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Role of PHLPP1 in Astrocytes and Stroke
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Epidemiological studies have identified tobacco use as a clinical risk factor for increasing the incidence of cardiovascular disease including cardiac arrest and stroke. The impeded flow of blood from a stroke starves the brain of oxygen, glucose, and other vital nutrients and this in turn activates signaling cascades within the cells of the brain resulting in an ischemic injury. An important signaling molecule that helps regulate the balance between cell survival and death in cells is the serine/threonine kinase Akt, also known as protein kinase B (PKB). The molecule puts phosphates on its targets, regulates a wide variety of cellular processes including cell survival, metabolism, and growth. Recently, a newly discovered protein phosphatase PHLPP (PH domain leucine-rich repeat protein phosphatase) was found to reverse this process by inhibiting Akt activity. Historically the focus in considering brain pathology has been on the survival or death of neurons, however, the brain also contains astroglial cells (astrocytes) which have both physiological and pathological roles in regulating neuronal activity and CNS homeostasis. The overall hypothesis to be tested here is that PHLPP is an important regulator of Akt signaling in astrocytes and that loss of PHLPP will accentuate Akt activation, protecting cells from dying in response to lack of oxygen by activating cell survival pathways or altering the proteins that the cell makes. Our proposed experiments will specifically determine if: 1) PHLPP modulates temporal activation of Akt and localization in astrocytes and neurons and whether sustained activation of Akt by removal of PHLPP protects astrocytes and neurons from ischemic injury; 2) removal of PHLPP has an effect on the brain and its response to stroke. Proposed work will examine the role of PHLPP on Akt activation and its role in preventing ischemic damage using in vitro and in vivo systems. Molecular and functional studies will be performed in astrocytes and mice that lack PHLPP in their genome. Using these systems we aim to test the proposed hypothesis and significantly impact current therapeutic strategies to improve stroke outcome associated with tobacco-use.