

B9

Title: STRUCTURE AND ASSEMBLY OF HUMAN MULTI-TRNA SYNTHETASE COMPLEX REVEALS NOVEL MECHANISM OF DISEASE ASSOCIATION

Author(s): Krishnendu Khan

Affiliation: Cleveland Clinic Lerner Research Institute

In mammalian cells, eight cytoplasmic aminoacyl-tRNA synthetases (AARS), and three non-synthetase proteins, forms a large multi-tRNA synthetase complex (MSC). AARSs have critical roles in interpretation of the genetic code during protein synthesis, and in functions unrelated to translation. Nonetheless, the structure, function and assembly of the MSC remain unclear. We used cross-linking mass-spectrometry (XL-MS) to interrogate the 3-dimensional architecture of the MSC in human HEK293T cells. Using the MS-cleavable cross-linker, DSSO, inter-protein crosslinks spanning all MSC constituents were observed, including cross-links between eight protein pairs not previously known to interact. Molecular docking of the AARS's using spatial restraints obtained by XL-MS resulted in the generation of a 3D model of human holo-MSC. Unexpectedly, an asymmetric AARS distribution was observed featuring a clustering of tRNA anti-codon binding domain on one MSC face which might improve the efficiency of delivery of charged tRNAs to an interacting ribosome during translation. The MSC has been hypothesized to be a molecular depot which helps in sequestering protein components that otherwise would be toxic to the cell in free form. We are currently probing this hypothesis in neurodegenerative diseases, where MSC constituents have been found to play a critical role. In combination with the 3D model of MSC our work provides new insights into translational control mechanisms with possible implications into disease etiology.