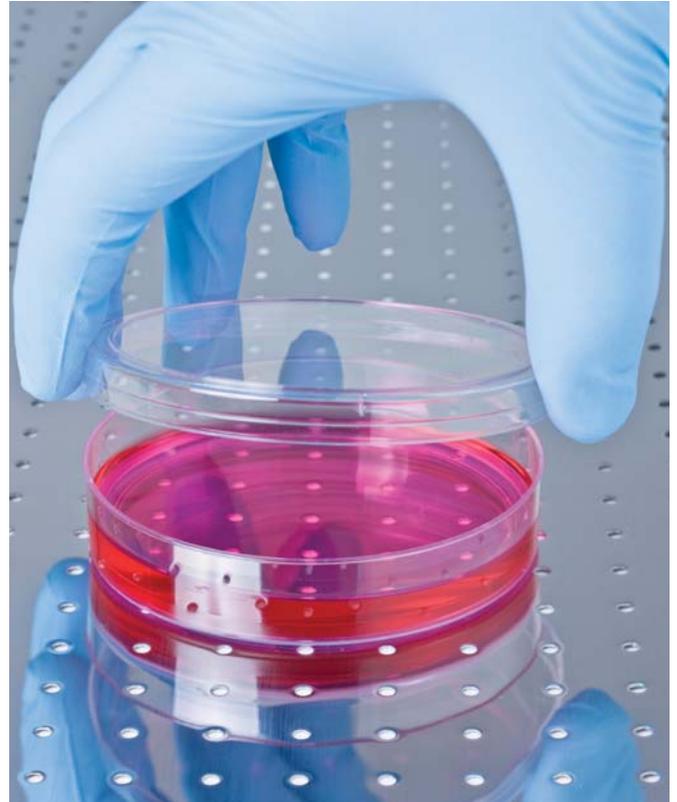


Upjohn Medal in Molecular Medicine 2009

Cancer stem cells – the key to carcinogenesis?

Sheryl Ramdass

Carcinogenesis is the process where normal cells are transformed into malignant cells. The classic genetic model describes the sequential accumulation of mutations in oncogenes and tumour suppressor genes as responsible for tumour development.¹ The cancer stem cell hypothesis adds another layer of complexity in the process of malignant transformation. It postulates that malignant tumours are initiated and maintained by a single abnormal population of adult stem cells, called cancer stem cells (CSCs). Studies supporting the CSC theory are based largely on xenotransplantation of a specific subpopulation of cells into immunodeficient mice. CSCs were first discovered in acute myeloid leukaemia cells and this study provided an impetus for similar experiments involving solid tumours. To date, the existence of CSCs has been shown in carcinomas of the brain, lung, prostate, testis, ovary, stomach, colon, skin, liver, and pancreas.²⁻⁶ Further



supporting evidence arises from observing the striking parallels that exist between normal stem cells and cancer cells, including the capacity for self-renewal, active telomerase expression, activation of anti-apoptotic pathways and the ability to migrate and metastasise.^{7,8} However, despite this persuasive evidence, the theory does not go unopposed as critics have highlighted a number of theoretical and methodological points that question the validity of the CSC hypothesis. For example, they argue that xenograft experiments do not adequately model the interaction between tumour cells and the tumour microenvironment that occurs in humans. Hence, although the CSC theory provides an attractive explanation of carcinogenesis, the current limitations that exist must be resolved before the hypothesis can be fully accepted. If proven, however, it will have profound implications for cancer prevention, diagnosis, and treatment.

References

1. Vermeulen L, Sprick MR, Kemper K, Stassi G, Medema JP. Cancer stem cells – old concepts, new insights. *Cell Death and Differentiation* 2008; 15 (6): 947-58.
2. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S *et al.* Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell* 2005; 121: 811-3.
3. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T *et al.* Identification of human brain tumour initiating cells. *Nature* 2004; 19: 396-401.
4. Al-Hajj M, Clarke MF. Self-renewal and solid tumour stem cells. *Oncogene* 2004; 23: 7274-82.
5. Woodward WA, Chen MS, Behbod F, Rosen JM. On mammary stem cells. *Cell Science* 2005; 118: 3585-94.
6. Moore KA, Lemischka IR. Stem cells and their niches. *Science* 2006; 311: 1880-5.
7. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature* 2001; 414: 105-11.
8. Wicha MS, Liu S, Dontu G. Cancer stem cells: an old idea – a paradigm shift. *Cancer Research* 2006; 66 (4): 1883-90.