJ, Greber B, et al. Efficient Hematopoietic Redifferentiation of Induced Pluripotent Stem Cells Derived from Primitive Murine Bone Marrow Cells. *Stem Cells Dev.* 2012; 21:689-701.

30. Sovalat H, Scrofani M, Eidenschenk A, Pasquet S, Rimelen V, Henon P. identification and isolation from either adult human bone marrow or G-CSF-mobilized peripheral blood of CD34(+)/CD133(+)/CXCR4(+)/Lin(-) CD45 (-) cells, featuring morphological, molecular, and phenotypic characteristics of very small embryonic-like (VSEL) stem cells. *Exp Hematol.* 2011; 39: 495- 505.

31. Wang R, Chadalavada K, Wilshire J, Kowalik U, Hovinga KE, Geber A, et al. Glioblastoma stem-like cells give rise to tumour endothelium. *Nature.* 2010; 468: 829-33.

32. Stella GM, Senetta R, Cassenti A, Ronco M, Cassoni P. cancers of unknown primary origin : current perspective and future therapeutic strategies. *J Translational Med.* 2012; 10: 12.

33. Tian C, Wang Y, Sun L, Ma K, Zheng JC. Reprogrammed mouse astrocytes retain a "memory" of tissue origin and possess more tendencies for neuronal differentiation than reprogrammed mouse embryonic fibroblasts. *Protein Cell.* 2011; 2:128-140.

34. Zhu XQ, Pan XH, Wang W, Chen Q, Pang RQ, Cai XM, et al. transient in vitro epigenetic reprogramming of skin fibroblasts into multipotent cells. *Biomaterials.* 2010; 31: 2779- 87.

35. Cui F, Wang J, Chen D, Chen YJ. CD133 is a temporary marker of cancer stem cells in small cell lung cancer, but not in non-small cell lung cancer. *Oncol Rep.* 2011; 25: 701- 8.

36. Nishino K, Toyoda M, Yamazaki-Inoue M, Fukawatase Y, Chikazawa E, Sakaguchi H, et al. DNA methylation dynamics in human induced pluripotent stem cells over time. *Plos Genet.* 2011; 7: e1002085.

37. Pierce GB, Pantazis CG, Caldwell JE, Wells RS. Specificity of the control of tumour formation by the blastocyst. *Cancer Res.* 1982; 42: 1082-7.