CDB SEMINAR

Andreas Trumpp

Division of Stem Cells and Cancer
Deutsches Krebsforschungszentrum (DKFZ)

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15:00 - 16:00 A7F Seminar Room

Dormancy in normal and malignant stem cells

Summary

Adult stem are required to maintain highly regenerative tissues such as the skin, the intestinal epithelium and the hematopoietic system. Mouse hematopoietic stem cells (HSCs) are the most well characterized somatic stem cell to date, and serve as a model for understanding other adult stem cells present in the mammalian body. Using two types of label-retaining assays we have identified a long-term dormant population within the most immature HSCs (Lin-Sca1+cKit+CD150+CD48-CD34-). Computational modeling suggests that dormant HSCs (d-HSCs) divide about every145 days, or 5 times per lifetime. d-HSCs harbor the vast majority of multi-lineage long-term self-renewal activity. While they form a silent reservoir of the most potent HSCs during homeostasis, they are efficiently activated to self-renew in response to bone marrow injury or G-CSF stimulation. After re-establishment of homeostasis activated HSCs return to dormancy, suggesting that HSCs are not stochastically entering the cell cycle, but reversibly switch from dormancy to self-renewal under conditions of hematopoietic stress[1,2]. One of the reasons cancer stem cells are thought to escape anti-proliferative chemotherapy is their relative dormancy[3]. We now have shown that treatment of mice with Interferon-alpha family leads to the activation and proliferation of dormant HSCs in vivo, which sensitizes them to chemotherapy drugs. HSCs lacking either the interferon-a/b receptor, STAT1 or Sca-1 are insensitive to IFNa stimulation, demonstrating that STAT1 and Sca-1 mediate IFNa induced HSC proliferation[4]. The implications of these results for the design of strategies to target dormant CML stem cells not targetable by Gleevec/Imatinib alone will be discussed.

[1]Wilson A. et al, (2008). Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. CELL, 135: 1118-1129.
[2]Laurenti E. et al., (2008). Hematopoietic stem cell function and survival depend on c-Myc and N-Myc activity. CELL Stem Cell, Dec. 4;3(6):611-24.
[3]Trumpp A. and Wiestler O.D., (2008). Targeting the evil Twin. NATURE Clinical Practice Oncology, Jun;5(6):337-47.
[4]Essers M. et al. (2009). IFNa activates dormant HSCs *in vivo*. Nature. 2009 Apr 16;458(7240):904-8

Host:
Shinichi Nishikawa
Stem Cell Biology, CDB
nishikawa@cdb.riken.jp
Tel:078-306-1893
(ext : 5301)