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Cytoskeletal Signaling Critical for Synapse Development, Plasticity and Repair

Dr. Kimberley Tolias is a Professor in the Department of Neuroscience and the Department of Biochemistry and Molecular Biology at Baylor College of Medicine (BCM) in Houston, Texas. Dr. Tolias received her bachelor's degree in Biochemistry from University of Minnesota. She then moved to Boston where she obtained a Ph.D. degree in Cell and Developmental Biology at Harvard Medical School working in the laboratory of Dr. Lewis Cantley. In the Cantley lab, Dr. Tolias identified phosphoinositide kinases as important effectors of Rho GTPases that mediate actin filament assembly critical for cell morphogenesis and migration. For her postdoctoral fellowship, Dr. Tolias worked in the laboratory of Dr. Michael Greenberg at Harvard Medical School where she investigated the mechanisms by which experience-driven neural activity shapes the developing mammalian nervous system. Her postdoctoral work identified key signaling pathways that regulate dendritic arbor growth and dendritic spine and synapse development by inducing local actin cytoskeletal remodeling. In 2006, Dr. Tolias left Harvard Medical School to start her own lab at BCM.

Research in the Tolias laboratory is focused on unraveling the molecular mechanisms that control neural circuit formation, plasticity, and repair in the mammalian brain and spinal cord. In particular, the Tolias lab studies the processes of synapse development and remodeling, dendritic growth, and cell migration. In addition to investigating how these processes are normally regulated, they examine how their dysregulation contributes to various neurological disorders (e.g., intellectual disabilities, autism spectrum disorder, Alzheimer's disease, depression, chronic pain), and whether targeting key signaling pathways can promote recovery following CNS injury or disease. To accomplish these goals, the lab utilizes a multidisciplinary approach, employing mouse models and a combination of state-of-the-art genetic, molecular, cellular, biochemical, electrophysiological, and behavioral methods. Research in the lab has provided fundamental insights into: (1) Rho GTPase signaling pathways that drive synapse development and plasticity by modulating cytoskeletal dynamics, (2) novel regulatory mechanisms (e.g., GEF/GAP complexes) that provide precise

spatiotemporal control of Rho GTPase signaling in neurons and glia critical for CNS development, (3) roles of the BAI1 Adhesion-GPCR in synapse and dendritic arbor development, (4) functions of RhoA GTPase signaling in locomotor circuit assembly and cerebellar morphogenesis, and (5) new approaches for blocking pathological synaptic remodeling caused by traumatic brain injury or radiation therapy. Recently, the lab has also branched out into new exciting research directions, including: (1) developing new tools to identify synapses in the brain undergoing remodeling during specific learning events or following injury, and (2) preventing and/or reversing pathological synaptic plasticity that underlies chronic pain, opioid-induced hyperalgesia and tolerance, and chronic pain-induced depression.

Abstract: Mood disorders such as depression are frequently observed in patients with chronic pain, and the coexistence of these disorders tends to intensify patients' suffering, making both disorders more difficult to treat. Clinical and preclinical studies have established that hyperactivity of pyramidal neurons in the anterior cingulate cortex (ACC) drives the comorbid depressive symptoms in chronic pain. However, the cause of ACC neuron hyperactivity remains unknown. Notably, the N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine is capable of inducing rapid and sustained antidepressant effects in both patients and animal models of chronic pain, but the underlying mechanism of ketamine's antidepressant effects has not yet been fully elucidated.

Here, I will present evidence that Tiam1, a Rac1-specific guanine nucleotide exchange factor (GEF) that we previously identified as a critical mediator of NMDAR-dependent synapse development, is activated in the ACC in chronic pain mice displaying depressive-like behaviors. We found that blocking Tiam1 function by genetic deletion in postnatal forebrain excitatory neurons, by specific ablation in ACC neurons, or by pharmacological inhibition of the Tiam1-Rac1 signaling pathway prevents chronic pain-induced depressive-like behaviors in mice. Biochemical, morphological, and electrophysiological assays indicate that Tiam1 orchestrates synaptic structural and functional remodeling in ACC neurons via actin cytoskeleton reorganization and synaptic NMDAR stabilization. Our results suggests that Tiam1-coordinated synaptic plasticity underpins ACC hyperactivity and drives chronic pain-induced depressive-like behaviors. Moreover, our data suggests that ketamine induces sustained antidepressant effects in chronic pain by blocking Tiam1-mediated synaptic structural and functional plasticity in ACC neurons. Together, these results reveal Tiam1 as a key factor in the pathophysiology of chronic pain-induced depression and in the sustained antidepressant effects of ketamine in ACC neurons.