Journal of
Stem Cell Research & Therapy

Hawley, J Stem Cell Res Ther 2012, 2:5
DOI: 10.4172/2157-7633.1000e110

Editorial Open Access

The Cancer Stem Cell Conundrum in Multiple Myeloma

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The cancer stem cell (CSC) hypothesis in its original form postulates that a small subpopulation of cancer cells is responsible for propagation of the tumor [1]. By comparison to normal stem cells, CSCs are predicted to be drug-resistant due to increased expression of proteins such as anti-alkylating enzymes like aldehyde dehydrogenase (ALDH) that neutralize the therapeutic agents [2] or members of the ATP-binding cassette (ABC) family of transporters that efflux them out of the cells [3].

Multiple myeloma (MM) is an incurable malignancy of B-lymphoid cells characterized by the accumulation of differentiated plasma cells in the bone marrow. MM is responsible for over 30,000 deaths each year in the United States and the European Union. While patients initially respond to therapy, they eventually relapse because the MM cells acquire drug resistance [4].

Demonstration of a low percentage of clonogenic cells in the bulk tumor mass prompted a search for the CSC in MM [5]. But contradictory results have been obtained regarding the phenotype of the proposed tumor-propagating cells; moreover, the relationship between drug-resistant MM cells at relapse and putative MM CSCs remains a matter of much debate [6-18]. A subpopulation of clonogenic MM cells has been described having a memory B cell-like phenotype ($CD19^+CD20^+CD27^+$) [6]. Although $CD19^+CD20^+CD27^+$ MM cells lacked the characteristic plasma cell antigen CD138, they were capable of differentiating into $CD138^+$ plasma cells [7]. These studies suggested that MM is organized in a hierarchical manner and that $CD19^+CD20^+CD27^+$ MM cells might represent a putative MM CSC [19] . However, other work indicates that such cells might represent a premalignant intermediate [20]. Their biological significance has also been questioned based on their rarity. For example, one study investigating the clonal hierarchy in light chain MM was unable to confirm the presence of tumor-specific immunoglobulin sequences in the memory B cell compartment [10]. A number of other recent reports have also failed to obtain evidence in support of this supposition [13,14,16]. These latter results are consistent with the prevailing assumption that neoplastic transformation in MM occurs at a post-memory B cell stage when somatic hypermutation of immunoglobulin genes has ceased [21,22].

Various strategies have been employed to prospectively isolate and study CSC-like tumor-propagating cells. One common approach is based on the expression of cell surface markers that are characteristic of the stem cell phenotype of the corresponding normal tissue. An example of this approach involves expression of the CD34 cell surface marker of immature hematopoietic cells (see [23] for review). It is of interest in this regard that a subpopulation of $CD138^+$ MM cells has been reported to express CD34 [8].

Another approach capitalizes on the functional properties of stem cells. As noted above, stem cells are highly resistant to damage by toxic agents through a combination of mechanisms [2,3,24,25]. Some of these attributes can be exploited by flow cytometry-based procedures to enrich for stem-like cells [23,26]. Efflux of the vital dye Hoechst 33342 by the ABCG2 and/or ABCB1 transporters identifies a subset of cells in a variety of normal and malignant tissues—termed "side population" (SP) cells—which displays stem cell-like properties [27,28]. Interestingly, variable results have also been obtained concerning the SP phenotype in human MM cell lines and patient samples. Using this assay, one group identified a clonogenic $CD138^{neg}$ MM subpopulation that was resistant to the anti-MM agent lenalidomide [7] whereas another group subsequently described the characterization of clonogenic SP cells in MM that primarily expressed CD138 and were sensitive to lenalidomide [9]. Likewise, ALDH has been shown to be a marker of CSC-like cells in a wide range of tumors, including the B-lymphoid malignancies Hodgkin lymphoma and mantle cell lymphoma [29,30]. Although it has been reported that certain MM cell cultures as well as patient samples contained subpopulations of $ALDH^+$ cells with a CSC-like phenotype [7,18], the generality of this finding has been questioned [17].

How can these discrepant observations be reconciled? On the one hand, it is important to appreciate that MM is characterized by significant molecular heterogeneity, comprising at least seven disease subtypes [31]. A potential scenario that could also help to integrate the incongruent observations would be if malignant transformation of $CD138^+$ post-memory B cells results in the acquisition of a CSC-like phenotype [32], e.g., by a "dedifferentiation" mechanism that is akin to the cellular reprogramming that occurs during the generation of induced pluripotent stem cells [22,33,34]. Indeed, activation of the *MYC* proto-oncogene, one of four transcription factors used in the initial reprogramming experiments [35], is a recurring event in MM pathogenesis [36].

Thus, the putative MM CSC would not be expected to be a single genetic entity; rather, genetically-distinct subtype-associated CSCs are predicted. Furthermore, it would not be surprising if MM CSCs exhibit phenotypic variability during tumor progression as a result of epigenetic changes and genomic instability [37]. Considered in this light, it will be a challenging task but well worth the effort to delineate all of the MM CSC subpopulations. The clinical implications are profound in that subtype-specific concerted therapies targeting the bulk as well as the various CSC fractions of the tumor will undoubtedly be necessary if an effective cure is to be found for this devastating collection of diseases.

Acknowledgement

This work was supported by a Grant from the Dr. Cyrus and Myrtle Katzen Cancer Research Center at The George Washington University.

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Received October 19, 2012; **Accepted** October 20, 2012; **Published** October 22, 2012

Citation: Hawley RG (2012) The Cancer Stem Cell Conundrum in Multiple Myeloma. J Stem Cell Res Ther 2:e110. doi:10.4172/2157-7633.1000e110

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