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The effect of Interferon α or Lipopolysaccharide treatment on hematopoietic stem and progenitor cells

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Hematopoietic stem cells (HSCs) are multipotent and have a life long self-renewal capacity. They reside in the bone marrow in so-called niches and remain quiescent for most of the time. However, upon bone marrow injury or stress dormant HSCs are induced to proliferate and re-establish the homeostasis of the hematopoietic system. Infection is a common, natural form of stress for the hematopoietic system. It is well known that mature immune cells are essential to fight against invading pathogens. Until recently, it was thought that HSCs were not directly responding to the infectious state. However, previous studies have shown that interferon α (IFNα) and interferon γ (IFNγ), two pro-inflammatory cytokines released during infection, lead to a direct activation of quiescent HSCs. Thereby, IFNα induces proliferation of HSCs through signaling via the IFNAReceptor, STAT1, and stem cell antigen-1(Sca-1).

This study addresses the question whether IFNα treatment has similar effects on cultured hematopoietic stem and progenitor cells (HSCPs). Interestingly, *in vitro* treatment with IFNα does not induce proliferation of HSPCs, but leads to a decrease in proliferation of HSPCs, even though Sca-1 expression is still increased. A plausible explanation for this difference between *in vitro* and *in vivo* treatment with IFNα might be a role for the bone marrow (BM) stem cell niche in the IFNα induced activation of HSCs.

In a search for other stress signals with similar effects, the endotoxin lipopolysaccharide (LPS) has been uncovered to activate even the most dormant HSCs *in vivo*. Similar to IFNα, LPS induced proliferation of HSCs is dependent on Sca-1. Furthermore, the response of HSCs to LPS is mediated by signaling via Toll like receptor 4 (TLR4), the main receptor for LPS. In contrast to *in vivo*, *in vitro* LPS treatment inhibits the proliferation of HSPCs further supporting a role for the BM stem cells niche in the activation of HSPCs. Of note, *in vitro* LPS treatment only affects HSPCs in the presence of other bone marrow cells indicating an indirect effect of LPS. *In vivo* LPS treatment of

wild-type- TLR4$^{-/-}$ mixed bone marrow chimeras confirmed this indirect effect. With the aid of multiple co-culture experiments, this study shows that the presence of monocytes and macrophages (CD11b^{+} CD115^{+} cells) in the culture restores the LPS induced effect on HSPCs. Interestingly, the collected data do not indicate a direct effect of LPS via the TLR4 receptor complex on HSCs, as has been suggested by previous studies.

This report clearly links the release of LPS during infection to activation of the quiescent HSC pool via CD11b^{+}CD115^{+} macrophages and monocytes present in the bone marrow. Thus, these cells are not only involved in the immune response but also in the reconstitution of a balanced hematopoietic system. Further experiments are needed to clarify the role of possible cytokines like IL-6, IL-1, TNFα, IFNα or IFNγ for the LPS induced activation of HSCs.

In summary, *in vivo* treatment with IFNα and LPS, two different ways of inducing stress to the hematopoietic system, lead to Sca-1 dependent activation of quiescent HSCs. However, the mechanism of activation by *in vivo* IFNα or LPS treatment is different. While IFNα directly acts on HSCs via the IFNAR, the effect of LPS on HSPCs is indirect via TLR4 dependent signaling on CD11b^{+}CD115^{+} cells. These monocytes and macrophages might in turn produce and secrete a still unknown factor leading to activation of HSCs. Thus, IFNα and LPS are two different stressors that activate HSCs by different but overlapping mechanisms.