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The role of bone marrow morphogenic signals in sustaining chronic myeloid leukemia

Chronic myeloid leukemia (CML) results from a genetic change in a haemopoietic stem cell (HSC), leading to a hierarchical clonal stem cell disease, with the expanding leukemic stem cell (LSC) population sustaining the malignancy within the bone marrow (BM) niche. The cells express the constitutively active tyrosine kinase BCR-ABL, which causes rapid cell division and leukemia. Therapy involves tyrosine kinase inhibitor (TKI), which effectively inhibits BCR-ABL, thereby controlling CML. However, TKI doesn't eliminate the LSC population; therefore, patients are not cured and require life-long therapy. This phenomenon of disease persistence under therapy, suggests BCR-ABL-independent mechanisms are being exploited to sustain the survival of LSC. Increasing evidence suggests that the BM microenvironment plays a pivotal role in the initiation and progression of the leukemia. Of particular interest are the morphogens, growth factors implicated in embryogenesis, developmental hemopoiesis and homeostasis. Microarray analysis, comparing chronic phase (CP), accelerated phase (AP) and blast crisis phase (BP) CML LSCs and progenitor populations to normal HSCs and progenitors, indicated that the Notch, Wnt, TGFbeta superfamily and Hedgehog (Hh) pathway are highly deregulated in CML. To investigate this further, we profiled mesenchymal stem cells (MSCs) from normal donors and CML, CP (n=12), myeloid BP (n=11), and lymphoid BP (n=5) stem and progenitor populations, for gene components of Wnt, Notch, Hedgehog, and BMP pathways. Data indicates that self-renewal pathways were highly deregulated between CP and BP with statistically significant upregulation in Wnt components in myeloid BP compared to CP. Targeting the pathways using small molecule inhibitors indicate that the BMP, Hh and notch pathways are viable therapeutic targets in combination with TKI and that Wnt upregulation is preventing Notch activation in myeloid BP-CML. These findings highlight the complexity of self-renewal pathway interaction especially in progressive disease.

Biography

Helen Wheadon has completed her PhD in 1997 at University College London. Her career then consisted of Postdoctoral studies at the University of Bath, an MRC Fellowship, followed by a tenured position at the University of Ulster. She is currently a Senior Lecturer at the University of Glasgow with expertise in stem cell signal transduction specializing in leukemia research. She is also an Associate Dean of Post-graduate Research within the College of Medical, Veterinary and Life Sciences at the University of Glasgow. She has published more than 25 papers in reputed journals and regularly reviews papers, grants and serves on Editorial Boards. She is active in promoting public understanding of stem cells and bioethics surrounding the use of stem cells and animal models in science.

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