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Iron-deprivation in human T cells induces non-proliferating, accessory helper cells.

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Iron uptake via CD71 is a pivotal mechanism for T cell proliferation. Yet, it is incompletely understood if targeting of CD71 is also affecting the differentiation and functional polarization of primary human T cells. Here we demonstrate that inhibition of iron ingestion with blocking mAb VIP-1 against CD71 prevents the proliferation of naïve T cells from cord blood and peripheral blood T cells. Targeting of CD71 with blocking or non-blocking mAbs did not alter major signaling pathways and the activation of the transcription factors NF-kB, NF-AT or AP-1 in activated T cells. The induction of the growth-stop in iron-deficient T cells (T cells) was prevented in the presence of iron in form of Ferric Ammonium Citrate (FAC) but was not reversible by exogenous IL-2 or stimulation with PMA/Ionomycin. Surprisingly, protein synthesis was found to be intact in T cells as demonstrated by CD69 upregulation or levels of cytokine production in T cells comparable with T cells upon stimulation with CD3/CD28 mAbs. Indeed, high amounts of IL-2 were detectable in the supernatant of T cells which was accompanied with a reduced cell surface expression of IL-2R subunits, CD25 and CD122. When we used such T cells in allogeneic MLRs we observed that these cells acquired an accessory cell function and stimulated the proliferation of bystander T cells. Thus, the results of our study demonstrate that iron-deprivation causes non-proliferating, altruistic T cells which can help and stimulate other immune cells by providing cytokines such as IL-2.

Human heme-albumin delivers iron via transferrin receptor for cell proliferation

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The severity of iron deficiency is more striking in mice or men with defective transferrin receptor than in transferrin deficient individuals. Here, we demonstrate that the human transferrin receptor (CD71) can utilize heme-albumin (heme-HSA) as an additional ligand to transport iron into cells. Uptake of heme-albumin via CD71 was sufficient to promote proliferation of various cell types and was dependent on heme-oxygenase 1 function. Import of heme-albumin via CD71 was further found to contribute to the efficacy of HSA-based drugs such as the chemotherapeutic medicine Abraxane. These results reveal a novel role of heme-HSA and CD71 in delivering iron to cells and suggest an impact of this route in the mechanism of HSA-based drug applications.