EDITORIAL

Cancer Stem Cells: A Paradigm Shift in Understanding Tumorigenesis and Implications in Cancer Care

Rahul Sharma

The genesis of tumours has long been considered a clonal evolution process. As per this clonal evolution model, tumours arise from a precursor cell with a competitive growth advantage, most likely due to the accumulation of mutations that permit dysregulated cell division and escape from the apoptosis. This model predicts that all cells within a given tumour are phenotypically homogenous (1). But in clinical practice we come across tumours that are predominantly heterogenous. The conventional anticancer agents that target all multiplying cells without trying to select the aberrant from the normal ones, initially appear to shrink tumours effectively. But the fact remains that tumours often return with vengeance, develop resistance to initially effective appearing drugs and metastasize. Tumour relapse and metastases remain major hindrances for improving overall cancer survival, which may be due to the existence of cancer stem cells (2).Cancer stem cells occupy the top position in the hierarchical model of tumour genesis. Cancer stem cells are analogous to normal stem cells and are postulated to possess the capacity of unlimited self renewal through symmetrical cell division, the ability to reproduce progeny cells through asymmetric division, and also an innate resistance to conventional chemotherapy drugs. A cancer stem cell is responsible for giving rise to an apparently immortal progeny that do not undergo terminal differentiation and undergo uncontrolled proliferation. Many of the aforesaid characteristics attributed to cancer stem cells are acquired by using many of the same signalling pathways that are found in normal stem cells such as Wnt, Notch, and Hedgehog. Therapeutic targeting of these cancer stem cells may provide a strategy to suppress tumour recurrence (3). Cancer stem cells were initially identified in human leukemias in landmark studies of John Dick and his colleagues. Subsequently similar cancer stem cells have been identified in solid tumours of the breast, colon, brain, prostate, malignant melanoma etc. Cancer stem cells exist in the proportion of 1:100 to 1:10000 in tumours and can be identified as separate from other tumor cells by using certain markers. John Dick and colleagues detected CD34+CD38- leukemia stem cells in AML 0.2-100 such cells in 1 million peripheral blood cells. Similarly Clarke and colleagues identified CD44+CD24- breast cancer stem cells and found that 100 such cells can give rise to a full blown tumour in NOD/SCID mice (4). Subsequently several studies have confirmed the intratumoral heterogeneity in breast cancers (5). The cancer stem cells remain quiescent and display chemoresistance as well as radioresistance because of their low mitotic rate and ability to prevent damage from intracellular toxins. It has recently been postulated that cancer stem cell phenotype represents a biologically aggressive clone that has the capacity to remain alive under adverse environment through constant evolution and efficient integration of processes that confer malignant phenotype on a normal cell. These cells are notorious for acquiring mutations that permit symmetric and asymmetric cell divisions, convert the host immune attack to its own advantage and are flexible enough to adjust to newer sites of metastases by changing adhesion molecular profile (6). Whatever be the origin or attributes of cancer stem cells, clinically drug resistance is the most relevant feature which has a direct bearing on survival outcome of the patients. The future of cancer management lies in taming these very cancer stem cells.

References

1. Wang JCY, Dick JE. Cancer stem cells: lessons from leukemia.*Trends Cell Biology* 2005;15:494-501
2. Curtin JC, Lorenzi MV. Drug discovery approaches to target Wnt signalling in Cancer Stem Cells. *Oncotarget* 2010 ;1(7):563-77
3. Takebe N, Harris PJ, Warren RQ, Ivy SP. Targeting Cancer Stem Cells by inhibiting Wnt, Notch, and Hedgehog pathways. *Nature Rev Clin Oncol* 2011 ; 8(2):97-108
4. Clarke MF, Dick JE, Dirks PB, Eaves CJ. Cancer Stem Cells- Perspectives on current status and future directions: AACR Workshop on Cancer Stem Cells. *Cancer Research* 2006; 66:9339-44
5. Campbell LL, Polyak K. Breast tumor heterogeneity: cancer stem cells or clonal evolution? *Cell Cycle (Georgetown,Tex)* 2007; 6:2332-38
6. Badve S, Nakshatri H. Breast Cancer Stem cells- beyond semantics. *Lancet Oncol* 2012 ;13(1):e43-48

From the Department of Radiotherapy & Oncology, Govt Medical College Jammu, J&K- India
Correspondence to : Dr Rahul Sharma, Associate Prof.,Department of Radiation Oncology & Radiotherapy Govt Medical College Jammu, J&K- India