Adaptive immunity: why some microbes have it others don't

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***Short Abstract* — CRISPR-Cas is an adaptive immune system found in 90% of archaea but only 40% of bacteria. To understand why 60% of bacteria lack CRISPR-Cas, we built a quantitative genetic model of virus-host coevolution. The model weighs CRISPR-Cas' immunological benefit against its parameterized fixed cost, determining prevalence through a cost-benefit analysis. Strikingly, model results capture viral mutation thresholds above which CRISPR is purged from hosts due to an inability to keep pace with viral diversity. With bioinformatic data suggesting that viral mutation rates are increased in bacterial viruses, our results offer a compelling explanation for CRISPR's relative rarity in bacteria.**

***Keywords* — CRISPR, coevolution.**

I. Background & Purpose

Faced with rapidly diversifying pathogens, single-celled bacteria and archaea have evolved striking immunological adaptability [1,2]. The microbial adaptive immune system is termed Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated genes (CRISPR-Cas). CRISPR-Cas loci can serially incorporate short DNA sequences from invading viruses and plasmids. Once transcribed, CRISPR-acquired sequences destroy cognate viral and plasmid DNAs in subsequent genomic invasions, providing highly specific immunological memory [2,3].

Because CRISPR-Cas offers adaptive immune memory against omnipresent lytic viruses, we wondered why 50% of bacteria lack CRISPR-Cas loci [2]. In contrast, 90% of archaea have CRISPR-Cas. Importantly, CRISPR-Cas is found on mobile plasmids and is widely distributed across prokaryotes. With barriers to CRISPR-Cas' acquisition unlikely, we probed how its selective benefit changes.

II. Methods and Results

We hypothesized that differing environments could drive the bacterial-archaeal dichotomy in CRISPR-Cas prevalence. In particular, sequenced bacteria are often mesophilic, with sequenced archaea commonly thermophilic. Compiling a representative sample of 389 prokaryotic species, we found that 46% of the 300 mesophilic bacteria had CRISPR-Cas, while 89% of the 45 thermophilic bacteria had CRISPR-Cas. Thus, most bacteria appeared to lack CRISPR-Cas, because, unlike archaea, most bacteria were mesophilic [4].

Thermophilic viruses have been predicted to have depressed mutation rates, due to limits on protein stability at high temperatures [5]. We next hypothesized that reduced viral mutation rates select for CRISPR-Cas by increasing the fraction of viruses targeted by each acquired sequence. To test whether CRISPR-Cas' prevalence in fact increases with a decreased (i.e., thermophilic) viral mutation rate, we built a population genetic model of virus-CRISPR coevolution. The model allows prokaryotes with CRISPR-Cas to serially acquire immunogenic viral sequences while simultaneously allowing lytic viruses to mutate targeted regions. To compete CRISPR+ and CRISPR- host populations, the model assumes a parameterized fixed cost to hosts possessing CRISPR-Cas. Natural selection is a cost-benefit analysis: CRISPR's immune benefit is continually weighed against its cost. Running the model across parameter space reveals striking phase transitions in which CRISPR-Cas is lost from hosts as the viral mutation rate is increased above a cost-dependent threshold. This extinction of CRISPR occurs whatever the CRISPR-Cas adaptation rate [4].

III. Conclusion

At a simple level, our results show that CRISPR-Cas' immunological memory is wasteful when hosts are unlikely to see the same viral sequences twice. More generally, these results suggest a fundamental limit on the adaptability of organisms that rely on sensors to directly evolve in response to environmental stochasticity [6].

Acknowledgements: This work was funded by NIH grant AI072360 (MSG) and intramural NIH funding (EVK).

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