First Look into the Epigenetic Impacts of TET1 Proteins on Post-Ischemic Stroke Recovery

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Introduction

Ischemic strokes are the result of something inhibiting blood flow to the brain, which prevents oxygen and glucose from reaching brain cells.

Ischemic strokes account for ~90% of strokes world-wide, but due to the slow-healing nature of the brain, there are no currently available medicines to address the damage they cause to the brain.

Within the brain are ten-eleven translocases (TETs) – a family of proteins that oxidize 5-methylcytosine and serve a role in synaptic transmission, gene expression, and memory extinction in the wake of trauma or injury.

Objectives

- Assess the general role of TET1 in brain damage after stroke

Method

Different cohorts of mice are bred to express different levels of TET1. Wild type mice are the the control, V/V mice are bred to overexpress a TET1 mutant with limited function, V/+ mice are heterozygous for normal TET1 and the TET1 mutant, and TET1 +/- mice are a heterozygous TET1 knockout (~50% normal-TET1 production).

All mice undergo middle cerebral artery occlusion (MCAO) surgeries that simulate a stroke. Afterwards, every other day, we take the mice's neuro score through a series of cognitive tests, as well as measure their weight.

Once the tests are done, the mice are euthanized and I cut, mount, and stain the brains to measure how much damage each brain sustained during stroke. Cresyl violet dye latches onto sugars, so glucose-deprived (dead) areas of the brain appear gray, while healthy sections look purple.

Results

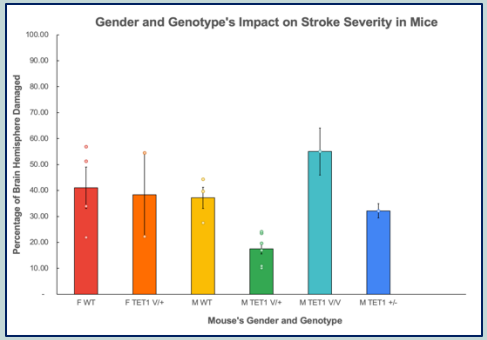
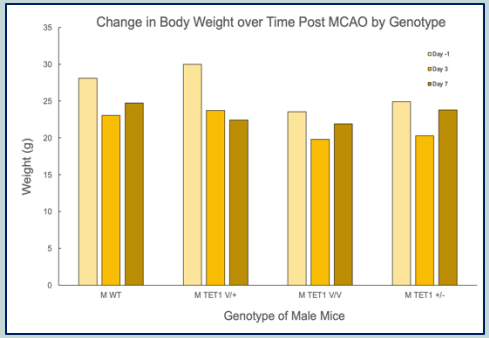


Figure 1: Brain Damage
Each bar in figure 1 represents the average percentage of damage done to the hemisphere that suffered a stroke (area of dead tissue / total area of hemisphere) by genotype. Upon first looks, V/V male mice brains suffered the worst, while TET1 V/+ male mice regularly sustained relatively low cell death levels.

Figure 2: Weight
In response to trauma, mice lose weight. The mice's weight was measured before MCAO, and in the week after. Figure 2 shows most cohorts losing weight right after the surgery, and then gaining more in the next week. The exception is the M TET1 V/+ group, which on average continued to lose weight, rather than recover it.



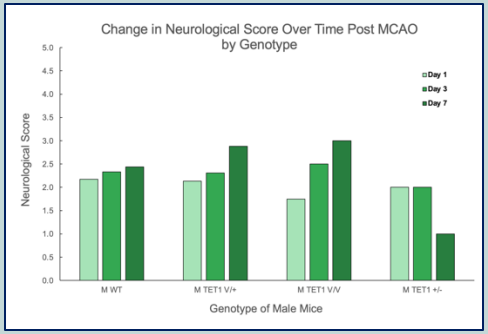
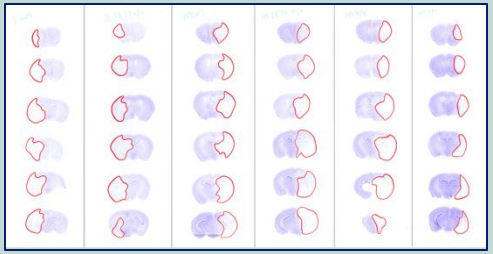


Figure 3: Neuro Score (0-5)
0 points represent a mouse functioning normally, while 5 means the mouse died. This figure shows the average change in neuro score across multiple days by cohort. Of the four cohorts, only mice with genotype TET1 +/- visibly improved over time, whereas the other genotypes declined: TET1 V/+ and V/V, especially.

Plate Examples



FWT | FV/+ | MWT | MV/+ | MV/V | M+/-

Conclusion

M TET1 V/+ mice on average suffered the smallest rates of tissue damage compared to other groups, but also had the most weight loss across time and their neuro score was on par with M TET1 V/V who suffered the greatest average tissue death of all the groups. M TET1 +/- mice are similar to the control with the exception that they are the only cohort whose neuro score improved with time.

Future Directions

- Test more mice and brains from each genotype for greater sampling size
- Use immunofluorescence to see exactly how many cells died during the stroke
- Use the infarct percentages to estimate what volume of the total brain was injured
- Locate where TET1 gathered in the brain during stroke recovery

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