Leukaemia cells have a remembrance of things past

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Although people generally talk about "cancer", it is clear that the disease occurs in a bewildering variety of forms. Even single groups of cancers, such as those of the white blood cells, may show widely differing properties. How do the various cancers arise and what factors determine their progression? Clues to these two issues, at least for leukaemias, have now been provided by Boris Kovacic and colleagues at the University of Veterinary Medicine, Vienna (Vetmeduni Vienna). The results are published in the current issue of the journal *EMBO Molecular Medicine* and have extremely important consequences for the treatment of a particularly aggressive type of leukaemia.

It is well known that many types of cancer arise as a result of a mutation within a cell and prevailing wisdom has held that the stage of differentiation of this cell determines exactly what form of cancer develops. For example, it was believed that so-called chronic myeloid leukaemia or CML arises from bone marrow stem cells, while a different type of leukaemia, known as B-cell acute lymphoid leukaemia or B-ALL, results from B-cell precursors. This belief has been spectacularly refuted by the latest results from Boris Kovacic and colleagues in the Vetmeduni Vienna's institutes of Animal Breeding and Genetics and of Pharmacology and Toxicology.

The researchers have now shown that both CML and B-ALL arise from the most primordial kind of blood cell (long-term haematopoietic stem cells), although the pathways by which the diseases progress are different. The usual causes of CML and B-ALL are two highly related

versions of the same oncogene, BCR/ABL. If the primordial blood cells are transformed – or made potentially cancerous – by a particular version of BCR/ABL, for technical reasons termed BCR/ABLp210, the result is chronic myeloid leukaemia or CML. The long-term haematopoietic stem cells remain and act as the dreaded cancer stem cells, or CSCs, which ensure that the disease persists. Curing chronic myeloid leukaemia requires the complete elimination of the CSCs. However, if the long-term haematopoietic stem cells are transformed by a related version of BCR/ABL, BCR/ABLp185, the result is a highly aggressive form of leukaemia, B-ALL. The finding that B-ALL actually originates from the same stem cells as CML was both unexpected and highly provocative.

Kovacic and colleagues have shown further that B-ALL only develops if the transformed stem cell is exposed to a particular growth factor, interleukin-7. If interleukin-7 is present (it usually is), the transformed long-term haematopoietic stem cells undergo a differentiation step to CSCs, which in this case correspond to pro-B cells. If interleukin-7 is absent during the initial phase of transformation, B-ALL cannot develop.

In other words, two distinct types of cell are involved in leukaemia development, the primordial cells (also termed the cells of origin of cancer) and the cancer stem cells that cause the disease to progress. Unless the CSCs are eliminated, fresh cancer cells can arise at any time and the leukaemia will recur. The problem is that current leukaemia therapies are not designed to target CSCs. The primordial CSCs in CML are highly quiescent and thus difficult to target. In contrast, the CSCs in B-ALL are abundant and have a high turnover rate, which makes them susceptible to treatment. Treatment of B-ALL may thus succeed in eliminating most CSCs but if even a single cell remains intact it is likely that the patient will relapse, possibly with an even more aggressive form of leukaemia. "A therapy that targets the bulk of tumour cells will not work," as Kovacic succinctly summarizes his results. "To treat B-ALL

successfully it will be necessary for us to learn much more about the development of the disease. A combined therapy is required, so future work should aim at developing drugs that target the long-term haematopoietic stem cells from which B-ALL is derived."

More information: The paper "Diverging fates of cells of origin in acute and chronic leukemia" by Boris Kovacic, Andrea Hoelbl, Gabriele Litos, Memetcan Alacakaptan, Christian Schuster, Katrin M. Fischhuber, Marc A. Kerenyi, Gabriele Stengl, Richard Moriggl, Veronika Sexl and the late Hartmut Beug is published in the current issue of the journal *EMBO Molecular Medicine* (2012, Vol. 4 pp. 283-297). onlinelibrary.wiley.com/doi/10 … /emmm.201100208/full

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