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Sex-Differences in Sport-Related Concussion(SRC) : A Novel Pathway-Based Evolutionary Hypothesis

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BACKGROUND

Sex-differences in clinical occurrence and response to sports-related concussion (SRC) include motor processing speed, reaction time composite scores, and injury to symptom time--all decreased in males with risk of cognitive and visual-ocular impairment and prolonged symptoms increased in women.(1) Numerous mechanistic explanations for sex-differences in brain repair following SRC have been advanced.(2) Missing from the literature are non-proximate (evolutionary) hypotheses explaining significant observed differences.

One selective pressure on female mammals only, that may have shaped phenotypic differences in brain repair, is the nearly 50% volume expansion that occurs during gestation.(3)To prevent pathologic elevation of pressures in the central nervous system during pregnancy, smooth muscle contraction regulates the flow of blood through the carotid arteries. Demonstrated sex-differences in cerebrovascular smooth muscle function are consistent with this theory.

Notably, some gene expression pathways activated with brain injury may overlap with canonic smooth muscle repair pathways.

The extent to which gene expression pathways central to brain repair mechanisms overlap with those regulating vascular smooth muscle contraction--known to express different phenotype in males vs females--points toward a novel evolutonary hypothesis for sex-differences in response to SRC.

OBJECTIVES

1) To identify gene expression pathways of significance for post-SRC brain repair mechanisms.
2) To identify overlapping gene expression pathways for cerebrovascular smooth muscle contraction and a key post-SRC brain repair pathway

HYPOTHESIS

Sex-differences in clinical response to SRC are a consequence of specific male and female cerebrovascular phenotypes, shaped by the presence of selective pressures on female but not male placental mammals. One such pressure is volume expansion in pregnancy. Observed sex-differences in cerebrovascular smooth muscle contraction may protect the brains of pregnant females from volume expansion and adverse pressure elevations.

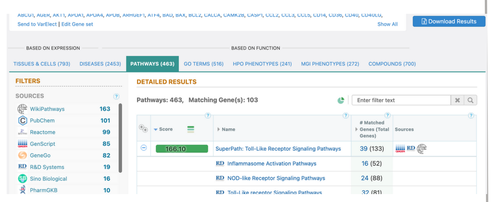
We hypothesize that sex differences in SRC responses may be a consequence of the close alignment between gene expression pathways for cerebrovascular smooth muscle contraction and key brain injury repair mechanisms.

METHODS

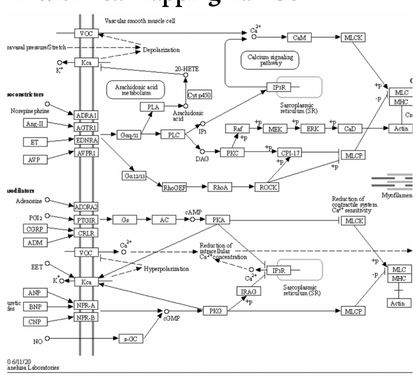
1 .We utilized KEGG (Kyoto Encyclopedia of Genes and Genomes) to source key genes in cerebrovascular smooth muscle contraction pathways.

ACTA2, ACTG2, ADCY1, ADCY2, ADCY3, ADCY4, ADCY5, ADCY6, ADCY7, ADCY8, ADCY9, ADM, ADM2, ADORA2A, ADORA2B, ADRA1A, ADRA1B, ADRA1D, AGT, AGTR1, ARAF, ARHGEF1, ARHGEF11, ARHGEF12, AVP, AVPR1A, AVPR1B, BRAF, CACNA1C, CACNA1D, CACNA1F, CACNA1S, CALCA, CALCB, CALCRL, CALD1, CALM1, CALM2, CALM3, CALML3, CALML4, CALML5, CALML6, EDN1, EDN2, EDN3, EDNRA, GNA11, GNA12, GNA13, GNAQ, GNAS, GUCY1A1, GUCY1A2, GUCY1B1, IRAG1, ITPR1, ITPR2, ITPR3, JMJD7, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KCNU1, MAP2K1, MAP2K2, MAPK1, MAPK3, MYH1, MYH10, MYH14, MYH9, MYL6, MYL6B, MYL9, MYLK, MYLK2, MYLK3, MYLK4, NPPA, NPPB, NPPC, NPR1, NPR2, PLA2G10, PLA2G12A, PLA2G12B, PLA2G1B, PLA2G2A, PLA2G2C, PLA2G2D, PLA2G2E, PLA2G2F, PLA2G3, PLA2G4A, PLA2G4B, PLA2G4C, PLA2G4D, PLA2G4E, PLA2G4F, PLA2G5, PLA2G6, PLCB1, PLCB2, PLCB3, PLCB4, PPP1CA, PPP1CB, PPP1CC, PPP1R12A, PPP1R12B, PPP1R12C, PPP1R14A, PRKACA, PRKACB, PRKACG, PRKCA, PRKCB, PRKCD, PRKCE, PRKCG, PRKCH, PRKCQ, PRKG1, PTGIR, RAF1, RAMP1, RAMP2, RAMP3, RHOA, ROCK1, ROCK2

2 We uploaded gene list to Gene Analytics platform to identify pathways with significant overlap with smooth muscle pathway, filtering for pathways central to known brain repair mechanisms. Chemokine signalling pathway meets criteria.

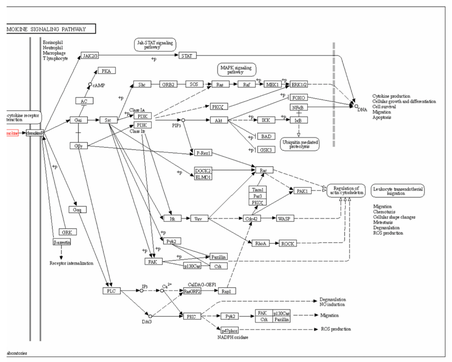


3 Visualized smooth muscle contraction pathways diagram using KEGG 2 pathway visualizing platform with hsa mapping number



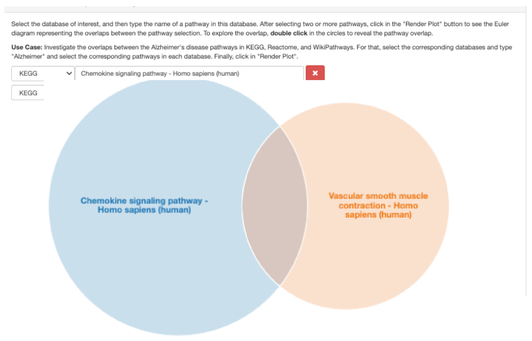
Cerebrovascular Smooth Muscle Contraction Pathway

4 Visualized chemokine signalliing pathways diagram using KEGG 2 pathway visualizing platform with mapping number



SRC Brain Repair Pathway

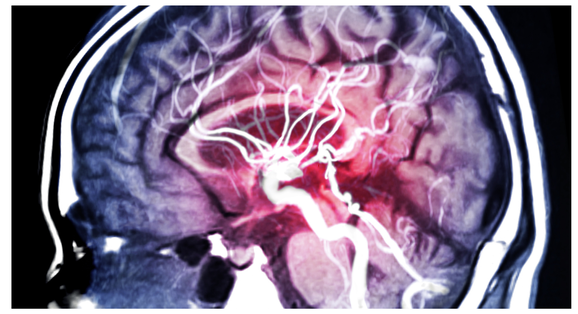
5 Both pathways entered into Fraunhofer SCAI pathway comparative function .



Courtesy the Fraunhofer Institute for Algorithms and Scientific Computing SCAI

RESULTS

Comparative analysis of gene ontology for cerebrovascular smooth muscle and cytokine signaling pathways (a central brain repair pathway) revealed notable overlaps in the gene expression signature of both. Finding duplicated on multiple pathway platforms.



CONCLUSION AND IMPLICATIONS

We found significant overlaps between a key gene expression pathway for brain repair following SRC, and of a cerebrovasculature pathway with known sex differences. The volume expansion hypothesis for cardiovascular sex differences (gestational volume being a significant selective pressure on females but not males) may have shaped a unique cerebrovascular phenotype in females that protects brains from dangerous pressure elevation despite rapidly increasing vascular volumes. The similarities between gene expression pathways for cerebrovascular smooth muscle and brain repair mechanisms following SRC points to sex differences in SRC responses as evolutionary by-products of an adaptive phenotype conferring protective support for brain function during gestation.

Our novel approach leverages publicly available gene expression pathways to develop novel, testable evolutionary hypotheses. Laboratory based studies on the activation of these pathways following SRC in male vs female animals can provide further clarity about this hypothesis. Given the rising rates of SRC and disproportionate impact on young women, such effort is highly warranted.

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