Targeted inhibition of hypusination pathway

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Hypusination is a modification described only for one protein: the eukaryotic translational factor eIF5A and spermidine is used as a substrate in this process. In the first step of hypusination, the enzyme deoxyhypusine synthase (DHS) attaches the 4-aminobutyl moiety of spermidine to the lysine residue present in eIF5A, resulting in the formation of a non-standard amino acid residue: deoxyhypusine. The deoxyhypusine is then modified to hypusine by deoxyhypsuine hydroxylase (DOHH) (Fig. 1). eIF5A is involved in the protein translation process, and hypusinated lysine is essential for its activity. eIF5A is also involved in the development of certain diseases such as diabetes, certain types of cancer, and malaria. Furthermore, hypusinated eIF5A promotes cell proliferation.

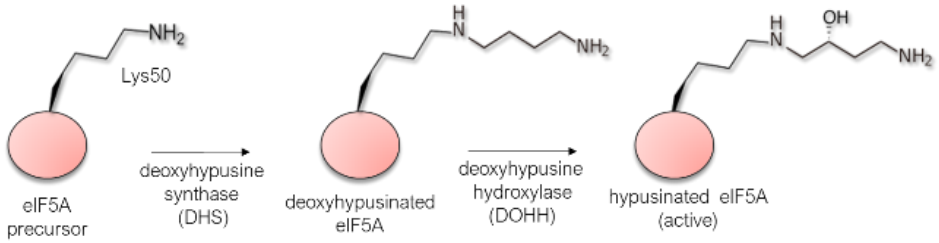

Figure 1. eIF5A hypusination scheme

Much attention is currently being paid to the molecular mechanism of selective control of protein translation by hypusinated eIF5A. Hypusinated eIF5A is indispensable for tumor growth and is closely related to the aggressiveness of cancers. Moreover, the expression of the second eIF5A-2 variant is a hallmark of many cancers. Furthermore, mutations in proteins involved in hypusination pathway are the cause of neurological disorders.

To date, we are simply lacking molecular compounds that enable us to specifically modulate the hypusination pathway and the structure-activity relationship of the currently used inhibitors is vaguely defined, as there are major concerns about the specificity of these molecules. Hence, the ultimate goal of the project is to obtain lead compounds selectively modulating the hypusination pathway that can be further optimized as pro-drugs or tool compounds to be used in diagnostics and clinical treatment.

In detail, we plan to transform the small molecules obtained in our previous research into novel lead compounds that can serve as pro-drug molecules. These molecules will be thoroughly tested in various activity screens as well as we will obtain crystal structures of DHS in complexes with developed compounds. Furthermore, using a high-throughput crystallographic screening we will discover new small-molecule DOHH binders which will pave the way for the synthesis of novel inhibitors and thus, together with DHS-interacting compounds, complement the landscape of hypusination pathway modulators. Last but not least, we plan a multifaceted strategy in which not only small compounds but also nucleic acid-based aptamers will be tested as possible hypusination modulators.