Half way to hypusine. Molecular basis of deoxyhypusination.

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The eukaryotic translation factor 5A (eIF5A) plays a pivotal role during translation. It is the only cellular protein known to undergo hypusination, a unique post-translational modification of a conserved lysine (Lys50 in human eIF5A). Hypusination is essential to resolve ribosomal stalling during the formation of proline-rich polypeptides. Recent findings show that the hypusination of eIF5A plays a role in many important cellular processes, including autophagy, senescence, polyamine homeostasis, and the determination of helper T cell lineages. Malfunctions of the hypusination pathway, including those caused by mutations within the pathway encoding genes, are associated with such conditions as cancer or neurodegeneration. Therefore, hypusination seems as an attractive molecular target for therapeutic interventions.

Hypusination involves two distinct enzymatic steps. First, deoxyhypusine synthase (DHS) catalyzes the transfer of 4-aminobutyl moiety of spermidine to a specific lysine of eIF5A precursor in an NAD-dependent manner. Subsequently deoxyhypusine is further hydroxylated to the mature form hypusine by second enzyme: deoxyhypusine hydroxylase (DOHH).

Here, we present the cryoEM structure of the human eIF5A-DHS complex at 2.8Å resolution and a crystal structure of DHS trapped in the key reaction transition state. Furthermore, using combined structural biology and biochemical analysis, we show that DHS variants that cause neurodegeneration influence complex formation and hypusination efficiency. Hence, our data provide the molecular basis of deoxyhypusine synthesis and reveal how clinically-relevant mutations affect this crucial cellular process.

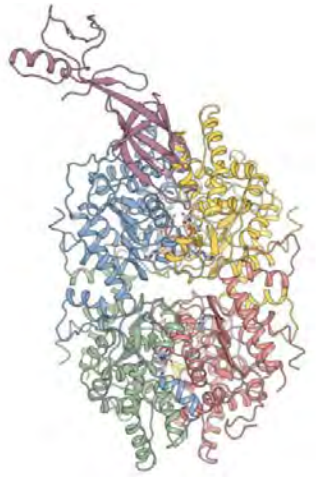

Figure 1. cryoEM structure of human IF5A-DHS complex. One molecule of IF5A (pink) binds to the tetramer of DHS.

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