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Clonogenic multiple myeloma cells have shared stemness signature associated with patient survival

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Many cancers are hierarchically organized and sustained by a subpopulation of clonogenic cells that have self renewal capacity. Tumor re-growth following initial reductions in disease burden suggests that tumor cells capable of clonogenic growth are relatively drug resistant, and in several human cancers these functional properties have been attributed to cancer stem cells (CSC) that are derived from mutated adult stem cells. Multiple myeloma (MM) is a neoplastic clonal expansion of phenotypically heterogeneous population of plasma cells in the bone marrow that secrete abnormal amounts of monoclonal antibodies. Terminally differentiated CD138+ plasma cells constitute the majority of the tumor cells in MM but are unable to sustain the clonogenic growth indefinitely. Chemoresistant self-renewing population of CD138- cells, isolated from myeloma patient samples and cell lines have been reported earlier. Human MM cell lines RPMI8226 and NCI H929 contained 2-5% of CD138- population. In this study, we showed that CD138- cells have increased drug efflux and ALDH1 activities, hallmark of normal and neoplastic stem cells. ALDH+CD138- cells were more clonogenic than ALDH-CD138+ cells and only CD138- cells differentiated into CD138+ cells. *In vivo* tumor initiation and clonogenic potentials of the CD138- population were confirmed using NOG mice. Gene expression profiling showed that compared to CD138+ cells, CD138– cells have an expression signature enriched with genes expressed in normal and malignant stem cells such as common progenitor cells (PC), hematopoietic stem cells (HSC) and leukemic stem cell (LSC). Differentially expressed genes included components of the polycomb repressor complex 2 (PRC2) and their targets. The EZH2 inhibitor DZNep (3- Deazaneplanocin) treatment showed differential activity on CD138- and CD138+ populations, suggesting that CD138- cells were more dependent on PCR2 proteins on survival and self renewal. This 'stemness signature' derived from the CD138- population was associated with poorer survival in different clinical datasets.

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