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 MM patients initially respond to therapy, they eventually relapse because the MM cells acquire drug resistance.

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, 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 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.

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References