The effects of APOE genotype on proteomic and lipidomic response to injury in different mouse models of TBI.

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Introduction
We have used different laboratory models of TBI and quantitative proteomics and lipidomics approaches to generate brain proteomic and lipidomic profiles and identify cellular mechanisms that are triggered in response to TBI. Moreover, we have carried out these studies in mice transgenic for different isoforms of human APOE in order to discriminate between the cellular mechanisms associated with favorable (APOE3) versus unfavorable (APOE4) outcomes after TBI.
Methods
We used the well characterized controlled cortical impact (CCI) model administered with a moderate (1.3mm depth) or severe (1.8mm) single injury in 6-8 month old APOE transgenic mice, and in targeted replacement APOE mice we administered a repetitive mild TBI (r-mTBI) model developed in house (Mouzon *et al.* 2012) with a paradigm of three hits per week for one month. Proteomic and lipidomic analyses employed liquid chromatography-mass spectrometry (LCMS) approaches with phospholipid analyses against internal standards and protein samples undergoing isobaric tagging for relative and absolute quantitation (iTRAQ). Using Ingenuity Pathway Analysis software, datasets of significantly modulated proteins were mapped onto known molecular relationships to determine the functional significance of the observed changes.
Results
In our CCI model our data identify significant changes in the expression of many proteins in the mouse hippocampus and cortex at 24hrs, 1 month and 3 months after TBI, including proteins with significantly different modulation in APOE3 compared to APOE4 mice. APOE-dependent lipidomic changes are also evident in our r-mTBI model.
Conclusions
In our different mouse models of TBI our datasets clearly demonstrate APOE dependent responses to injury that may represent targets for therapeutic intervention.