The Importance of the Stem Cell Marker Prominin-1/CD133 in the Uptake of Transferrin and in Iron Metabolism in Human Colon Cancer Caco-2 Cells

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As the pentaspan stem cell marker CD133 was shown to bind cholesterol and to localize in plasma membrane protrusions, we investigated a possible function for CD133 in endocytosis. Using the CD133 siRNA knockdown strategy and non-differentiated human colon cancer Caco-2 cells that constitutively over-expressed CD133, we provide for the first time direct evidence for a role of CD133 in the intracellular accumulation of fluorescently labeled extracellular compounds. Assessed using AC133 monoclonal antibody, CD133 knockdown was shown to improve Alexa488-transferrin (Tf) uptake in Caco-2 cells but had no impact on FITC-dextran or FITC-cholera-toxin. Absence of effect of the CD133 knockdown on Tf recycling established a role for CD133 in inhibiting Tf endocytosis rather than in stimulating Tf exocytosis. Use of previously identified inhibitors of known endocytic pathways and the positive impact of CD133 knockdown on cellular uptake of clathrin-endocytosed synthetic lipid nanocapsules supported that CD133 impact on endocytosis was primarily ascribed to the clathrin pathway. Also, cholesterol extraction with methyl-beta-cyclodextrine up regulated Tf uptake at greater intensity in the CD133(high) situation than in the CD133(low) situation, thus suggesting a role for cholesterol in the inhibitory effect of CD133 on endocytosis. Interestingly, cell treatment with the AC133 antibody down regulated Tf uptake, thus demonstrating that direct extracellular binding to CD133 could affect endocytosis. Moreover, flow cytometry and confocal microscopy established that down regulation of CD133 improved the accessibility to the TfR from the extracellular space, providing a mechanism by which CD133 inhibited Tf uptake. As Tf is involved in supplying iron to the cell, effects of iron supplementation and deprivation on CD133/AC133 expression were investigated. Both demonstrated a dose-dependent down regulation here discussed to the light of transcriptional and post-transciptional effects. Taken together, these data extend our knowledge of the function of CD133 and underline the interest of further exploring the CD133-Tf-iron network.

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