Iron Binding in IscA and Iron Delivery for the Biogenesis of Iron-Sulfur Clusters

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The pioneering work by Dean's group has demonstrated that sulfur in iron-sulfur clusters is provided by L-cysteine via cysteine desulfurases. However, it is still not clear how the intracellular iron is mobilized and delivered for the biogenesis of iron-sulfur clusters in proteins. In searching for potential iron donors, we find that IscA, a key member of the iron-sulfur cluster assembly machinery, is a novel iron binding protein with an apparent iron association consistent of $3.0x10^{19}M^{-1}$. The iron binding activity of IscA requires physiological thiol reductants such as thioredoxin and thioredoxin reductase system which likely provide a reducing environment for IscA to bind iron. The iron-loaded IscA has a dominate UV-Vis absorption peak at 315 nm and an unusual EPR signal at g = 4-6 reflecting an *S* = 3/2 spin ferric iron center in the protein. Importantly, the iron-loaded IscA can efficiently provide iron for the iron-sulfur cluster assembly in a proposed scaffold IscU in the presence of L-cysteine and cysteine desulfurase (IscS). Additional studies reveal that L-cysteine, but not IscS or IscU, is responsible for mobilizing the iron center in IscA and transferring iron for the iron-sulfur cluster assembly in IscU. Our results suggest that IscA is capable of recruiting the intracellular iron and transferring the iron for the iron-sulfur cluster assembly in IscU, and that L-cysteine may have two distinct roles in the biogenesis of iron-sulfur proteins: to facilitate iron transfer from IscA to IscU and to provide sulfur via IscS for the iron-sulfur cluster assembly in IscU.