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Reprogramming the reactivity of iron in cancer

CD44 is a transmembrane glycoprotein that is linked to various biological processes reliant on the epigenetic plasticity of cells, including development, inflammation, immune responses, wound healing and cancer progression. While thoroughly studied, functional regulatory roles of this so-called 'cell surface marker' remain elusive. We have discovered that CD44 mediates endocytosis of iron interacting with hyaluronates in tumorigenic cell lines and primary cancer cells. We found that this glycan-mediated iron endocytosis mechanism is enhanced during epithelial-mesenchymal transition, unlike the canonical transferrin-dependent pathway. This transition is further characterized by molecular changes required for iron-catalyzed oxidative demethylation of the repressive histone mark H3K9me2 that governs the expression of mesenchymal genes. CD44 itself is transcriptionally regulated by nuclear iron, demonstrating a positive feedback loop, which is in contrast to the negative regulation of transferrin receptor by excess iron. Finally, we show that epigenetic plasticity can be altered by interfering with iron homeostasis using small molecules. This comprehensive study reveals an alternative iron uptake mechanism that prevails in the mesenchymal state of mammalian cells, illuminating a central role of iron as a rate-limiting regulator of epigenetic plasticity.