Modeling the Impact of a T Cell-escaping Mutation on the Within-host and Population Dynamics of Influenza A Virus

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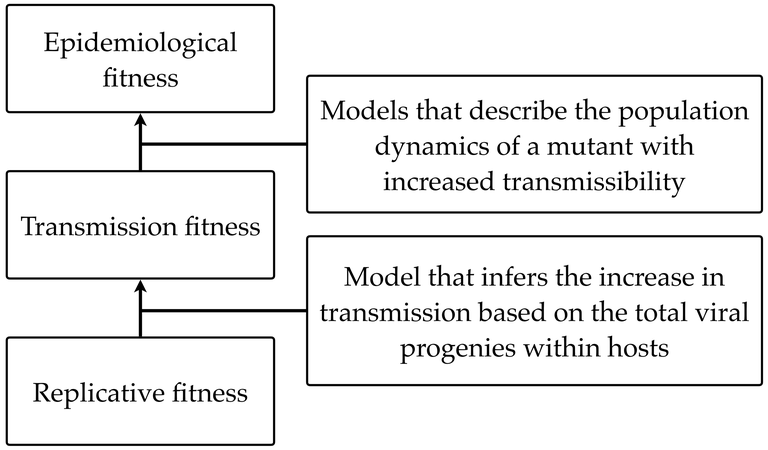
Research Question

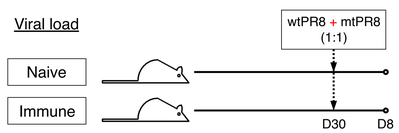
Why are the T cell epitopes of influenza A virus conserved?

- The internal proteins have lower nonsynonymous mutation rates than the surface proteins.
- Within NP and M1, the CD8 T cell epitope region has less sites of $dN/dS > 1$ than nonepitope region.
- Heterosubtypic infection is cross-protected by pre-existing CD8 T cells in mice and human.

Model Framework



Experimental Design



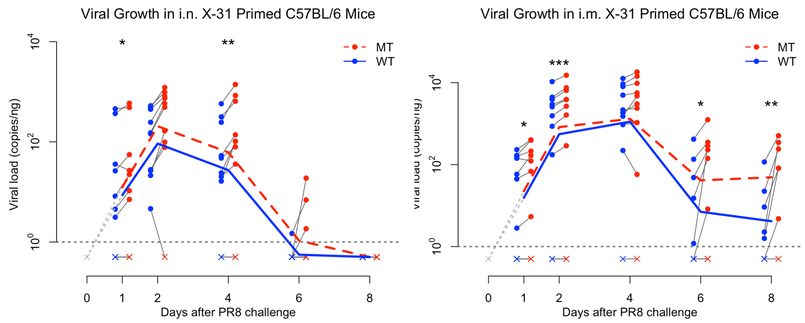
Virus	Subtype	$NP_{366-374}$
HKx31	H3N2	ASNENMETM
wtPR8	H1N1	ASNENMETM
mtPR8	H1N1	ASNEQMETM

Priming	Systemic $NP_{366-374}$	Lung-resident $NP_{366-374}$	Systemic Others	Lung-resident Others
i.n. x31	✔	✔	✔	✔
i.m. x31	✔		✔	

Scientific Contributions & Funding

- Li ZT et al. Quantifying memory CD8 T cell-mediated immune pressure on influenza A virus infection *in vivo*. Submitted to *PLoS Pathogens*. Accessible on BioRxiv.
- Li ZT et al. Why are CD8 T cell epitopes of human influenza A virus conserved? *J Virol*. 2019 Mar 5;93(6):e01534-18.
- This project is funded by the NIH grant U01 HL139483.

Relating replicative fitness and transmissibility



- Transmission fitness is modeled by the area under the log-transformed viral growth curve, i.e.,

$$w = \int_0^T V(t)\,dt \approx \sum_{i=1}^{T} [\log V(t_i) - \log V(t_{i-1})](t_i - t_{i-1})$$

- The increase in transmission of MT is expressed as the ratio of fitness of MT to fitness of WT.

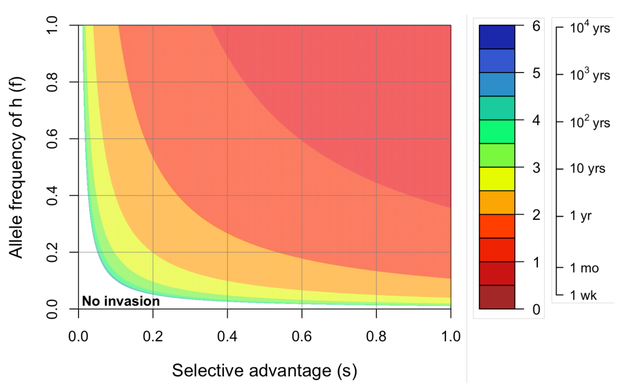
	Early stage (0-4 dpi)	Whole infection course
i.n. x31 B6	0.16 [0.08, 0.23]	0.24 [0.15, 0.35]
i.m. x31 B6	0.05 [0.03, 0.07]	0.20 [0.13, 0.29]

Population Genetics Model

	Host genotypes		
	HH	Hh	hh
Genotype frequency	$(1-f)^2$	$2f(1-f)$	f^2
Relative fitness of WT	1	1	1
Relative fitness of MT	$1-m$	$1-m+Rs$	$1-m+s$

m : Fitness cost
s : Selective advantage
R : Heterozygous effect
f : Allele frequency of h

$$q_t = \frac{q_{t-1}K}{(1-q_{t-1}+q_{t-1}K)} \Rightarrow \frac{q_t}{1-q_t} = K^t\left(\frac{q_0}{1-q_0}\right)$$

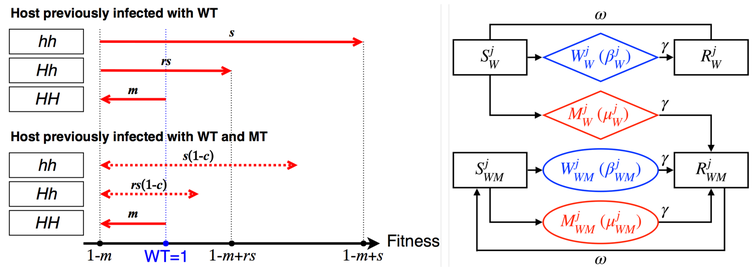


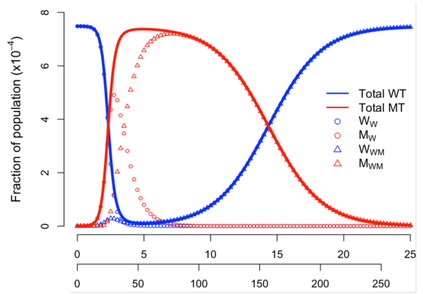
Epidemiological Model

Escaping mechanisms

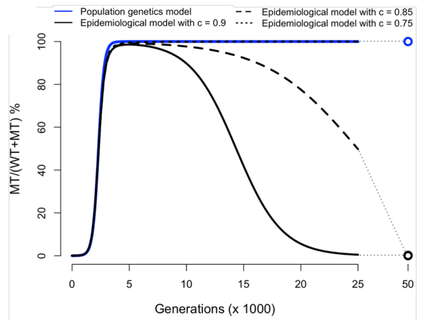
1. Mutation abrogates peptide-MHC binding.
2. Conformation change prevents TCR recognition.

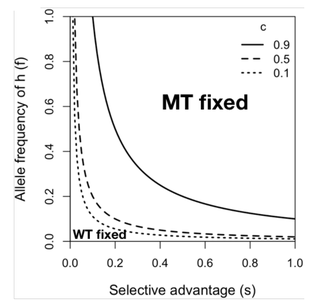
Compensatory immunity may be induced by the MT infection and decreases the selective advantage.





S	Susceptible
I	Infective
R	Recovered
β_{WW}	Transmission rate of I_{WW} (0.4/day)
γ	Recovery rate (0.25/day)
ω	Drifting rate (0.0027/day)





Conclusion

1. In mouse, escaping from an immunodominant CD8 T cell response confers ~25% of advantage. Lung T_{RM} may be the primary driver of immune pressure.
2. If invasion depends entirely on selection, it will take 5 to 10 years for the mutant to reach 50% prevalence. Furthermore, compensatory immunity may render the invasion transient.
3. Therefore, the small selection pressure and MHC polymorphism may explain the conservation of T cell epitopes of IAV, in addition to functional constraint.