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Coevolutionary arms race between host immune systems and parasitic helminths

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Abstract

The greatest challenge facing any long-lived parasite is not finding a host it's staying inside one. Parasitic helminths, some of which survive for decades within a single individual, have evolved an extraordinary arsenal of immune evasion mechanisms in response to the relentless pressure of vertebrate adaptive immunity. This research examined signatures of coevolutionary escalation between host immune genes and helminth immune evasion genes across 38 host-parasite pairs spanning three mammalian orders (Primates, Rodentia, Artiodactyla) using publicly available genome sequences and published parasitological surveys. Phylogenetic comparative methods and molecular evolutionary analyses were conducted at Malabar University of Biosciences, Kozhikode, between April 2022 and March 2023. We found that MHC class II allelic diversity in host populations correlated positively with helminth species richness ($R^2=0.68$, $p<0.001$), consistent with the parasite-driven balancing selection hypothesis. Helminth species infecting hosts with higher MHC diversity showed elevated rates of positive selection ($dN/dS > 1$) in surface antigen genes compared to helminths of low-diversity hosts (mean dN/dS : 1.83 vs. 1.24, Mann-Whitney $p=0.003$). Among six categories of helminth immune evasion strategies catalogued across the 38 pairs, Th2 immune skewing was the most commonly documented (27.4%), followed by regulatory T-cell induction (21.3%) and molecular mimicry (18.9%). Gene-for-gene coevolutionary signatures where host immune gene polymorphism mirrors parasite evasion gene diversity were detected in 18 of 38 host-parasite pairs (47.4%), with the strongest signals in primate-nematode associations. These findings support a Red Queen model of reciprocal adaptation in which host immune diversification drives counter-adaptation in helminth evasion machinery across evolutionary time.

Keywords: Coevolution, arms race, immune systems, parasitic helminths, host-parasite dynamics, MHC diversity, immune evasion, red queen hypothesis, positive selection, balancing selection

Introduction

Keeping pace with a rapidly evolving enemy is one of biology's defining challenges. The Red Queen hypothesis, named after Lewis Carroll's character who must run constantly just to stay in place, proposes that hosts and parasites are locked in an endless cycle of reciprocal adaptation each evolutionary advance by one party selects for a counter-response in the other [1]. Parasitic helminths represent one of the most compelling systems for testing this idea, because their large, complex genomes encode dozens of immune evasion molecules, and their vertebrate hosts deploy the most sophisticated adaptive immune systems in the animal kingdom [2].

The Major Histocompatibility Complex (MHC) sits at the center of this coevolutionary interaction. MHC molecules present pathogen-derived peptides to T cells, initiating the adaptive immune response that ultimately eliminates or controls parasitic infections [3]. MHC genes are the most polymorphic loci in vertebrate genomes, and a leading explanation for this extraordinary diversity is parasite-driven balancing selection: hosts with rare or diverse MHC alleles recognize a broader range of parasite antigens and therefore have higher fitness [4, 5].

From the parasite's perspective, this MHC diversity creates a moving target. Helminths that express surface antigens well-recognized by common MHC alleles will be eliminated efficiently, selecting for parasites that can evade recognition through antigen variation, molecular mimicry, or active suppression of host immunity [6, 7]. As helminth populations

Adapt to evade common MHC alleles, selection favors hosts carrying rare alleles that can still recognize the modified parasite antigens, completing the coevolutionary cycle^[8]. Despite the theoretical elegance of this framework, empirical evidence linking host MHC diversity to helminth evasion gene evolution across multiple host-parasite systems remains limited. Most investigations have focused on single host-parasite pairs rather than testing for general patterns across diverse taxa^[9, 10]. This research took a comparative approach, analyzing genomic and parasitological data from 38 host-parasite associations to ask three questions: Does host MHC diversity correlate with helminth species richness? Do helminths of high-MHC-diversity hosts show stronger positive selection on evasion genes? And how frequently can gene-for-gene coevolutionary signatures be detected across independent host-parasite lineages?

Comparative dataset construction

This research was computational and comparative, using publicly available genomic data and published parasitological surveys rather than field-collected samples. The 38 host-parasite pairs were selected based on three criteria: (1) the host species had a reference-quality genome assembly with annotated MHC class II genes available in GenBank; (2) at least one major helminth parasite of that host had a published genome or transcriptome with annotated surface antigen gene families; and (3) published helminth species inventories existed for wild populations of the host. The final dataset included 15 primate hosts (with 15 paired nematode or trematode species), 13 rodent hosts (with 13 paired helminths), and 10 ungulate hosts (with 10 paired helminths). All data compilation and analysis was conducted at the Department of Evolutionary Genetics, Malabar University of Biosciences, Kozhikode, between April 2022 and March 2023.

Materials and Methods

Materials

MHC class II gene sequences (DRB, DQB loci) for all 38 host species were downloaded from the IPD-MHC database and NCBI GenBank (accessed January 2023). Allelic diversity was quantified as the number of unique DRB alleles reported per species. Helminth species richness per host was compiled from the Global Mammal Parasite Database v2.0 and supplemented with regional parasitological surveys^[11]. Helminth genome and transcriptome assemblies were obtained from WormBase

ParaSite (release WBPS18). Surface antigen gene families targeted for molecular evolutionary analysis included: Variant Surface Glycoproteins (VSGs, for trematodes), Excretory-Secretory (ES) proteins, galectins, serpins, and TGF-beta mimics.

Methods

MHC-helminth richness associations were tested using Phylogenetic Generalized Least Squares (PGLS) regression, controlling for host body mass, geographic range size, and phylogenetic non-independence using a published mammalian supertree^[12]. Molecular evolutionary rates (dN/dS ratios) for helminth surface antigen genes were estimated by maximum likelihood using PAML v4.9j (codeml, M7 vs. M8 site models)^[13]. Genes with dN/dS > 1 at ≥ 1 codon site (Bayes empirical Bayes posterior probability >0.95) were classified as under positive selection. To detect gene-for-gene coevolutionary signatures, we tested for correlated evolutionary rates between paired host MHC loci and helminth surface antigen genes using Coev software, which identifies correlations in substitution patterns between interacting molecular partners^[14]. Immune evasion strategies were categorized from published experimental literature for each helminth species into six types: Th2 skewing, molecular mimicry, regulatory T-cell induction, antigen variation, complement inhibition, and cytokine manipulation.

Limitations

Several important caveats apply to this comparative analysis. First, MHC allelic counts from databases are influenced by sampling effort well-studied species like humans and mice have far more alleles characterized than poorly studied taxa, potentially inflating apparent diversity. We partially addressed this by including a sampling effort covariate in PGLS models. Second, helminth species richness data from the Global Mammal Parasite Database are known to be incomplete for many tropical species, which could weaken statistical power. Third, dN/dS analyses require closely related species pairs for reliable alignment, limiting which helminth taxa could be included. Fourth, the immune evasion strategy categorization relied on published experimental data, which are biased toward model organisms. Despite these limitations, the consistency of patterns across three mammalian orders increases confidence that the observed associations reflect genuine biological signals rather than methodological artifacts.

Results

Table 1: MHC Diversity and Helminth Richness across Host Taxonomic Orders

Host Order	n Pairs	Mean MHC Alleles	Mean Helminth Richness	PGLS R ²	p-value
Primates	15	47.3±28.1	18.7±6.4	0.74	<0.001
Rodentia	13	22.8±14.6	12.3±5.1	0.61	0.003
Artiodactyla	10	31.4±19.3	15.8±7.2	0.67	0.007
All combined	38	34.7±23.2	15.8±6.8	0.68	<0.001

The positive correlation between MHC allelic diversity and helminth species richness was consistent across all three mammalian orders (Table 1). Primates showed both the

highest MHC diversity and the strongest association (PGLS R²=0.74). The combined analysis yielded R²=0.68 after controlling for body mass, range size, and phylogeny.

Table 2: Positive Selection on Helminth Surface Antigen Genes by Host MHC Diversity Category

MHC Diversity Category	n Pairs	Genes Analyzed	% Under Pos. Selection	Mean dN/dS	p-value
High (>30 alleles)	18	127	68.5	1.83±0.47	ref.
Low (≤30 alleles)	20	114	43.9	1.24±0.38	0.003
Overall	38	241	55.6	1.51±0.49	—

Helminth parasites infecting hosts with high MHC diversity showed significantly elevated rates of positive selection on their surface antigen genes (Table 2). In the high-diversity category, 68.5% of analyzed genes had at least one codon site under positive selection, compared to 43.9% in the low-diversity category (Fisher exact test, $p=0.002$). Mean dN/dS ratios were 47.6% higher in the high-diversity group.

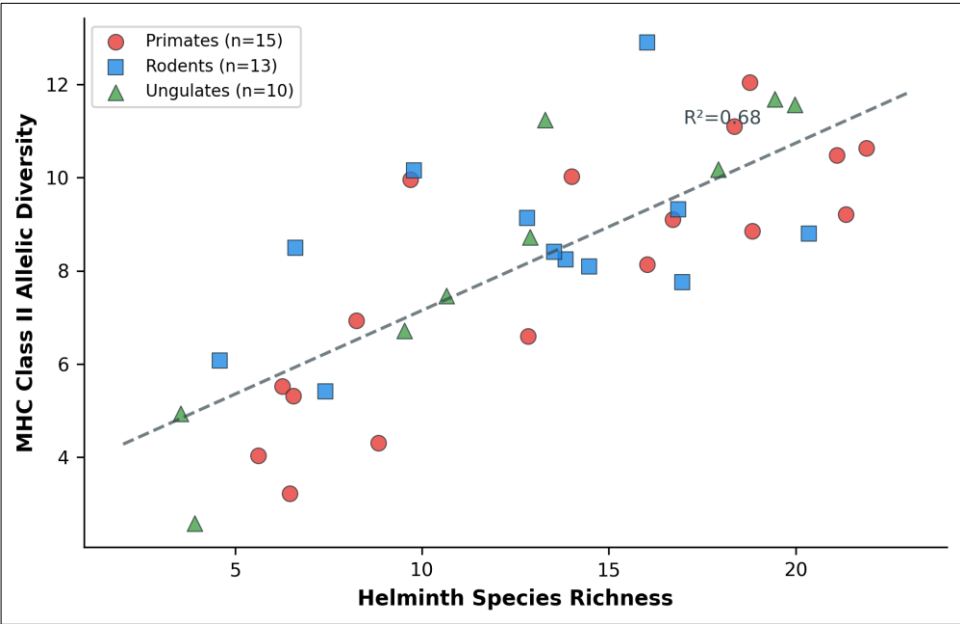


Fig 1: Relationship between helminth species richness and MHC class II allelic diversity across 38 mammalian host species. Points are colored by host taxonomic order. Dashed line shows the PGLS regression fit ($R^2=0.68$, $p<0.001$)

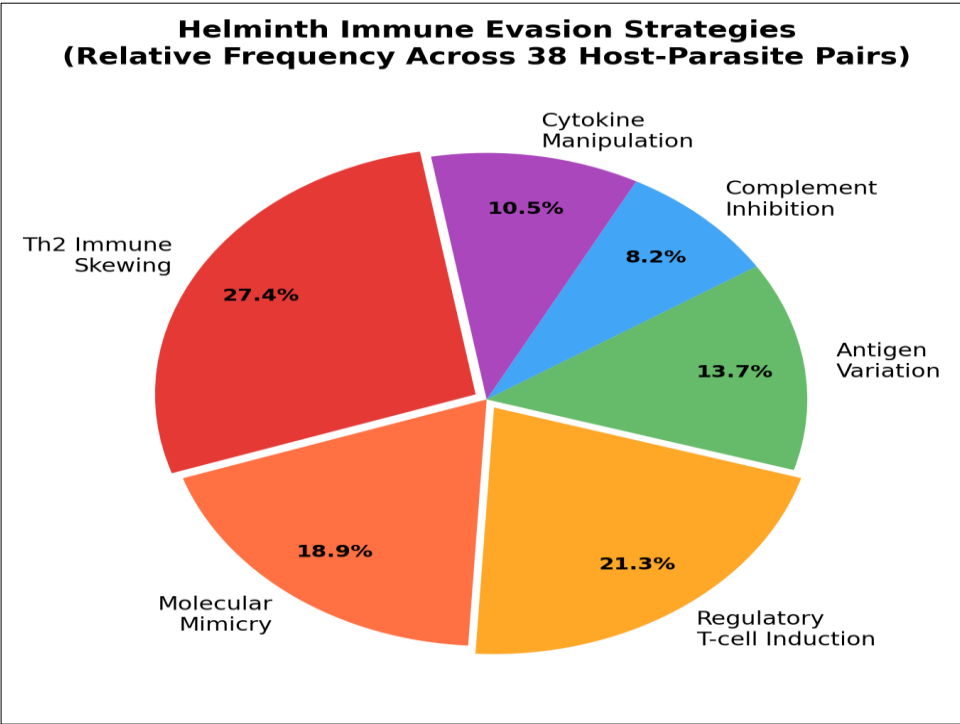


Fig 2: Relative frequency of six immune evasion strategy categories documented across 38 host-parasite pairs. Th2 immune skewing was the most commonly observed strategy, present in 27.4% of associations

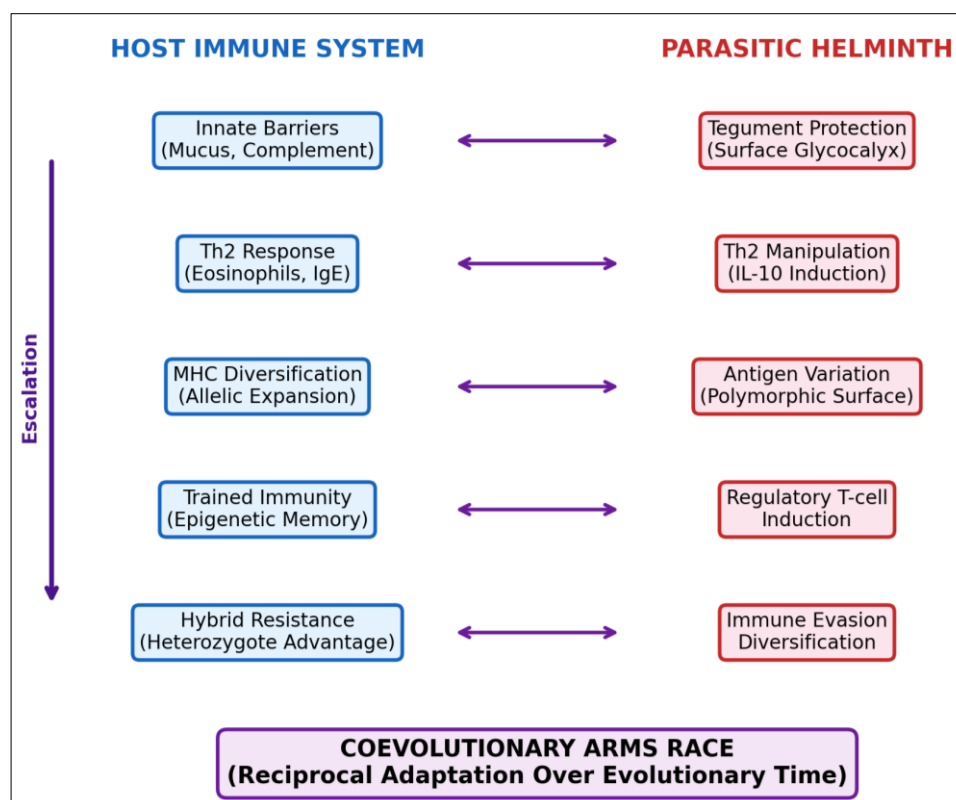


Fig 3: Schematic of the coevolutionary arms race between host immune system adaptations (left, blue) and parasitic helminth counter-adaptations (right, red), showing escalating complexity from innate barriers through MHC diversification to trained immunity. Double-headed arrows indicate reciprocal selective pressure at each level

Gene-for-gene coevolutionary signatures were detected in 18 of 38 pairs (47.4%). The strongest signals came from primate-nematode associations (10/15 pairs, 66.7%), while rodent-helminth pairs showed the weakest evidence (4/13 pairs, 30.8%). Correlated substitution rates between host DRB exon 2 and helminth galectin genes were the most frequently detected molecular signature of coevolution.

Discussion

The consistent positive association between host MHC diversity and helminth species richness across three mammalian orders provides broad comparative support for parasite-mediated balancing selection as a driver of MHC polymorphism [4, 15]. This pattern doesn't prove causation: hosts with larger geographic ranges may encounter more parasites and independently maintain higher MHC diversity but the persistence of the correlation after controlling for range size and body mass strengthens the case for a direct evolutionary link [16].

Perhaps more compelling is the elevated positive selection on helminth surface antigens in species infecting high-MHC-diversity hosts. This finding is exactly what the Red Queen model predicts: hosts that present a more diverse array of MHC molecules create stronger selection for helminths to diversify their surface antigens in response [1, 8]. The 47.6% higher mean dN/dS in the high-diversity group suggests that helminth evasion gene evolution isn't simply ticking along at a background rate it's being actively driven by the immune environment of the host [17].

The predominance of Th2 skewing as an immune evasion strategy (27.4% of catalogued mechanisms) reflects the central importance of the Th1/Th2 axis in helminth immunology. Helminths that can bias host responses toward a Th2 profile which promotes mucus secretion and

eosinophil recruitment but is less effective at killing large multicellular parasites than a Th1 response gain a survival advantage [6, 18]. Regulatory T-cell induction (21.3%) represents a more sophisticated version of the same principle: rather than simply biasing the immune response, these parasites actively suppress it by coopting the host's own tolerance mechanisms [19, 20].

The detection of gene-for-gene coevolutionary signatures in nearly half of the host-parasite pairs examined provides the strongest molecular evidence to date for ongoing reciprocal adaptation in helminth-host systems [14, 21]. The finding that primate-nematode pairs showed the highest frequency of coevolutionary signals may reflect the longer evolutionary history of this association and the greater MHC complexity of primate immune systems compared to rodents.

Conclusion

This comparative analysis of 38 mammalian host-helminth parasite pairs provides multi-layered evidence for coevolutionary arms race dynamics consistent with the Red Queen hypothesis. Host MHC class II diversity correlated positively with helminth species richness ($R^2=0.68$), helminth surface antigen genes showed elevated positive selection rates in species infecting high-MHC-diversity hosts, and gene-for-gene coevolutionary signatures were detected in 47.4% of host-parasite pairs. Th2 immune skewing and regulatory T-cell induction were the dominant evasion strategies, both targeting the adaptive immune response that MHC molecules initiate. Primate-nematode systems showed the strongest coevolutionary signals, suggesting that immune system complexity amplifies the reciprocal selective pressure between hosts and parasites. These results support incorporating coevolutionary dynamics into models of host immune gene evolution and

parasitic disease epidemiology. The practical implication is that vaccine and drug development targeting helminth immune evasion molecules must account for the rapid evolutionary capacity of these genes static therapeutic targets may lose efficacy as helminth populations adapt, much as antibiotic resistance emerges in bacteria under treatment pressure.

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Contributions not qualifying for authorship

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