Targeting a chronic problem: elimination of cancer stem cells in CML

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The eradication of tumours by targeting malignant stem cell populations, or cancer stem cells (CSCs), is a promising new strategy for cancer treatment. In a paper published in a recent issue of *The EMBO Journal*, pharmacogenetic evidence has been obtained that this is indeed feasible in a mouse model of human chronic myeloid leukaemia. These and further similar experiments will be essential to determine the validity and practical usefulness of the CSC hypothesis.

The cancer stem cell (CSC) hypothesis, the idea that tumours are sustained by a discrete cellular compartment with self-renewal and tumour-reinitiating capacity, has generated both excitement and controversy. The original observation by Dick and colleagues (Lapidot *et al.*, 1994; Bonnet and Dick, 1997) was that human acute myeloid leukaemias could be re-initiated in immunodeficient mice only by a rare CD34+CD38– cell population that would regenerate both the CSC compartment and the non-CSC bulk tumour in the recipient. This hierarchical organization of leukaemias formed the conceptual basis for the CSC hypothesis, and similar results have now been obtained in a number of tumour types, including brain, breast, prostate, skin and intestinal cancers (Cho and Clarke, 2008; Malanchi *et al.*, 2008).

A corollary of the hypothesis is that specific eradication of the CSCs would be both necessary and sufficient to extinguish a tumour, as the non-CSC tumour cells would be unable to continue proliferation in the long term. Studies that identified CSC and non-CSC tumour fractions have relied on tumour re-initiation following transplantation, rather than *in situ* elimination of the CSCs to establish a hierarchical structure within the tumour. The latter type of experiment is, however, necessary both to formally validate the CSC hypothesis, and to determine its therapeutic potential, as transplantation experiments face additional barriers including survival, homing and immune rejection not present in the intact tumour, and may therefore not accurately determine CSC activity in all cases.

The study by Pérez-Caro and colleagues in a recent issue of *The EMBO Journal* provides an important step forward (Pérez-Caro *et al.*, 2009): the authors generated a mouse model of chronic myeloid leukaemia (CML), a haematopoietic disease caused by the oncogenic BCR–ABL fusion protein. When BCR–ABL expression was driven from the Sca-1 promoter, which is specifically expressed in the haematopoietic stem cells (HSCs) within the haematopoietic system, mice developed CML-like disease, characterized by elevated neutrophil numbers and splenomegaly with progression to blast crisis, the acute phase of CML to which all human patients progress.

The HSC compartment is known to contain the BCR–ABL oncoprotein in human CML, and although BCR–ABL kinase inhibitors, such as imatinib/STI571, can target the bulk of the CML tumour cells, it fails to eradicate the BCR–ABL-expressing HSCs, which constitute the CML CSCs (Graham *et al.*, 2002; Jorgensen and Holyoake, 2007). By transplantation of the Lin–Sca-1+ tumour fraction from the Sca-1–BCR–ABL transgenic mice that had developed CML-like disease, the presence of CSCs within the HSC compartment was confirmed.

The prediction from these observations would be that elimination of the Sca-1+ cell population would be sufficient to eradicate CML in the transgenic model. This was addressed by modification of the transgene to include expression of the herpes simplex virus thymidine kinase (HSV-TK), an enzyme that renders cells sensitive to the prodrug gancyclovir (GCV). Mice expressing the Sca-1–TK–IRES–BCR–ABL transgene also developed CML-like disease. However, if treated with GCV 70% of the mice were able to recover. As the bulk of the CML tumour does not express Sca-1, this showed that the elimination of the CSC containing Sca-1+ compartment was sufficient to eradicate the disease in the majority of the cases.

These results are important, as they provide support for the concept that specific targeting of CSCs can lead to tumour regression. It should be noted that CSCs in CML are not necessarily a static population: evidence exists that in blast crisis CSCs with a committed myeloid progenitor phenotype similar to the granulocyte–macrophage progenitor (GMP) are generated and sustained by ectopic β -catenin stabilization, causing activation of the canonical Wnt pathway (Jamieson *et al.*, 2004; Minami *et al.*, 2008). As the Sca-1–BCR–ABL transgenic model does not express the oncogene in this cell population it therefore has to be considered whether restriction of the BCR–ABL expression pattern in the mouse model used generates a less complex, and more readily targeted, disease compared with that occurring when BCR–ABL is more generally expressed.

In addition, the CML induction by the Sca-1–BCR–ABL transgene was insensitive to STI571, consistent with observations from human tumours that BCR–ABL inhibitors were unable to efficiently target the leukemogenic HSC compartment, but only the bulk tumour. Although this reinforces the argument that the hierarchical structure of the tumours in the present transgenic model, despite the similar pathology, may not accurately reflect that of human CML, it also provides a potentially useful model system in which to determine how BCR–ABL-expressing HSCs may be sensitized to current or new drugs.

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