Subject: Dissertation Defense - Alexandru Graur, PhD Biosciences
Date: Tuesday, July 2, 2024 at 4:58:08 PM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
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Dissertation Defense Announcement
To: The George Mason University Community

Candidate: Alexandru Graur

Program: PhD Biosciences

Date: Monday, July 15, 2024

Time: 11:00 AM Eastern Time (US and Canada)

Location: In Person, Fairfax campus, Krasnow building, room #229
And Via Zoom

Join Zoom Meeting:

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Committee chair: Dr. Nadine Kabbani

Committee members: Dr. James L. Olds, Dr. Alessandra Luchini, Dr. Remi Veneziano

Title: “Targeting the Cholinergic Synapse in Development and Disease”

Abstract:

The cholinergic system is an essential modulatory neurotransmitter system in the mammalian brain responsible for the regulation of memory, attention, and cognitive processing. This dissertation investigates several key components of the cholinergic system that are important for human neurodevelopment and disease. **First:** I investigated the non-enzymatic role of the T30 neuropeptide, a 30-amino acid peptide endogenously produced as a cleavage product of synaptic acetylcholinesterase. I show that T30 activates neuronal growth in axons as well as dendrites via the activation of the mammalian target of rapamycin (mTOR) pathway. Using the SH-SY5Y neuroblastoma cell line as a cholinergic model, I define the proteomic adaptations within developing cells to an exposure to T30. My proteomic analysis shows that T30 operates by regulating intracellular proteins important for structural growth, ribosomal function, and autophagy regulation. Critically, these processes are driven by the mTOR pathway and functional experiments confirm that rapamycin inhibition of mTOR can effectively block T30 mediated α7 nicotinic acetylcholine receptor (nAChR) activation of mTORC1. **Second:** The targeting of cholinergic nAChR, with small molecules or peptides, shows exciting promise in the development of drugs for treating human neurodegenerative and inflammatory disorders. Drug development however is often hampered by limitations in initial compound screening and target validation due to limitations in structural protein analysis and the computational limitations of crystallized modeling. To address this, I optimized the use of protein painting-based mass spectrometry to identify ligand interaction sites of the nAChR using the Aplysia californica acetylcholine-binding protein structural surrogate model. I show specific residues involved in the binding of nAChR ligands including α-bungarotoxin, choline, nicotine, and the pathogenic amyloid beta 1–42 peptide. Protein painting is thus presented as a novel strategy for drug development targeting the nAChR. **Third:** Human immunodeficiency virus (HIV) continues to be a major global health problem with infected individuals at a heightened risk for cognitive decline, dementia, and memory deficits. Moreover, almost half of all HIV-positive individuals also smoke tobacco products and studies have shown that smoking can worsen cognitive functions in HIV infected individuals. I examined interaction between the HIV structural glycoprotein gp120 and nicotine within human microglia (HMC3) cells. Microglia are a primary reservoir for HIV and have been recently shown to contribute to neuroinflammation during HIV infection. Mass spectrometry analysis of gp120 treated cells shows that HIV impacts the mitochondrial proteome of human microglia. Specifically, in the presence of nicotine, gp120-was found to increase mitochondrial fusion as well as network size, and to reduces fission. The effect of nicotine on gp120 correlated with an increase in amyloid peptide release as well as increase in autophagy within microglia. These results show that nicotine potentiates gp120 inflammatory effect on microglia by modulating both mitochondrial activity and amyloid peptide processing and release. Thus, these findings present a mechanism for HIV associated neurocognitive decline and heightened risk in the brain of smokers. Ultimately, this dissertation underscores the critical role of the cholinergic system in mediating neurodevelopmental processes, serving as a key target for therapeutic interventions, and contributing to the pathological consequences of neurodegenerative diseases.

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