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Leukaemia suppressing normal bone marrow – how long does it last?

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Patients with newly diagnosed leukaemia often present with signs and symptoms of bone marrow failure rather than with symptoms caused by proliferation of the leukaemia itself: e.g. paleness, tiredness and lack of energy due to anaemia; prolonged or severe infections due to neutropenia; and petechial rash and nose bleeds due to thrombocytopenia. Bone marrow failure is a relatively late event during leukaemia development. It is thought to be either a direct, cyto-/chemokine-mediated effect of the leukemic cells or an indirect effect via re-modelling of the bone marrow environment. Either or both lead to suppression of normal bone marrow function. Many studies have investigated the interaction of normal hematopoietic stem and leukaemia cells with their bone marrow niche. It has been shown that different types of leukaemia affect differentiation and function of various cells in the bone marrow, including bone progenitor cells, endothelial cells, nerve fibres and myofibroblasts (1), leading to a loss of support of normal hematopoiesis.

In this issue of *Haematologica*, Jensen et al. investigated the effect of B-lineage ALL on residual normal hematopoiesis (2). They use a spontaneous murine leukaemia model with heterozygote deletions of *Pax5* and *Ebf1* and study the effect of the leukaemia on normal hematopoiesis by transplanting leukaemic blasts onto wild-type mice. Interestingly and different to what one might expect as a consequence of modulation of the bone marrow niche, the most immature Lin⁻Kit⁺SCA1⁺ (LSK) and CD150⁺LSK stem-like compartment persists while more mature, lineage-restricted progenitors disappear from the leukaemic marrow. A similar observation was made in 19 human patients with B-lineage ALL in which the frequency of non-leukemic CD19⁻CD34⁺CD38⁻ putative stem-like cells was comparable to normal controls. Most intriguingly, the authors describe a lasting effect of the leukaemia on the reconstitution potential of these murine stem cells after primary and secondary transplantation. Secondary mice transplanted with “leukaemia exposed” hematopoietic stem cells showed lower levels of reconstitution. The “leukaemia-exposed”CD150⁺LSK cells displayed an expression profile suggestive of mitochondrial dysfunction with fluorescent dye tracking confirming a reduced mitochondrial membrane potential in this residual stem cell population. Impaired mitochondrial function is a hallmark of cellular aging (3) and these data are, therefore, suggestive of pre-mature ageing of “leukaemia-exposed” hematopoietic stem cells.

There are two key questions that arise from this work:

1) **What is the mechanism how the leukaemia impose such a long-lasting effect on the repopulation potential of normal stem cells leading to mitochondrial dysfunction and premature ageing of the hematopoietic compartment?**

Mitochondrial dysfunction is a common feature of many types of cancer, including leukaemia. To meet their high energetic demands, leukaemia cells rely on mitochondrial oxidative metabolism.
Pharmacologic inhibition of oxidative metabolism has been demonstrated to inhibit leukaemia cell growth and to increase sensitivity to chemotherapy, both \textit{in vitro} and \textit{in vivo} (4, 5). Intriguingly, the damaging effects of chemotherapy can, at least in part, be rescued by transfer of mitochondria between leukaemia cells and their surrounding bone marrow stroma (6, 7). Similarly, bone marrow stromal cells were found to transfer mitochondria to healthy haematopoietic stem cells as a means to promote their capacity to respond to proliferative stress (8). Although direct exchange of mitochondria between leukaemia cells and healthy haematopoietic stem/progenitor cells has not been demonstrated, it is interesting to think about whether/how mitochondrial transfer could account for the findings by Jensen et al. Alternatively, one could envisage a tripartite exchange in which BM niche cells are the intermediate party, transferring mitochondria from leukaemia cells towards the resident normal haematopoietic stem cells (and potentially, vice versa). Although a role of mitochondrial exchange remains speculative, if confirmed, could provide the route to develop new therapeutic interventions to protect the healthy haematopoietic stem cell compartment from leukaemia-mediated suppression.

2) Does this long-lasting effect of the leukaemia on normal haematopoietic stem cells also occur in human patients? Or is the described effect on stem cells unique to this mouse model?

Clonal haematopoiesis has been studied in long-term survivors of paediatric cancer (9). There is a significant increase in clonal haematopoiesis in childhood cancer survivors, however, this is mainly thought to be therapy-related rather than there being evidence for a leukaemia-mediated accelerated ageing of normal haematopoietic stem cells. Late bone marrow failure is usually not regarded as a typical late effect after acute lymphoblastic leukaemia (10). However, data on clonal haematopoiesis in survivors of childhood acute lymphoblastic leukaemia, particularly in very long-term survivors, are scarce. This interesting observation suggests that ageing of the haematopoietic system in our patients warrants further attention and future prospective studies looking at the bone marrow function in long-term survivors.
References


Figure legend

Figure 1. Leukaemia-induced mitochondrial dysfunction in haematopoietic stem and progenitor cells (HSPCs) limits their ability for long term reconstitution, recapitulating ageing. B ALL-exposed HSPCs produce reduced numbers of lineage-restricted progenitor cells, and exhibit mitochondrial dysfunction. Some of these effects may be indirectly mediated, by cross-talk of B ALL blasts, bone marrow MSCs and the healthy HSPC compartment. Abbreviations: B ALL: B cell acute lymphoblastic leukemia; HSPCs: Hematopoietic stem and progenitor cells; MSCs: Mesenchymal stromal cells. Created with BioRender.com.