The Neuroscience Graduate Program

presents:

JULIANNE FEOLA
ADVISOR: GAIL JOHNSON

IN A PHD THESIS DEFENSE

TUESDAY, 17 JANUARY 2017

9:00AM IN K-207 AUDITORIUM
(2-6408)

The Role of Astrocytic Transglutaminase 2 in mediating Cellular Viability Processes

There is a large body of literature describing the powerful influences that astrocytes exert on neuronal function. In many cases, astrocytic processes provide support to neurons under both basal and stressed conditions. Astrocytes are also vulnerable, however, to cellular stress, and disruptions in their normal functions can impede neuronal survival. The identification of astrocytic factors that play a significant role in mediating both astrocytic and neuronal viability is therefore imperative in further elucidating cellular disease processes. Transglutaminase 2 (TG2) is a molecular factor with widespread functionality and ubiquitous cellular expression. TG2 has been considered to be both pro-cell death and pro-survival in various cellular contexts and disease states. Our lab has demonstrated that the expression of TG2 in neurons is beneficial to their survival following an ischemic injury, but TG2 expression in astrocytes is detrimental to astrocytic survival. Furthermore, astrocytic TG2 expression negatively impacts neuronal survival in ischemic conditions.

The aim of this body of work was to expand upon this finding and further elucidate the characteristics and functions of TG2 within astrocytes that contribute both to astrocytic and neuronal cellular damage. Cellular models of ischemia were utilized to induce stress in primary astrocyte and neuron cultures. Results demonstrate that both lentiviral-mediated knockdown of TG2 and treatment with an irreversible inhibitor of TG2 protect astrocytes from oxygen/glucose deprivation (OGD). To further identify mechanisms by which TG2 may be contributing to astrocytic cell death, we examined its subcellular localization and molecular interactions under basal and hypoxic conditions. TG2 levels are reduced in the nucleus of hypoxic astrocytes, which is in direct contrast to what has been shown in neurons. In addition, shRNA-mediated knockdown of TG2 increases basal and hypoxic NF-κB transcriptional activity, whereas treatment with an irreversible TG2 inhibitor slightly reduces this activity. Studies were also conducted to investigate the mechanism(s) by which astrocytic TG2 depletion is beneficial to neuronal survival in OGD. With the use of a transwell assay, we show that TG2 depleted astrocytes can enhance neuronal survival in the absence of direct cellular contact. Overall, these studies have increased our understanding of the significant impact that TG2 has on both astrocytic and neuronal viability under conditions of cellular stress. In addition, these studies elucidate mechanisms by which TG2 may be contributing specifically to ischemic cell death and provide future directions for investigations into therapeutic targets for ischemic brain injury.