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Journal club

ANTIVIRAL RESPONSES OF INBRED MICE

So many of us in biomedical research rely on the use of inbred mice to test our hypotheses. An overlooked report by Haller *et al.*, published in *Nature* in 1980, suggests that we should be more cautious about the use of inbred mouse strains to study antiviral responses.

The inbreeding practice started in 1902 when William E. Castle and his students began generating homozygous mice. Some inbred strains of mice are quite docile, whereas others are more aggressive. Behavioural features such as these, as well as physical features (such as coat colour and eye colour), are readily distinguishable in inbred strains. However, there are numerous 'quiet mutations' throughout the genome that require stressors to reveal a phenotype (reviewed by Stevens *et al.*, 2007). It turns out that there are several such mutations in key innate immune genes throughout the genomes of common inbred mouse strains.

> "the *Mx1* locus … is mutated in almost all strains of inbred mice"

One striking example of this is the MX dynamin-like GTPase 1 (*Mx1*) locus, which is mutated in almost all strains of inbred mice. Five years after Jean Lindenmann and colleagues discovered the interferons (IFNs) as virus-resistance factors secreted by cells (in 1957), they found quite serendipitously that one strain of inbred mice, the A2G strain, had natural resistance to influenza virus infection. However, it took 18 more years and collaboration with Ion Gresser to realize that these two discoveries were linked. The study published by Haller *et al.* in 1980 put MX1 on the map as one of the first IFN-stimulated antiviral effectors (reviewed by Haller *et al.*, 2015; and Mitchell *et al.*, 2013). Until this study, it was not known exactly how IFNs protected the host against viruses.

Of course, we now understand that IFNs induce hundreds of genes, collectively known as IFN-stimulated genes (ISGs), that function to combat viral infections at multiple levels. The discovery that a particular locus (*Mx1*) can control specific virus infection in an IFN-dependent manner spurred a flurry of discoveries of other ISGs that control virus infections. However, of the hundreds of publications on the impact of IFNs on influenza virus infection in mice, only a small number uses wild-type (*Mx1*-intact) mice, which makes the study by Haller *et al.* one of the most underappreciated papers in the field.

Akiko Iwasaki
Howard Hughes Medical Institute, Department of Immunobiology, Yale University School of Medicine, 300 Cedar Street, New Haven, Connecticut 06520, USA.
akiko.iwasaki@yale.edu

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ORIGINAL ARTICLE Haller, O. *et al.* Host gene influences sensitivity to interferon action selectively for influenza virus. *Nature* **283**, 660–662 (1980)
FURTHER READING Stevens, J. C. *et al.* Quiet mutations in inbred strains of mice. *Trends Mol. Med.* **13**, 512–519 (2007) | Haller, O. *et al.* Mx GTPases: dynamin-like antiviral machines of innate immunity. *Trends Microbiol.* **23**, 154–163 (2015) | Mitchell, P. S., Emerman, M. & Malik, H. S. An evolutionary perspective on the broad antiviral specificity of MxA. *Curr. Opin. Microbiol.* **16**, 493–499 (2013)