

Role of CD48 in Hematopoietic Stem Cell Self-Renewal

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We are interested in the molecular mechanisms controlling hematopoietic stem cell (HSC) self-renewal. We have thus examined the gene expression profile of HSC during a time-course of 5-fluorouracil (5FU) treatment, which stimulates self-renewal. One gene that is tightly regulated during HSC cycling is CD48, a GPI-linked antigen shown to be essential for activation of T cells. CD48 RNA is expressed at a low level in quiescent HSC; then at the peak of HSC cycling, 6 days after 5FU treatment, it is highly up-regulated. CD48 protein showed a similar sharp upregulation. In fetal liver, a source of cycling stem cells, CD48 was also expressed at both the RNA and protein levels. CD48 is also highly expressed in short-term, but not long-term, HSC, according to other studies (Akashi, et al, 2003). Because CD48 is most highly expressed at day 6, when the largest proportion of HSC are in cycle, we examined whether it correlated directly with the cycle status of HSC. When the CD48 bright versus negative/low fraction was sorted from day-6-5FU-HSC, the CD48-bright fraction contained the vast majority of the cells in S-G2M. Also, in untreated bone marrow, the CD48 bright cells lie predominantly at the top of the SP fraction, where the short-term progenitors are found. The CD48+ cells also up-regulate Flk2, another marker of short-term HSC. Together, these data strongly indicate that CD48 is associated with activated or cycling HSC. This is consistent with its presence on activated T cells and the inability to activate T cells from CD48 knockout mice. Finally, we have recently competitively transplanted CD48+ versus CD48- cells from 5FU-treated bone marrow. The CD48+ cells showed lower long-term HSC activity relative to the CD48 negative cells, suggesting that many of these cells are marked for commitment to differentiation, as short-term progenitors. The fact that some of the CD48+ cells retain long-term activity indicates that some of the activated HSC (marked by CD48) return to quiescence. We are further examining the function of CD48, using knockout mice, to understand the role of CD48 in HSC self-renewal.