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Excess of circulating apo-transferrin enhances dietary iron absorption

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Transferrin maintains plasma iron in a redox-inert state and delivers it to developing erythroblasts and other cells. It captures iron that is either recycled from erythrophagocytic macrophages of the liver and spleen, or newly absorbed from duodenal enterocytes. Thus far, transferrin has not been considered to have any regulatory function on iron entry into the bloodstream. Under physiological conditions, about two thirds of the protein remains as iron-free apo-transferrin (apo-Tf), to prevent accumulation of redox-active and potentially toxic non-transferrin bound iron (NTBI). We and others showed that NTBI uptake by liver sinusoidal endothelial cells induces expression of bone morphogenetic protein 6 (BMP6), an activator of the iron hormone hepcidin.

In this study, we utilized apo-Tf as a tool to prevent NTBI formation and hepcidin induction following high dietary iron intake. To this end, iron deficient mice were provided a high-iron diet and at the same time were intravenously injected with apo-Tf. Surprisingly apo-Tf injection did not eliminate but rather drastically increased plasma NTBI levels, triggering hepcidin induction in the liver. We demonstrate that NTBI formation following apo-Tf injection was due to increased dietary iron absorption, rather than iron redistribution in the body. Injected fluorescent-labeled transferrin colocalized with macrophages in the lamina propria, but not liver or spleen. These data are consistent with a recent study showing that lamina propria macrophages have the capacity to degrade transferrin.

Our data uncover an unexpected function of circulating apo-Tf as an iron regulator. It acts as a driver of iron absorption presumably by virtue of its iron acceptor function, in a process that appears to be negatively regulated by lamina propria macrophages via proteolysis.

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