00364 Elucidating the Transcriptional Regulation of Glycogen Metabolism in Hippocampal Astrocytes

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Aims: In the brain, astrocytes provide neurons with additional sources of energy by converting stored glycogen into lactate to fuel neuronal activity. Deficits in this metabolic pathway can impair long-term memories. While the glycogen cycle is well-studied, the stimulus-driven transcriptional regulation that drives this pathway in astrocytes is poorly characterized. We want to understand how gene expression is regulated during glucose and glycogen metabolism in astrocytes by studying the function of CRTC2, a potent CREB transcriptional coactivator.

Methodology: To achieve this, we use a variety of cell molecular and imaging techniques on neuron-astrocyte cultures or slice preparations as well as in diabetic mouse models.

Result: Here, we report that CRTC2 mRNA can be detected in the mouse hippocampus throughout development into adulthood and the protein is localized both in neurons and astrocytes. Unlike CRTC1 that undergoes activity-dependent synapse-to-nucleus translocation in neurons, we discovered stimulus-driven translocation of CRTC2 occurs mainly in astrocytes and not in neurons. The signals that drive regulated nuclear import of CRTC2 in astrocytes include glucose deprivation, noradrenaline and the hormone peptide VIP (vasoactive intestinal peptide). Collectively, these signals can trigger glycogen metabolism in astrocytes. We have mapped the upstream signaling pathways for CRTC2 translocation in astrocytes and showed that it is calcium independent and requires PKC but not PKA activation. This result indicates that CRTC2 signaling cascade in astrocytes is divergent from CRTC1 signaling in neurons which requires calcium. We also found that CRTC2 is basally localized in the nucleus of hippocampal astrocytes in adult mice, suggesting a constitutive transcriptional response to regulate glycogen metabolism. While in a diabetic mouse model where the brain glucose levels are high, CRTC2 nuclear levels are significantly lower.

Conclusion: To conclude, we have identified CRTC2 as a key transcriptional coactivator that responds to multiple stimuli associated with glycogen metabolism in astrocytes.