PHAGOCYTOSIS

# Don't eat the HSCs

In two papers published recently in *Cell*, Irving Weissman and colleagues identify an important role for CD47 in protecting circulating haematopoietic stem cells (HSCs) and their progenitors (HSPCs) from phagocytosis. They also show that targeting CD47, which is constitutively upregulated on self-renewing leukaemia stem cells (LSCs), with monoclonal antibodies enables phagocytosis of human LSCs and provides a rationale for the use of CD47-specific antibodies as a therapy for acute myeloid leukaemia (AML).

The absence of CD47 expression on cells results in their phagocytosis and therefore CD47 acts as a 'don't eat me' signal through the interaction with its receptor, signal-regulatory protein-α (SIRPα), which is expressed by phagocytes. But does differential expression of CD47 have a role in HSC fate? The authors showed that the expression of CD47 is transiently upregulated on HSCs by strong mobilizing or inflammatory stimuli. HSCs from *Cd47*$^{-/-}$ mice failed to engraft in wild-type mice owing to phagocytosis of the cells by macrophages. In addition, more *Cd47*$^{+/-}$ than wild-type HSPCs were cleared by macrophages when chimeric mice with both types of cell were given a strong inflammatory stimulus.


Previous data have shown that CD47 expression is upregulated in bulk leukaemia cells in several mouse models. The authors showed that upregulation of CD47 expression occurred even in the stem and progenitor cells of these mouse leukaemias and also showed an upregulation of CD47 expression by HSCs and HSPCs from patients with AML and chronic myeloid leukaemia in blast crisis. Overexpression of CD47 in a human myeloid leukaemia cell line that normally expresses low levels of CD47 increased the tumorigenicity of these cells in a dose-dependent manner by increasing their ability to evade macrophage phagocytosis.

Further analyses, published in a second paper, confirmed that the expression of CD47 is higher on human AML LSCs than on normal bone marrow HSCs and multipotent progenitors and showed that increased CD47 expression in patients with AML is associated with poor clinical outcomes. Indeed, HSCs could be separated from leukaemia cells based on CD47 expression. Targeting of human CD47 with monoclonal antibodies that block the CD47–SIRPα interaction enhanced macrophage phagocytosis of these cells *in vitro*. Furthermore, a CD47-specific antibody was shown to ameliorate AML *in vivo* in immunocompromised xenotransplanted mice by specifically targeting AML LSCs for phagocytosis. However, no increase in the phagocytosis of normal HSCs or HSPCs or toxicity was detected in wild-type mice.

So, these papers show that CD47 is transiently upregulated on HSCs during mobilization to protect them from phagocytosis by macrophages and that AML LSCs use this protective strategy to evade macrophage killing. Targeting of CD47 preferentially enables the targeting of AML LSCs for phagocytosis and therefore monoclonal antibodies that disrupt the CD47–SIRPα interaction could be an effective therapy for human AML.

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**ORIGINAL RESEARCH PAPERS** Jaiswal, S. *et al.* CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell* **138**, 271–285 (2009) | Majeti, R. *et al.* CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell* **138**, 286–299 (2009)