Autism and **a**utism **s**pectrum **d**isorders (**ASDs**) are a heterogenous group of brain development diseases. Their typical symptoms include impaired communication (verbal and non-verbal) and social interactions along with repetitive, stereotypical behavior. The number of cases is steadily increasing – currently 1 child in 100 is diagnosed with autism (1 in 68 in the U.S.). It points to the long-underestimated significance of autism and its cost for the society. ASDs are currently viewed as synaptopathies – brain diseases affecting the number and structure of synapses. Since plasma membrane receptors for extracellular nucleosides (adenosine) and nucleotides (ATP, ADP, UTP, UDP and sugar UDP) are important for vital functions of the central nervous system (CNS) and can modulate synaptic function and structure, the role of extracellular nucleotide and nucleoside signaling in autism was suggested. On the other hand, disturbances in mTOR (mammalian target of rapamycin) pathway is a characteristic biochemical feature of ASDs. Extracellular nucleotide signaling may affect 5'AMP-activated protein kinase (AMPK), one of the main sensors of the cellular metabolic status, that can inhibit mTOR. However, the engagement of adenosinergic and purinergic receptors in the synaptic disturbances of ASDs is not thoroughly examined mechanistically and the crosstalk between extracellular nucleotide signaling and AMPK/mTOR-pathway has not been investigated. Our preliminary investigations in the rat model of environmentally-linked autism induced by prenatal exposure to valproic acid (VPA) showed behavioral and ultrastructural synaptic disturbances accompanied by elevated mTOR activity, and alterations in its target proteins engaged in the modulation of translation, synaptic vesicles, or neurotransmitter release in the offspring. We have also found that prenatal VPA exposure affect selected ionotropic (P2X5 and P2X7) and metabotropic (P2Y1 and P2Y2) purinergic receptors gene expression. We hypothesize that the dysfunction of synapses in autism and related disorders is linked to the interactions between extracellular nucleotide receptors (P1 and P2) signaling and AMPK/mTOR-regulated autophagy and translation of proteins. In order to verify this hypothesis we provide the implementation of the following specific aims:

A. Determine the involvement of extracellular nucleotide dependent signaling in AMPK/mTOR pathway dysfunction.

B. Investigate the mechanism of mTOR-evoked changes in synaptic proteins – with special attention to the role of mTOR-dependent autophagy and mRNA translation.

C. Evaluation of the involvement of P1/P2 receptors as well as mTOR-dependent autophagy and translation of proteins in autistic-like behaviors.

Because both environmental and genetic factors play an important role in the etiology of autism, leading to a wide range of molecular, structural and behavioral changes, this project will be carried out using animal models of ASDs induced by both genetic and environmental factors.

The cross-talk between nucleotide signaling and the regulatory mechanisms responsible for the maintenance of synaptic protein homeostasis has not been investigated so far. Addressing the role of AMPK and mTOR pathway at the crossroads of neuronal co-transmission and the metabolism of synaptic proteins holds the promise for better understanding of autism pathomechanism and the identification of therapeutic targets. These study will clarify the complex relationship between the P1/P2 receptors signaling, AMPK-mTOR pathway, and synaptic function, and defines a therapeutic targets for autism and related diseases.