The influence of genetic background on neurological responses to viral infection

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Introduction

Infection by a single virus can elicit diverse neurological outcomes and disease pathologies, depending on the genetic background of the host. Theiler's murine encephalomyelitis virus (TMEV) infection, for example, induces neurological conditions in mice that are similar to human neurological conditions. These include Parkinson's Disease, epilepsy, and demyelination, depending on the genetic background of the infected mouse strain.

To further our understanding of how a host's genetic background impacts neurological changes in response to viral infection, we used the genetically heterogeneous Collaborative Cross (CC) to model human genetic diversity. The CC was developed by intercrossing eight genetically diverse mouse strains, and is a powerful translational tool for genetic analyses of complex phenotypes including diseases caused by viruses.

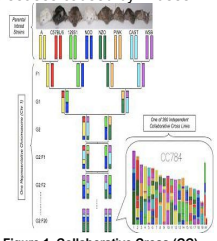
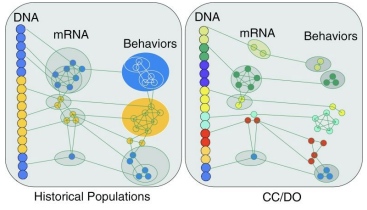


Figure 1. Collaborative Cross (CC).



Left: http://compgen.unc.edu/wp/?page_id=135
Above: Adapted from Chesler, E. J. Mammalian genome 25, 3-11 (2014).

Figure 2. Historical populations and Collaborative Cross (CC) behavior variation.

Purpose

The purpose of the present work is to evaluate the immunological and genetic determinants that drive the differences in neurological disease symptoms we see in genetically distinct mice.

Materials and Methods

- Animal care protocols were in accordance with NIH Guidelines for Care and Use of Laboratory Animals and were approved by the Texas A&M University Laboratory Animal Care and Use Committee (AUP 2014-0050 and 2017-0082)
- 69 mice from 18 different CC strains were infected intracranially with BeAn strain of TMEV.
- Qualitative phenotyping was performed weekly until the end of the experiment (~90 days post-infection, dpi), as previously described[1].

See Figure 3 for experimental timeline and Figure 6 for assessed phenotypes.

- Histopathology (H&E staining) was performed on brains (~90 dpi) of both infected and uninfected mice to locate lesions, as described[1].

Experimental Timeline

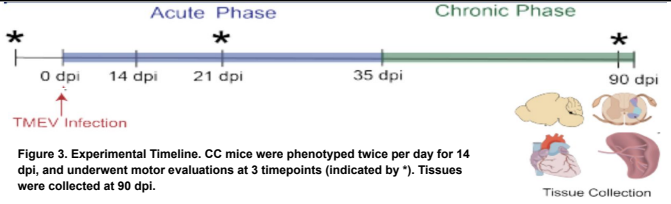


Figure 3. Experimental Timeline. CC mice were phenotyped twice per day for 14 dpi, and underwent motor evaluations at 3 timepoints (indicated by *). Tissues were collected at 90 dpi.

Quantitative Phenotyping

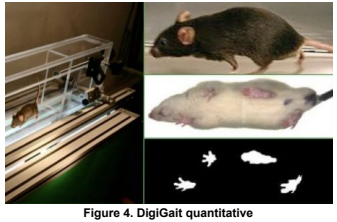


Figure 4. DigiGait quantitative imaging.

Figure 5. Rotarod quantitative analysis.

Qualitative Phenotyping

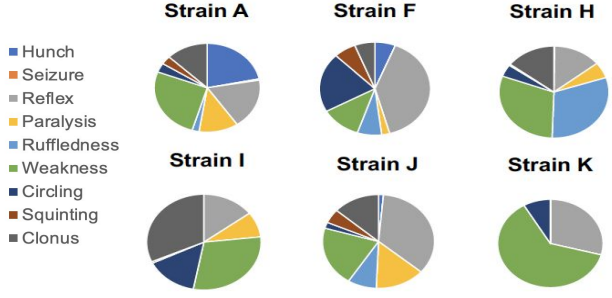


Figure 6. Qualitative phenotypes resulting from TMEV infection were diverse in CC strains. We observed varying frequencies of phenotypes depending on the CC strain. Phenotypes described in 1.

Results

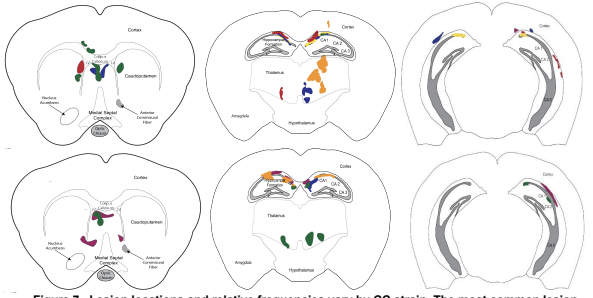


Figure 7. Lesion locations and relative frequencies vary by CC strain. The most common lesion types included neuronal degeneration and necrosis, mineralization, and vacuolation in hippocampal and thalamic regions. Locations described in 1.

Discussion

We have demonstrated that genetic diversity of CC inbred mouse strains results in differences in CNS lesion location and phenotypic differences following TMEV infection, depending on the genetic background of the host.

Future Directions

- Evaluate CNS lesions following TMEV infection of additional CC strains at more time points
- Map lesion location and perform further behavioral analysis to determine if there is a relationship between lesion size/location and phenotypic outcomes on more CC strains
- Identify drivers of sex differences in TMEV response
- Measure TMEV load in collected tissues
- Identify QTL associated with observed phenotypes in CC strains

References

1. Brinkmeyer-Langford CL, Rech R, Amstalden K, Hillhouse A, Kochan K, Young C, Welsh CJ, Threadgill DW. Host genetic background influences diverse responses to viral infection in mice. 2017. Sci Rep. 7(1):12194. PMC5610195
2. Bolon B, Garman RH, Pardo ID, Jensen K, Sills RC, Roulois A, Radovsky A, Bradley A, Andrews-Jones L, Butt M, Gumprecht L. STP position paper: Recommended practices for sampling and processing the nervous system (brain, spinal cord, nerve, and eye) during nonclinical general toxicity studies. 2013. Toxicol Pathol. 41(7):1028-48.

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