[Proc Amer Assoc Cancer Res, Volume 47, 2006]

Tumor Biology 4: Stem Cells in Cancer 1
Abstract #314

Cancer Stem Cells (CSC) ablation as a treatment strategy for cancer

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Despite a better understanding of the biology of tumor cells the treatment of most cancers has not significantly changed for the past three decades. Accumulating evidence has implicated that cancer is a disease of stem cells. In this context, a small fraction of cancer cells adopt the properties of stem cells. In some cases, the cancer stem cells (CSC) could be the close derivative of normal tissue stem cells. In either situation the net result will be the same, in that CSC are the cells to be used as targets in the development of molecular and pharmaceutical therapeutics to treat and prevent human cancer. This could be a paradigm shift in the treatment of cancer, away from targeting the blast cells and towards the targeting of the CSC. Before using CSC as target in therapy programs (target identification, drug discovery, etc.), it is important to ascertain that their ablation implies elimination of cancer in vivo following cancer formation in a whole animal. For this purpose, we generated mice by specific BCR-ABLp210-IRES-tk targeting to the somatic stem cell compartment. This strategy specifically restricts both BCR-ABLp210 and tk (thymidine kinase gene) expression to the stem cells as confirmed by real-time PCR. These mice develop chronic myeloid leukemia which spontaneously evolve to blast crisis. The size of the stem cell compartment is not increased in these mice. Gleevec treatment of these mice where BCR-ABL expression is exclusively restricted to stem cells does not show survival benefit. We further show that Gleevec is not able to affect BCR-ABL-expressing CSC in vivo. Therefore, these mouse models reproduce for the first time both the biology of human chronic leukemia and the therapeutic response in humans. Thus we next test whether leukemia elimination can occur in vivo by specific targeting of CSC by ganciclovir treatment. Group of mice (n=60) carrying either chronic myeloid leukemia or blast crisis were subjected to ganciclovir treatment in which tk expression is restricted to the stem cells. Dosing started when the mice were leukemic by peripheral blood analysis. During this period, cancers disappeared completely and these mice carrying the cancers that disappeared following treatment were observed for an additional 3 months in which no tumor recurrence was observed. Similar results have been obtained for stem cell driven cancers by other oncogenes like BCL6, K-RAS, etc. using an identical approach. This work demonstrates for the first time that killing CSC is an effective therapeutic strategy for cancer treatment and its potential applications are broad. Supporting this view, gene expression studies showed that CSC differ from normal stem cells. A challenge to this approach will be to find a way to specifically target CSC without toxicity to normal cells.