

Role of Ceruloplasmin in Cellular Iron Uptake: Addendum

We recently reported that ceruloplasmin (Cp) stimulates iron uptake by HepG2 cells by a transferrin-independent mechanism (1). We are grateful to Ian Trowbridge, at the Salk Institute, for a comment about our use of the anti-transferrin receptor monoclonal antibody H68.4 in this study. He correctly points out that H68.4 (originally produced in his laboratory) binds to an epitope of the transferrin receptor cytoplasmic tail inaccessible to antibody in intact cells, and is thus not the preferred reagent for determining the role of the receptor in iron uptake by intact cells. We further thank Trowbridge for his generous gift of anti-transferrin receptor monoclonal antibody 42/6, which blocks transferrin binding to its receptor (2), and transferrin-mediated iron uptake in intact cells (3). We have repeated our original studies and have obtained the same results with the 42/6 antibody as before, namely, that 42/6 does not inhibit Cp-mediated ^{55}Fe -nitritotriacetate uptake by HepG2 cells. In a positive control experiment, 42/6 antibody effectively blocks ^{55}Fe -transferrin uptake. In view of Trowbridge's comment, we have reexamined our studies with the original antibody. H68.4, in fact, does block ^{55}Fe -transferrin uptake in HepG2 and K562 cells, but only under conditions of iron deficiency, the condition used in our studies. The mechanism underlying this observation is not clear.

In complementary studies, we have shown that Cp-stimulated iron uptake occurs in K562 cells, which do not secrete transferrin, and in the presence of endocytosis inhibitors, which block transferrin uptake (1, 4). Furthermore, our recent results indicate that Cp stimulates iron uptake through a trivalent cation transporter, a mechanism completely distinct from that used by transferrin (4). Together, these studies provide compelling evidence that Cp-stimulated iron uptake is transferrin- and transferrin receptor-independent.

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8 December 1998; revised 15 April 1999; accepted 1 May 1999

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Science **284** (5418), 1235.

DOI: 10.1126/science.284.5418.1235b

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