Structure of human Fe-S assembly sub-complex

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Iron-sulfur (Fe-S) clusters are essential cofactors for all organisms. In eukaryotes, Fe-S cluster are primarily synthesized in the mitochondria and distributed to target proteins involved in substrate activation, oxidative respiration, and gene regulation.[1] At the center of the Fe-S cluster biosynthetic complex, the cysteine desulfurase (NFS1) and LYR protein (ISD11) form a tight complex and catalyze the conversion of cysteine to alanine in which persulfide sulfur is delivered via a mobile loop to the scaffold protein, ISCU2.[1] Additionally, FXN appears to act as an allosteric activator of this process.[2,3] On ISCU2, persulfide sulfur, Fe^{2+}, and electrons are assembled to form [2Fe-2S]. Each of the aforementioned proteins are involved in human disease.[1] Additionally, recent functional and proteomic studies have revealed acyl-carrier protein (ACP) as an essential component of Fe-S cluster biosynthesis and as an interacting partner of ISD11 and other LYR proteins respectively.[4,5] Interestingly, ACP and ISD11 are eukaryotic specific adaptors for the Fe-S cluster biosynthetic complex, and to date, the structural basis for their essentiality has yet to be described. We have determined a 3.09 Å and 15 Å x-ray crystal and electron microscopy structures respectively of human NFS1-ISD11 in complex with *E. coli* ACP. Our structure reveals a dramatically different global architecture in comparison to all previously determined cysteine desulfurase structures. To support this architecture, we also interrogated protein-protein interfaces *in vivo* using *S. cerevisiae*. Overall, the structure reveals that ACP threads its lipid bound cofactor into ISD11 providing stabilization and a structural framework the assembly of a new cysteine desulfurase global architecture. We hypothesize that this new architecture facilitates the use of function-control elements such as FXN, and that ACP interacts with all LYR proteins via a lipid insertion motif serving as a regulatory element of both oxidative respiration and Fe-S cluster biosynthesis.

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