

SHARE & BioSyM Joint Seminar on Cancer Research

Noncanonical Roles of Lysyl tRNA Synthetase

from immune stimulation to Egfr stimulation and cancer

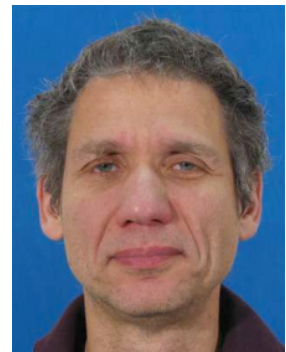
Professor Hovav Nechushtan

Hadassah Hebrew University Medical Center

Date: 14 Sep 2016, Wednesday

Time: 4pm to 5pm

Venue: Perseverance Rooms, Level 5 of Enterprise Wing @
UTown, S'138602



Abstract

Nearly 20 years ago we isolated 12 genes encoding proteins with high affinity binding to the transcription factor MITF. Among them we identified HINT1, a nucleotide binding protein which can inhibit MITF activity and somewhat surprisingly Lysyl tRNA synthetase (KARS) – an enzyme with a critical role in translation. Subsequent studies revealed that KARS may exist in the cell in at least two conformation- one as a tRNA synthetase bound to a cytoplasmatic protein complex and the other as a translationally incapable protein that has an "open" conformation and can translocate to the nucleus and bind a transcription factor and induce its activation. This translationally inactive phosphorylated protein can produce Ap4A (diadenosine tetraphosphate) which can release the HINT1 inhibitor from the bound transcription factor. Ap4A can be degraded by NUDT2 – a protein belonging to the nudix family of nucleotide metabolizing genes. I will elaborate on the mechanistic aspect of this pathway.

Besides immune activation in mast cells we have obtained evidence for activation of this pathway in cancer by EGFR. Furthermore evidence obtained from immunohistochemistry analysis of resected lung cancer tumors utilizing anti phosphor - KARS revealed a correlation between higher expression of this protein and longer disease free survival in EGFR mutation positive patients. I will describe in detail these latest results as well as initial results in Melanoma. Our observations suggest that a pathway linking important translation regulatory protein with transcriptional regulation exists and may play important physiological functions in different cell types .

Biography

Dr. Hovav Nechushtan is an Associate Professor in Hadassah Hebrew University Medical Center, and Head of the Genomic Oncology Service in Hadassah Medical Center. He is an attending physician treating mainly lung and kidney cancers. Dr. Hovav Nechushtan obtained his B.Sc. degree in 1984, and completed his Ph.D. and M.D. studies in 1991 and 1996, respectively, all from Hebrew University. His research focuses on transcriptional control and the LySRS pathway.