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IMMUNE EVASION AND THE EVOLUTION OF MOLECULAR MIMICRY IN PARASITES

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Parasites that are molecular mimics express proteins which resemble host proteins. This resemblance facilitates immune evasion because the immune molecules with the specificity to react with the parasite also cross-react with the host's own proteins, and these lymphocytes are rare. Given this advantage, why are not most parasites molecular mimics? Here we explore potential factors that can select against molecular mimicry in parasites and thereby limit its occurrence. We consider two hypotheses: (1) molecular mimics are more likely to induce autoimmunity in their hosts, and hosts with autoimmunity generate fewer new infections (the "costly autoimmunity hypothesis"); and (2) molecular mimicry compromises protein functioning, lowering the within-host replication rate and leading to fewer new infections (the "mimicry trade-off hypothesis"). Our analysis shows that although both hypotheses may select against molecular mimicry in parasites, unique hallmarks of protein expression identify whether selection is due to the costly autoimmunity hypothesis or the mimicry trade-off hypothesis. We show that understanding the relevant selective forces is necessary to predict how different medical interventions will affect the proportion of hosts that experience the different infection types, and that if parasite evolution is ignored, interventions aimed at reducing infection-induced autoimmunity may ultimately fail.

KEY WORDS: **Antigenicity, autoimmunity, clonal deletion, immunopathology, pathogen, within-host.**

Parasites that are molecular mimics express proteins which resemble host proteins (also termed "self proteins"). There are numerous examples of parasites that mimic human cells (Oldstone 1998) including *Campylobacter jejuni*, which causes food poisoning and mimics a human ganglioside (Ang et al. 2004), human cytomegalovirus, which infects 10% of infants under 6 months age (Landolfo et al. 2004) and mimics endothelial receptors (Michelson 2004) and the protozoan *Trypanosoma cruzi*, which mimics myocardial cells (Petkova et al. 2000). Parasites that are mimics are likely to evade the immune system because the host is averse to harming itself. Autoimmunity refers to host tissue damage caused by the host immune system. To the extent that mimicking parasites are structurally similar to self-proteins, the immunological processes that protect the host against autoimmunity leave mimics protected from an immune response as well. The process that prevents autoimmunity is clonal deletion. During clonal deletion lymphocytes are tested against self-proteins, and highly self-reactive lymphocytes are destroyed as a means of preventing an immune response to self (Goodnow et al. 2005; Hogquist et al. 2005). Therefore, parasites that are molecular mimics presumably obtain a fitness advantage over their non-mimicking counterparts through the evasion of an immune response (Damain 1964; Young et al. 2002; Elde and Malik 2009; Wölfl and Rutebemberwa 2008).

Although these benefits of mimicry seem clear (Begon et al. 1990, p. 963; Elde and Malik 2009), the costs of such mimicry are

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less obvious. Such costs presumably exist, however, because there are a great number of parasite species that have not evolved to be molecular mimics. Although hypotheses for why mimicry does not evolve have been presented, understanding why such mimicry is not a ubiquitous feature of most organisms is a long-standing, and unanswered, problem in evolutionary ecology (Ruxton et al. 2004). Our goal is to use a mathematical model to explore two hypotheses for how molecular mimicry is selected against in parasites.

There exists substantial evidence that parasites which are molecular mimics are more likely to induce an autoimmune response in their host (Kirchoff 1993; Appelmelk et al. 1996; Kohm et al. 2003; Ang et al. 2004; Rahbar et al. 2006; Dobbs et al. 2008). Our first hypothesis is therefore that hosts which develop an autoimmune response are less productive for the parasite because they produce fewer new infections. Thus, the risk of inducing autoimmunity selects against mimicry in parasites (the "costly autoimmunity hypothesis"; Damain 1964). The autoimmune response occurs because, although clonal deletion in hosts removes a large number of self-reactive lymphocytes, some self-reactive lymphocytes nevertheless remain in circulation (Wing 2006). These lymphocytes might then be activated by parasites that are molecular mimics and cross-react with self tissues, causing autoimmunity (von Herrath and Oldstone 1995, 1996; Ohashi 1996; Hausmann and Wucherpfennig 1997).

The second hypothesis is that the shape of the parasite's proteins is constrained, such that becoming a mimic necessarily entails a compromise in other aspects of parasite function (the "mimicry trade-off hypothesis"). There is evidence for such a trade-off in influenza A, for example, because the viral nucleoprotein that is targeted by cytotoxic T cells also plays a critical role in viral replication (Docherty et al. 2006; Ye et al. 2006). Consequently, there might be little scope for modifying this nucleoprotein to evade the immune response without also compromising its function in viral replication and transmission.

To determine the conditions under which each of the above hypotheses might provide a plausible explanation for the lack of mimicry in parasites, we first construct a general mathematical model describing the epidemiological dynamics of parasite spread (section "Model"). We then determine the evolutionarily stable level of parasite mimicry under each hypothesis, and these results are used to determine if there are characteristics of protein expression or predictions specific to each hypothesis that allow us to distinguish between them (sections "General properties of the parasite ESS" and "Selection for mimicry"). Finally, we consider the potential consequences of certain public health interventions on the evolution of parasite mimicry and on the occurrence of the different types of host disease (section "The effect of medical interventions on the evolutionarily stable parasite phenotype and the types of infections that are induced in the host").

Model

To derive our mathematical model, we begin by describing the between-host epidemiological spread of a parasite. Different parasite genotypes are assumed to correspond to different parasite phenotypes and are represented in the epidemiological model as different parameter values. We derive an expression for parasite fitness as it depends on the between-host spread (section "Epidemiological dynamics"). Next, we formalize each of our two hypothesis in terms of between-host spread and parameters corresponding to the within-host reproduction of the parasite (section "Formalizing the costly autoimmunity and the mimicry trade-off hypotheses"). We then link the within-host and between-host parameters that have been defined (section "Relating the parasite phenotype to the types of infections"), and finally, we derive an expression that quantifies mimicry (section "Defining mimicry"). Definitions of the notation used are provided in Table 1.

EPIDEMIOLOGICAL DYNAMICS

The epidemiological model describes the rate of change in the number of hosts that are susceptible to an infection, S, or that are experiencing one of three different kinds of infectious states (denoted with I, A, and U), or either of two different postinfection states (denoted Z and R; Fig. 1). For the three different types of infectious states, the type of disease that is induced depends on the nature of the interaction between the parasite and the host's immune system. The first type of infection that may occur is an acute infection. An acute infection occurs if lymphocytes effectively react with the parasite, but not with normal host cells (i.e., self). We use I to denote the number of these infections. The second type of infection is one that leads to autoimmune disease. This can occur if lymphocytes react with both the parasite and with self (i.e., cross-react). We use A to denote the number of hosts that experience an infection that is cross-reactive and may lead to autoimmunity. The third type of infection is an uncontrolled infection. An uncontrolled infection can occur if the immune response is ineffective against the parasite, and we use U to denote the number of such infections in the population.

Hosts that experience an acute infection or an infection that may lead to autoimmune disease may clear the parasite, thus becoming noninfectious. We use R to denote the number of hosts that are postacute infection and no longer infectious or susceptible, and we use Z to denote the number of hosts that have autoimmunity, but are no longer infectious. It is assumed that hosts that develop autoimmunity cannot be reinfected, because the continued immune response to self prevents the establishment of the parasite. We use a general model formulation where, following an acute infection, hosts may either return to the susceptible state (SIS) or recover (SIR). In applying this model to a particular parasite species, either the SIS or the SIR formulation will be

Table 1. List of notation.

Characteristics of the parasite	
α_j	The probability the parasite activates a type j lymphocyte.
$\vec{\alpha}$	A vector of length k with elements given by the α_j's.
z_j	The contribution that a protein targeted by a type j lymphocyte makes to parasite replication.
$\rho = \text{corr}(\alpha_j, \Delta_j)$	Mimicry. If $\rho > 0$ a parasite is then classified as is a mimic.
$\lvert\vec{\alpha}\rvert = \frac{1}{k}\sum_{j=1}^{k}\alpha_j$	Antigenicity, i.e., the potential for a parasite to elicit an immune response.
$f(\vec{\alpha}) = \sum_{j=1}^{k}\alpha_j z_j$	The parasite replication rate.
Characteristics of host immunology	
Δ_j	The self-reactivity of a type j lymphocyte.
ω_j	The frequency of type j lymphocytes.
r	The total number of lymphocytes that the parasite is tested against.
Jointly determined immunological param	
$\bar{\alpha} = \sum \alpha_j \omega_j$	The probability that a randomly selected lymphocyte reacts to the parasite.
$\overline{\alpha\Delta} = \sum \alpha_j \Delta_j \omega_j$	The probability that a randomly selected lymphocyte cross-reacts.
$q = 1 - (1 - \bar{\alpha})^r$	The probability of an effective immune response.
$p = (1 - (1 - \overline{\alpha\Delta})^r)/q$	The probability of an autoimmune disease given an effective immune response.
Epidemiological parameters	
R_i	The number of secondary infections generated by a host with a disease of type i.
$\beta_i = \beta(\cdot)\nu_i$	The transmission rate for a disease of type i. The parameter ν_i is a scalar that reflects the effect of the type of disease on the transmission rate.
$\beta(\cdot)$	The transmission rate of the parasite as it depends on the parasite replication rate.
$\mathcal{R}_i = R_i/\beta(\cdot)$	A factor that multiplies $\beta(\cdot)$ to give R_i.
$\phi = 1 - \frac{R_U - R_I}{R_U - R_A}$	The relative cost of autoimmunity.
$\psi = \frac{R_U - R_I}{R_U}$	The relative cost of an acute infection.
$\tau = 1 - \frac{1-(1-\omega_k c)^r}{1-(1-\omega_1 c)^r}$	The relative rarity of highly self-reactive lymphocytes.

more appropriate, but these different cases can be treated within the general framework by setting the appropriate rate parameters equal to 0.

Given an infection, let q be the probability of an effective immune response to the parasite, and let p be the probability of autoimmunity given that an immune response occurs. Then, the above assumptions can be embodied in the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= -\Lambda S + b_S S + b_I I + b_A A + b_U U + b_R R + b_Z Z \\
&\quad + \gamma_I I + \gamma_A A - dS, \\
\frac{dI}{dt} &= \Lambda S(1-p)q - v_I I - u_I I - \gamma_I I - dI, \\
\frac{dA}{dt} &= \Lambda S p q - v_A A - u_A A - \gamma_A A - dA, \\
\frac{dU}{dt} &= \Lambda S(1-q) - v_U U - dU, \\
\frac{dR}{dt} &= u_I I - dR, \\
\frac{dZ}{dt} &= u_A A - v_Z Z - dZ, \qquad (1)
\end{aligned}$$

where $\Lambda = \beta_A A + \beta_I I + \beta_U U$ is the force of infection, b_i is the birth rate, γ_i is the rate of becoming noninfectious and susceptible, u_i is the rate of becoming noninfectious (and either recovered or with an autoimmune disease), v_i is the disease-induced mortality rate for hosts in the state $i \in \{S, I, A, U, Z, R\}$, and the background mortality rate is d (Fig. 1).

Our model is structured such that given an infection, one of an acute infection, autoimmunity, or an uncontrolled infection, will occur. This is an appropriate formulation given that our objective is to understand parasite evolution rather than to faithfully recreate the epidemiology of modern day parasites. In other words, it is irrelevant if uncontrolled infections are rare among extant parasite species, because we are interested in considering all of the phenotypes that are theoretically possible. Nevertheless, there are several examples of extant parasite species that support our model formulation (Table 2).

From the model of the epidemiological dynamics, we determine the parasite evolutionarily stable strategy (ESS). This is a parasite phenotype that, if it becomes established in the host population, cannot be invaded by another phenotype given that the new phenotype is rare (Maynard Smith 1982). The probabilities p and q depend jointly on characteristics of the host and the parasite, but for this analysis we assume that host phenotypes are fixed on the time scale of parasite evolution, and so we can assume that different parasite phenotypes may result in different values of p and q. If there are two types of parasites present in the population simultaneously (one of which is rare), and these

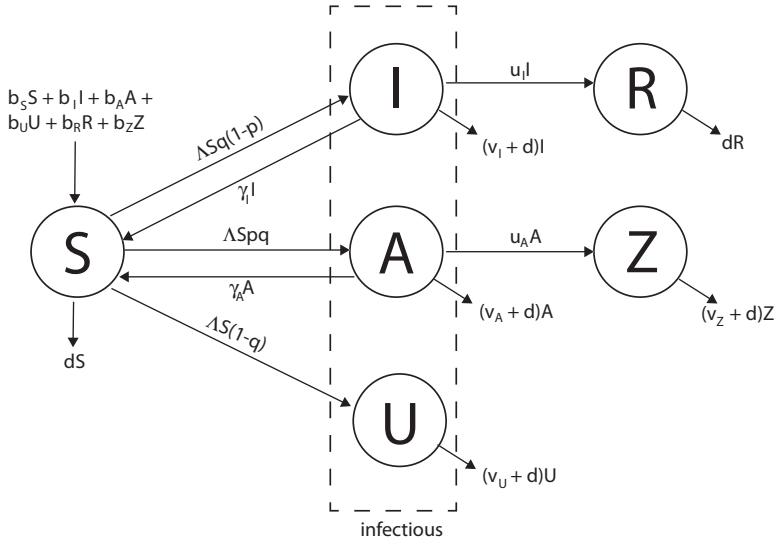

Figure 1. Given an infection susceptible hosts, *S*, will develop one of three types of diseases: an acute infection, *I*, an autoimmune disease, *A*, or an uncontrolled infection, *U*. In each of these three states (*I*, *A*, and *U*), hosts are infectious and may transmit the parasite to susceptible hosts. Hosts with an acute infection either recover (*R*) or become susceptible again. Host with autoimmune disease may clear the parasite then becoming uninfectious but still experiencing autoimmunity (*Z*), or return to the susceptible state. The prevalence of lymphocytes and the types of lymphocytes that are activated by the parasite determines the probability that susceptible hosts enter the *I*, *A*, or *U* state given an infection (see section "Relating the parasite phenotype to the types of infections"). Biological evidence to justify this framework is provided in Table 2.

parasites compete to infect susceptible hosts, then the ESS is the phenotype p and q that maximizes,

$$R_0 = R_I(1-p)q + R_A pq + R_U(1-q), \tag{2}$$

(see Appendix A of Supporting Information for the derivation). This quantity is the expected number of secondary infections that the host generates while infected with a parasite of a particular phenotype. Here R_i is the expected number of secondary infections generated by a host with an infection of type i, where

$$R_I = \frac{\beta_I}{v_I + d + \gamma_I + u_I}, \qquad R_A = \frac{\beta_A}{v_A + d + \gamma_A + u_A},$$
$$\text{and} \quad R_U = \frac{\beta_U}{v_U + d}.$$

Understanding parasite evolution requires identifying trade-offs that exist between different parameters in the expression for R_0. Next, we will explicitly characterize the dependence of p, q, and the R_is on characteristics of the host immune system and properties of the proteins expressed by parasites, to mechanistically characterize the interrelatedness of the parameters in eq. (2).

FORMALIZING THE COSTLY AUTOIMMUNITY AND THE MIMICRY TRADE-OFF HYPOTHESES

The parasite phenotype

Each parasite genotype is assumed to correspond to a distinct parasite phenotype. Parasite phenotypes affect the probability of inducing autoimmunity, an acute infection, or an uncontrolled infection through the expression of different types of proteins that are broken down into antigens and presented to immune system molecules (i.e., lymphocytes). Lymphocytes are indexed by j from 1 to k, where this index is chosen so that more highly self-reactive lymphocytes have higher values of j. This indexing is needed to distinctly identify each different lymphocyte, and the assumption that higher values of j correspond to higher values of self-reactivity is made so that some meaning can be taken from the indexing, rather than using an arbitrary labeling scheme.

Each parasite phenotype activates different lymphocytes with different probabilities. The parasite phenotype is $\vec{\alpha}$, a vector whose elements, $0 \leq \alpha_j \leq 1$, are the probabilities of activating the different types of lymphocytes, j. All else equal, a parasite's within-host reproductive success will always increase with reduced reactivity. Thus, natural selection will tend to favor those parasites with as little reactivity as possible (i.e., parasites whose phenotype $\vec{\alpha}$ has elements that are as small as possible), however, many parasites have not evolved such complete mimicry and our goal is to explore potential reasons why. The costly autoimmunity hypothesis is based on the idea that constraints exist among the elements of $\vec{\alpha}$. The mimicry trade-off hypothesis is based on the idea that there is a trade-off between low reactivity (i.e., having all elements of $\vec{\alpha}$ be small) and other aspects of parasite function.

Both the costly autoimmunity hypothesis and the mimicry trade-off hypothesis can be formulated using a common modeling framework. To do so, let $f(\chi(\vec{\alpha}), \theta_i)$ represent the average

Table 2. **The model assumes that a parasite may generate any of three different possible diseases (Fig. 1). Biological evidence justifying this framework is provided for four different parasites. An acute infection occurs when parasite proliferation is limited by the immune system. Autoimmunity occurs when the lymphocytes activated by a parasite cross-react and destroy human tissues. Uncontrolled infections are defined by the absence of an immune response to the parasite.**

Parasite	Acute infection	Autoimmunity	Uncontrolled infection
Campylobacter jejuni	Gastroenteritis, Asymptomatic (Havelaar et al. 2009)	Guillain Barré, Miller-Fisher Syndrome (Rees et al. 1995; Nachamkin 2002)	In an immunocompromised patient (Johnson et al. 1984)
Human cytomegalovirus	Latent infection shed throughout lifetime, Asymptomatic (Landolfo et al. 2004)	Systemic lupus erythematosus, Crohn's disease and ulcerative colitis (Hrycek et al. 2005; Rider et al. 1997; Chang et al. 2003; Rahbar et al. 2006)	In immunocompromised patients (Landolfo et al. 2004)
Trypanosoma cruzi	None	Chagas' disease (Higuchi et al. 1993; Kirchoff 1993)	Chagas' disease (Tarleton et al. 1999; Tarleton 2001)
Helicobacter pylori	None	Idiopathic Parkinsonism, *H. pylori*-linked autoimmunity, Thyrobocytopenia (Dobbs et al. 2008; Appelmelk et al. 1996; Franchini et al. 2007)	Gastritis, peptic ulcers (Kuipers et al. 1995)

within-host density of the parasite during an infection, as a function of the parasite's replication rate, $\chi(\vec{\alpha})$, and parameters related to the type of infection induced, θ_i. Furthermore, suppose that the between-host transmission rate is an increasing function of average within-host parasite density. This assumption is supported by empirical results (Mackinnon and Read 1999; Fraser et al. 2007; de Roode et al. 2008) and is related to the common transmission-virulence trade-off assumption made in theoretical evolutionary epidemiology (Antia et al. 1994; Alizon et al. 2009). Thus, we define the between-host transmission rate when an infection of type i is induced as,

$$\beta_i = \beta[f(\chi(\vec{\alpha}), \theta_i)], \tag{3}$$

where β_i is a monotonically increasing function of $f(\chi(\vec{\alpha}), \theta_i)$ to reflect the assumption that higher between-host transmission occurs for parasites with higher within-host densities. The two hypotheses can then be viewed, mathematically, as corresponding to different assumptions about the form of the function $f(\chi(\vec{\alpha}), \theta_i)$.

The costly autoimmunity hypothesis

The costly autoimmunity hypothesis is based on an assumption that there are constraints among the elements of $\vec{\alpha}$. In particular, we suppose that the average of the α_j across all lymphocytes must be at least c. Put another way, there is a minimum level of conspicuousness that the parasite must exhibit, and alternative parasite phenotypes differ in terms of *which* lymphocytes they activate. Biologically, this assumption is made because the immune system possesses the potential to respond to almost any antigen (Kindt et al. 2007; p. 12, 111, 248). Mathematically, this hypothesis is modeled by assuming that the parasite's replication rate $\chi(\vec{\alpha})$ is a constant for all values of $\vec{\alpha}$ yielding an average at least as large as c, and 0 otherwise:

$$\chi(\vec{\alpha}) = \begin{cases} c & \text{if } \frac{1}{k}\sum_{j=1}^{k} \alpha_j \geq c \\ 0 & \text{otherwise.} \end{cases} \tag{4}$$

The assumptions, thus far, constrain parasite evolution to prevent the evolution of a parasite that completely evades the immune system. To embody the necessary property that autoimmunity is costly, we additionally require that $R_U > R_I > R_A$. As such, the cost of autoimmunity is that the fewest number of new infections are generated when autoimmunity occurs.

The mimicry trade-off hypothesis

For the mimicry trade-off hypothesis, selection against mimicry occurs because specific proteins contribute to some other aspect of parasite function, and evolving mimicry would compromise functionality in these other respects. For example, known targets of the immune system are a viral nucleoprotein of Influenza A (Docherty et al. 2006) and a component of bacterial flagellum (Hayashi et al. 2001), and failure to express these proteins compromises viral replication (Ye et al. 2006) and bacteria locomotion. Therefore, we assume that the parasite's replication rate, $\chi(\vec{\alpha})$, is given by the function,

$$\chi(\vec{\alpha}) = \frac{1}{k}\sum_{j=1}^{k} \alpha_j z_j. \tag{5}$$

The quantity z_j is the maximum contribution that the parasite antigen targeted by a lymphocyte j could make to the rate of production of new parasites. We assume that this maximum contribution can only be realized when $\alpha_j = 1$ because the immune

system targets proteins that contribute to parasite replication as discussed earlier. For simplicity we assume that a particular protein is either functional or nonfunctional, and therefore, we let z_j be equal to either 0 or 1 for all j. Under the mimicry trade-off hypothesis, the number of secondary infections generated by hosts that have autoimmunity is no different than for hosts that have an acute infection, and so $R_I = R_A$; however, we still assume that $R_U > R_I$ owing to the lack of immune response when an uncontrolled infection occurs. Notice that these assumptions do not imply that greater reactivity leads to greater within-host density per se, but rather that reactivity to certain specific lymphocytes (i.e., those for which z_j is not equal to 0) leads to greater average within-host density because certain specific antigens are necessary for significant parasite replication.

RELATING THE PARASITE PHENOTYPE TO THE TYPES OF INFECTIONS

Upon infection we assume that a parasite is tested against a subset of r lymphocytes, where r_j is the number of type j lymphocytes in this subset, and $r = \sum_{j=1}^{k} r_j$. Before an infection, many different unactivated lymphocytes circulate in the lymphatic system and the blood, and these lymphocytes have a particular specificity which is indexed by j. The probability that a type j lymphocyte reacts with the infecting parasite and is activated is α_j.

Unactivated circulating lymphocytes may also be activated by proteins derived from self. The probability that a type j lymphocyte is activated by a self protein is Δ_j. Although the self-reactivity of a type j lymphocyte may be any value between zero and one, for simplicity we assume that the lymphocytes of all different specificities are evenly spaced such that,

$$\Delta_j = \frac{j-1}{k-1} \quad \text{for } j \text{ from 1 to } k \text{ where } k \text{ is large.} \tag{6}$$

Lymphocytes that are highly self-reactive are less common, and so ω_j, the expected fraction of lymphocytes that are of the type j, is a decreasing function of Δ_j with $\sum_{j=1}^{k} \omega_j = 1$. The composition of the subset of lymphocytes that the parasite is tested against is given by the multinomial distribution with the parameters ω_j and r. We assume that the probability of an uncontrolled infection, $1-q$, is the probability that none of the r lymphocytes that the parasite is tested against are activated by the parasite. From the multinomial theorem, this is calculated as,

$$\begin{aligned} 1-q &= \sum_{r_1,r_2,\ldots,r_k} \frac{r!}{r_1!\cdots r_k!} \omega_1^{r_1}\cdots\omega_k^{r_k}(1-\alpha_1)^{r_1}\cdots(1-\alpha_k)^{r_k}, \\ &= \left(\sum_{j=1}^{k} \omega_j(1-\alpha_j)\right)^r = (1-\bar{\alpha})^r, \end{aligned} \tag{7}$$

where

$$\bar{\alpha} = \sum_{j=1}^{k} \alpha_j \omega_j, \tag{8}$$

is the probability that a randomly selected lymphocyte reacts with the parasite.

A similar argument is used to derive an expression for the probability that an autoimmune disease occurs, pq, which is assumed to be the probability that at least one lymphocyte cross-reacts. In particular,

$$pq = 1 - \left(\sum_{j=1}^{k} \omega_j(1-\alpha_j\Delta_j)\right)^r = 1-(1-\overline{\alpha\Delta})^r, \tag{9}$$

where

$$\overline{\alpha\Delta} = \sum_{j=1}^{k} \alpha_j\Delta_j\omega_j, \tag{10}$$

is the probability that a randomly selected lymphocyte cross-reacts.

The term "antigenic" refers to the potential to cause an immune response, whereas "immunogenic" is when this potential is actually realized (Sulitzeanu and Weiss 1981; Kindt et al. 2007, p. 77). For our model formulation, the antigenicity of a particular parasite is,

$$\tilde{\alpha} = \frac{1}{k}\sum_{j=1}^{k} \alpha_j, \tag{11}$$

and under the costly autoimmunity hypothesis, parasite phenotypes are constrained to have a minimum level of antigenicity (see section "Formalizing the costly autoimmunity and the mimicry trade-off hypotheses"). This is in contrast with the immunogenicity of a parasite which is $\bar{\alpha}$ (eq. 8). The difference between the values of antigenicity and immunogenicity reflect the benefit of mimicry under the costly autoimmunity hypothesis; namely, that parasites that are mimics are less immunogenic for a fixed level of antigenicity, owing to the lower prevalence of highly self-reactive lymphocytes.

DEFINING MIMICRY

So far, we have related the parasite phenotype to characteristics of the immune response (p and q) and the number of new infections (the R_is), which then corresponds to parasite fitness (R_0), but we also need to determine whether a particular parasite phenotype should be classified as a mimic. When random mutations produce a parasite with different proteins, the result is that a different type of lymphocyte j will be activated, and this lymphocyte type will correspond to a different probability of self-reaction, $0 \le \Delta_j \le 1$. We develop a definition of mimicry that captures the *functional* significance of structural similarities

between host and parasite proteins. A parasite is classified as a mimic if lymphocytes respond in the same way to the parasite and to self. Our definition of mimicry accounts for the similarity between the parasite and self that might occur by chance, depending on the range of parasite phenotypes that are possible. To this end, suppose we take a sample of lymphocytes and determine the values of α_j and Δ_j for each. We define mimicry as the correlation,

$$\rho = \mathrm{corr}(\alpha_j, \Delta_j), \tag{12}$$

where this correlation is taken over the frequency of the different lymphocyte types, j. Thus, if there is little difference between how lymphocytes react to the parasite and to self this correlation will be high. However, if the correlation is 0, then there is no relationship between the parasite and self on average, and thus no mimicry. Also note that, with this definition, anti-mimicry can occur if the correlation is negative. In this case, the parasite would react most strongly with lymphocytes that are very unreactive to self, and in this way, parasites that are anti-mimics would be more noticeable to the immune system than phenotypes that occur purely by chance. The correspondence between this definition of mimicry and one based on the structural similarity of parasite and host proteins is shown in Figure 2.

This definition can be used to test for mimicry by specifying a null hypothesis (e.g., that the parasite is not a mimic, $\rho \leq 0$) and performing an appropriate statistical test (e.g., Sokal and Rohlf 1994, p. 576; noting that this significance test assumes that α_j and Δ_j are distributed according to a bivariate normal distribution).

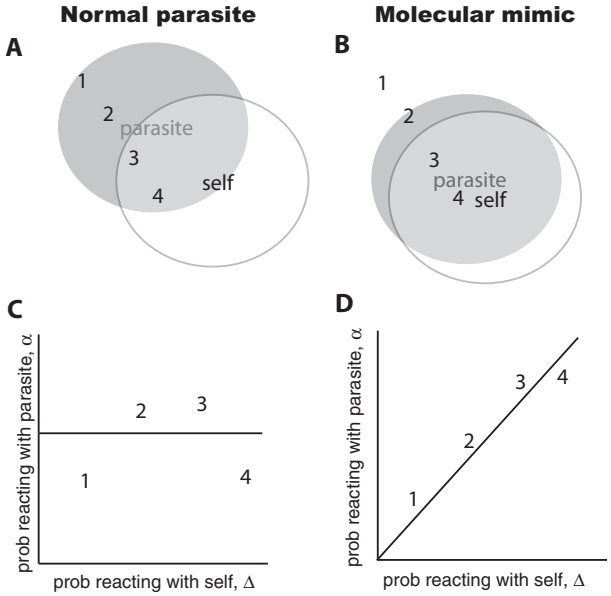

Figure 2. A normal parasite (*A*) and a molecular mimic (*B*) drawn in structural space as conceptualized in Perelson and Oster (1979). Nearness in structural space indicates that the parasite and self antigens have the same shape and that the parasite is a mimic (*B*). The parasite's structure is represented as the center of the gray circle, while the structure of the self antigen is the center of the white circle. Different lymphocytes (numbered 1–4) have specificities that match most closely with particular points in structural space. The probability that a particular lymphocyte reacts with an antigen depends on the distance in structural space. For the parasite that is a mimic (*B*), $\alpha_j \approx \Delta_j$ for all j (*D*), and so the lymphocytes cannot discriminate between self and parasite antigens, and as such, we define mimicry as a correlation (see eq. (12)).

Results

Having defined the relationships between the parasite phenotype, mimicry, and fitness, we now determine the conditions for mimicry to be evolutionarily stable. The parasite ESS is denoted as $\vec{\alpha}^*$ which is a vector with the elements α_j^*. In Appendix A of Supporting Information, we show that the parasite ESS maximizes eq. (2). In this section "Results", first we describe the general characteristics of the parasite ESS by solving a constrained (the costly autoimmunity hypothesis), and an unconstrained (the mimicry trade-off hypothesis) optimization problem. Next, we describe the conditions that select for mimicry. Finally, we describe how two different medical interventions affect parasite evolution and the probabilities of the different host infections.

GENERAL PROPERTIES OF THE PARASITE ESS

For the costly autoimmunity hypothesis, the minimum value of R_0 occurs when $\chi(\vec{\alpha}) < c$ (eqs. (3–4)). Therefore, the parasite phenotype that maximizes fitness must satisfy $\chi(\vec{\alpha}) \geq c$. The selection gradient is a vector whose elements are the partial derivatives of R_0 with respect to each α_j. Assuming that $\chi(\vec{\alpha}) \geq c$,

$$\frac{\partial R_0}{\partial \alpha_j} = -r(R_U - R_I)(1-\bar{\alpha})^{r-1}\omega_j - r(R_I - R_A) \times (1-\overline{\alpha\Delta})^{r-1}\Delta_j\omega_j, \tag{13}$$

where this partial derivative describes the direction and magnitude of natural selection to express proteins that activate the different lymphocytes, j. This derivative is negative for all j, because an increase in the probability that any lymphocyte reacts to the parasite decreases the chance of an uncontrolled infection and thereby decreases fitness (see eq. 2; recall that $R_U > R_I > R_A$ for the costly autoimmunity hypothesis). Because the selection gradient is negative, R_0 (eq. 2) is maximized for the smallest value of $\chi(\vec{\alpha}) = \frac{1}{k}\sum_{j=1}^{k}\alpha_j$ such that $\chi(\vec{\alpha}) \geq c$. Therefore, the parasite ESS for the costly autoimmunity hypothesis is a constrained optimization problem: to maximize R_0 (eq. 2) under the constraint that $\chi(\vec{\alpha}) = c$.

The shape of the selection gradient (eq. 13) is either monotonically increasing, monotonically decreasing, or increasing to a single maximum and then decreasing (see Appendix B of Supporting Information, Lemma 1). The parasite ESS is to activate the lymphocytes that correspond to the least negative values of the selection gradient, and these occur near $j = 1$ and/or $j = k$. Furthermore, for the costly autoimmunity hypothesis, a parasite phenotype that is evolutionarily stable displays an all-or-nothing phenotype; for each j, the parasite will have either $\alpha_j = 0$ or $\alpha_j = 1$ (except under exceptional circumstances). This result arises from a direct application of the Karash–Kuhn Tucker theorem as shown in Appendix B of Supporting Information (Lemma 2). Therefore, under the costly autoimmunity hypothesis, the parasite ESS has the general form,

$$\alpha_j^* = \begin{cases} 1 & \text{for } \Delta_j < x^*, \\ 0 & \text{for } x^* < \Delta_j < 1 - c + x^*, \\ 1 & \text{for } 1 - c + x^* < \Delta_j, \end{cases} \tag{14}$$

provided that $\Delta + \omega(\Delta)/\omega'(\Delta)$ is monotonically increasing where $\omega(\Delta_j) = \omega_j$ (see Appendix B of Supporting Information; Theorem 1 for details). The implication of eq. (14) is that, for the costly autoimmunity hypothesis, the parasite ESS will either activate strongly or weakly self-reactive lymphocytes, or both. The quantities x^* and $1 - c + x^*$ correspond to the minimum and maximum self-reactivities of lymphocytes that are not activated by the parasite. A procedure for identifying these values numerically is described in Appendix C of Supporting Information and the computer code for all numerical results is publicly available at Dryad Digital Repository, doi:10.5061/dryad.3vf7p. Parasite ESSs as described by eq. (14) are shown in Figure 3A and B, and the corresponding selection gradients are shown in Figure 3C and D.

For the mimicry trade-off hypothesis, there is no antigenicity constraint, and so the sign of the derivative of R_0 with respect to α_j for each α_j, determines whether selection favors the expression of proteins that activate the lymphocyte, j. The selection gradient for the mimicry trade-off hypothesis is,

$$\begin{aligned} \frac{\partial R_0}{\partial \alpha_j} = &-r(R_U - R_I)(1 - \bar{\alpha})^{r-1}\omega_j \\ &+ ((1-q)\mathcal{R}_U + q\mathcal{R}_I) z_j \beta'(f), \end{aligned} \tag{15}$$

where $\mathcal{R}_i = R_i/\beta[f(\chi(\vec{\alpha}), \theta_i)]$, $\beta'(f) = \frac{\partial \beta[f(\chi(\vec{\alpha}),\theta_i)]}{\partial f(\chi(\vec{\alpha}),\theta_i)}$ and $\frac{\partial f(\chi(\vec{\alpha}),\theta_i)}{\partial \alpha_j} = z_j$. The first term in eq. (15) is negative since expressing proteins decreases the probability of an uncontrolled infection and decreases fitness (recall that an assumption of the mimicry trade-off hypothesis was that $R_U > R_I$, see section "The mimicry trade-off hypothesis"). The second term in eq. (15) is positive when $z_j = 1$, and 0 otherwise, because expressing proteins that contribute to parasite replication and transmission increases fitness. Highly self-reactive lymphocytes are less prevalent, such that ω_j is a decreasing sequence in j, and the first term of eq. (15) is negative. Therefore, there may exist a threshold value of j for which the selection gradient (eq. 15) changes sign from negative to positive, z^*. For any j, such that the selection gradient is positive, expressing a protein that activates the lymphocyte j increases parasite fitness, and so the parasite ESS is $\alpha_j^* = 1$, for all j where eq. (15) is positive. For any j, such that the selection gradient is negative, expressing a protein that activates the lymphocyte j decreases parasite fitness, and so the parasite ESS is $\alpha_j^* = 0$, for all j where eq. (15) is negative. As such, the general form of the parasite ESS under the mimicry trade-off hypothesis is,

$$\alpha_j^* = \begin{cases} 0 & \text{for } \Delta_j < z^*, \\ 1 & \text{for } z^* \le \Delta_j \text{ and } z_j = 1. \end{cases} \tag{16}$$

where $z^* \ge 0$. If $z^* > 1$ there is no value of j corresponding to a positive value of the selection gradient. The interpretation of eq. (16) is that only proteins that contribute to parasite function are expressed, and in some cases only a subset of these are expressed. Examples of the parasite ESS for the mimicry trade-off hypothesis are shown in Figure 3E and F along with the corresponding selection gradients (Fig. 3G,H).

SELECTION FOR MIMICRY

Given the general forms of the parasite ESS, under both the costly autoimmunity hypothesis and the mimicry trade-off hypothesis mimicry may be selected for, or selected against, depending on the magnitude of the parameters in R_0 (Fig. 4). Let, ϕ be the relative cost of autoimmunity, ψ be the relative cost of an acute infection, and τ be the relative rarity of highly self-reactive lymphocytes, where

$$\begin{aligned} \phi = 1 - \frac{R_U - R_I}{R_U - R_A}, \qquad \psi = \frac{R_U - R_I}{R_U}, \\ \text{and} \qquad \tau = 1 - \frac{1 - (1 - \omega_k c)^r}{1 - (1 - \omega_1 c)^r}. \end{aligned} \tag{17}$$

Note that each of these quantities lie between 0 and 1. In general, as shown in Figure 4, mimicry is selected against when τ is small (i.e., when highly self-reactive lymphocytes are common). Then, the effect of clonal deletion is mild such that weakly and highly self-reactive lymphocytes have relatively equal frequencies, and so the probability that a mimic fails to elicit an immune response is only marginally greater than the same probability for any other parasite phenotype (Fig. 4D,H). Under the costly autoimmunity hypothesis, a high cost of autoimmunity (i.e., that hosts with autoimmunity generate substantially fewer secondary infections relative to hosts with other infection types)

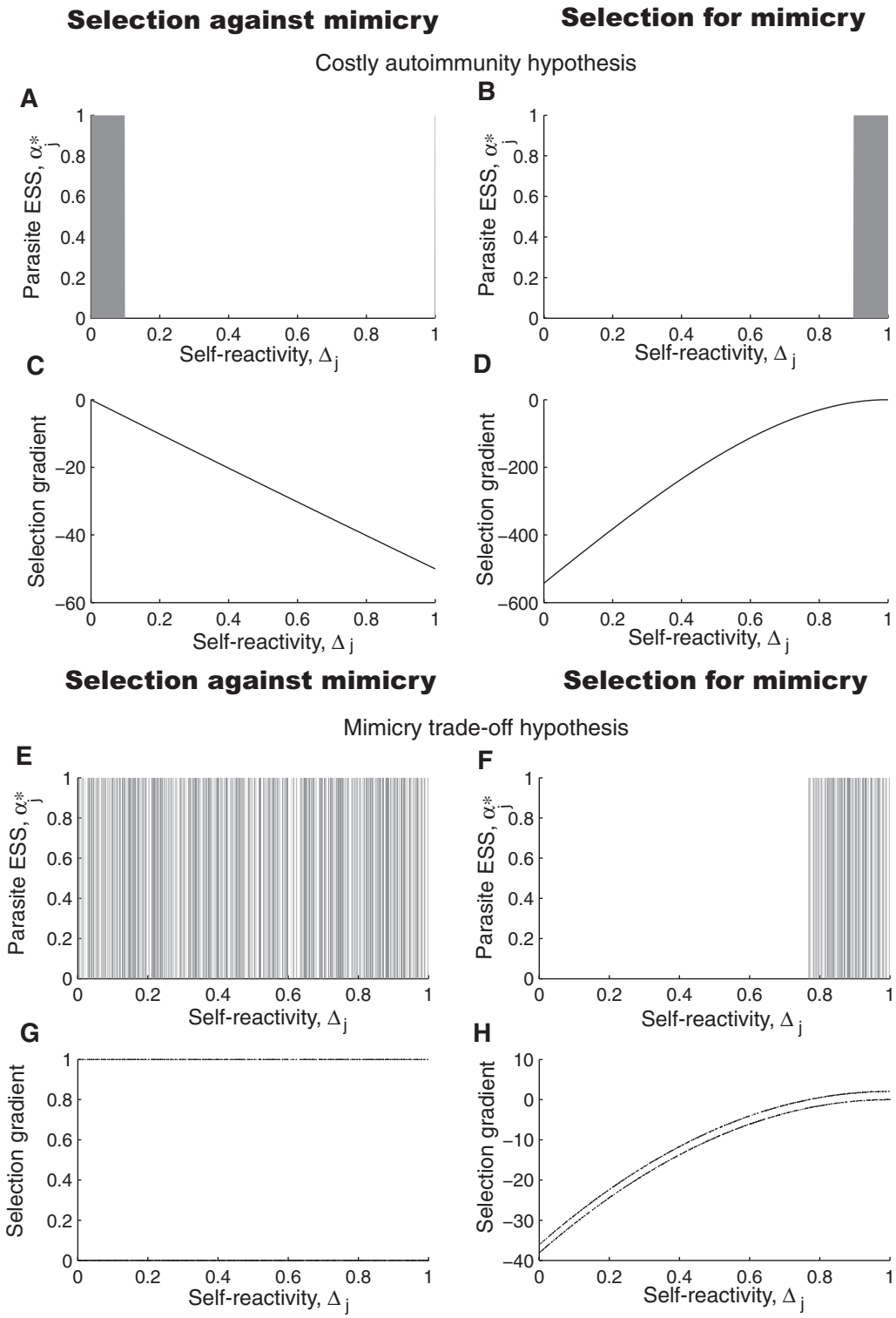

Figure 3. Examples of parasite ESSs corresponding to selection against mimicry (*A* and *E*) and selection for mimicry (*B* and *F*) for the costly autoimmunity hypothesis and the mimicry trade-off hypothesis and the corresponding selection gradients (*C*, *D*, *G*, and *H*). The conditions for selection against mimicry are described in section "Selection for mimicry". The general form of the parasite ESSs are described by eq. (14) (the costly autoimmunity hypothesis) and eq. (16) (the mimicry trade-off hypothesis) and the formulae for the selection gradients are given by eqs. (13) and (15). In *E*–*H*, the z_j are Bernoulli random variables with probability 0.5. The two lines that appear in *H* correspond to $z_j = 0$ and $z_j = 1$. In *G*, the selection gradient when $\Delta_j \approx 1$ and $z_j = 1$ is positive and the selection gradient is close to 0, but slightly negative when $\Delta_j \approx 1$ and $z_j = 0$. All parameters and functions are described in the Appendix C of Supporting Information. The same parameters and functions are used for Figs. 3–5.

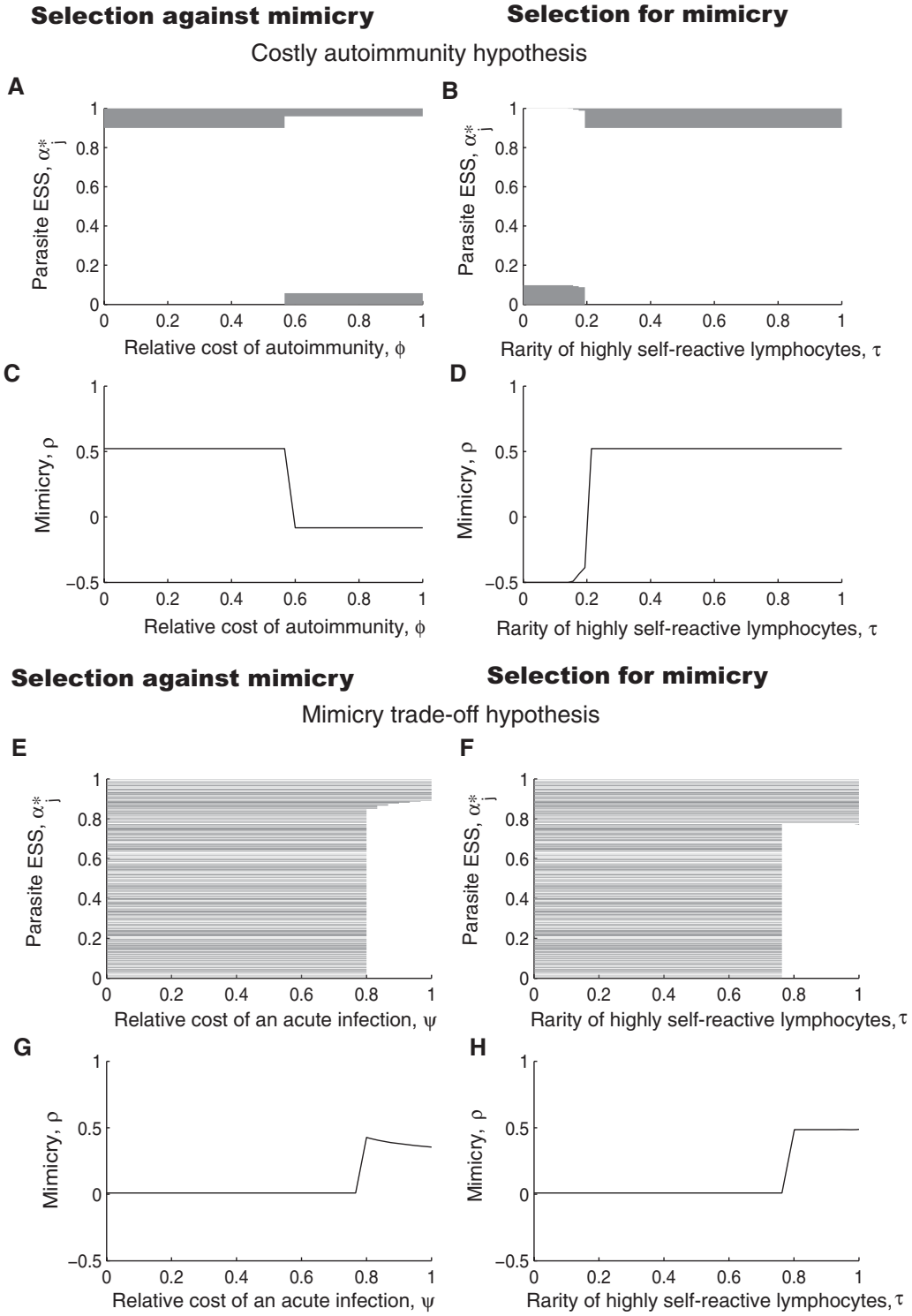

Figure 4. The parasite ESSs and the evolution of mimicry for the costly autoimmunity hypothesis (*A–D*) and the mimicry trade-off hypothesis (*E–H*). In *A–B* and *E–F*, the parasite ESSs are $\alpha_j^* = 1$ in the gray regions, and $\alpha_j^* = 0$ in the white regions. Under the costly autoimmunity hypothesis, mimicry is selected when the relative cost of autoimmunity is low (*C*) and highly self-reactive lymphocytes are rare (*D*). Under the mimicry trade-off hypothesis, mimicry is selected when the relative cost of an acute infection is high (*G*) and highly self-reactive lymphocytes are rare (*H*). The parameters used to generate these figures are provided in the Appendix C of Supporting Information.

selects against mimicry because mimics are more likely to induce autoimmunity (Fig. 4). Under the mimicry trade-off hypothesis, when ψ is small there is little difference between the number of secondary infections generated by hosts with uncontrolled infections, or acute infections, and so the incentive to express all proteins, irrespective of whether they activate highly or weakly self-reactive lymphocytes, is nearly the same (Fig. 4G).

A simple condition for the evolution of mimicry under the costly autoimmunity hypothesis can be derived by assuming that c is small, that is, that the expression of only a few surface proteins is necessary for transmission to occur (eq. (4)). When $R_I - R_A$ is large, autoimmunity is extremely costly in terms of the reduction in the number of secondary infections (large ϕ) and the least negative values of the selection gradient occur near $j = 1$ (these lymphocytes are weakly self-reactive), and possibly near $j = k$ (depending on how rare these highly self-reactive lymphocytes are, and how likely it is that an uncontrolled infection will occur). When autoimmunity is less costly, there is no longer a significant drawback to evolving mimicry, and so the maximum in the selection gradient occurs at $j = k$, because autoimmunity or an uncontrolled infection is likely to result.

Formally, the condition for mimicry to be selected against when c is small is determined by comparing the values of R_0 (eq. (2)), when the parasite phenotype corresponds to mimicry ($x^* = 0$), and when the parasite phenotype corresponds to anti-mimicry ($x^* = c$). These are approximated as,

$$R_U + (R_A - R_U)(1 - (1 - \omega_k c)^r) \quad \text{(mimicry)}, \qquad (18)$$

$$R_U + (R_I - R_U)(1 - (1 - \omega_1 c)^r) \quad \text{(anti-mimicry)}. \qquad (19)$$

Here, $\omega_k c$ and $\omega_1 c$ approximate $\sum_j \alpha_j \omega_j$ for small c, for mimicry and anti-mimicry, respectively. The condition that mimicry is selected against is that eq. (18) is less than eq. (19), and this reduces to the inequality $\tau < \phi$, which has an interpretation that is consistent with the above general discussion of selection against mimicry for the costly autoimmunity hypothesis.

From eq. (15), we can discern that mimicry would be selected if functional protein expression happened to coincide with activating highly self-reactive lymphocytes (i.e., if z_j and Δ_j are positively correlated). If this were the case, then mimicry would evolve because parasites that are mimics are the most functional, rather than necessarily because expressing proteins that correspond to highly self-reactive lymphocytes increases the chance of an uncontrolled infection. There is no evidence to suggest a relationship between the contribution of proteins to parasite replication and the self-reactivity of the lymphocytes that these proteins activate, and so we assume no such relationship. Therefore, from eq. (15) for mimicry to be selected, R_U must be much bigger than R_I (i.e., large ψ), and there must be some functional proteins ($z_j = 1$) for which the benefit of expressing these proteins exceeds the cost of detection by the immune system (i.e., there must be some j for which the selection gradient is positive).

THE EFFECT OF MEDICAL INTERVENTIONS ON THE EVOLUTIONARILY STABLE PARASITE PHENOTYPE AND THE TYPES OF INFECTIONS THAT ARE INDUCED IN THE HOST

From a human disease perspective, the two most serious types of infections are an uncontrolled infection (since then there is no effective immune response) and autoimmunity (since then the immune system causes damage to the host itself). Here, we consider two possible types of medical interventions and we determine whether these interventions would select for the types of parasites that cause the most serious types of human infections. Our analysis focuses on the probability of an uncontrolled infection, $1 - q$, and the probability of autoimmunity, pq, given a parasitic infection. We note that these quantities are different than the number of people who experience each type of disease, as this would depend both on the transmission rate and the duration of the different disease types. In particular, a decreased probability of an uncontrolled infection, or autoimmunity, given an infection does not imply that fewer individuals will experience these diseases.

Referring to Table 1 in Hausmann and Wucherpfennig (1997), Influenza A, Herpes Simplex Virus, and *Mycobacterium bovis* (the infectious agent of bovine tuberculosis; also causing tuberculosis in humans) are parasites that activate lymphocytes that cross-react with host cells, and may lead to infection-induced autoimmunity. The spread of the acute infections due to these parasites may be reduced by school closures (Influenza A), antiviral drugs (Herpes Simplex Virus), and antibiotics (tuberculosis). The first medical intervention that we consider is one that reduces the spread of parasites that induce acute infections only. Such interventions would decrease ϕ, the relative cost of autoimmunity, and increase ψ, the relative cost of an acute infection to the parasite.

Among the proposed treatments for autoimmune diseases are gene therapies (Alderuccio et al. 2009) and the targeted elimination of self-reactive lymphocytes (Lopez-Diego and Weiner 2008; Berger and Houff 2009). The suggested method of action for gene therapy is that the increased expression of defined self antigens leads to an increase in the presentation of these self antigens in the thymus, and to an increased chance that the lymphocytes specific for these self antigens are destroyed during clonal deletion (Alderuccio et al. 2009). Antigen-specific therapies, such as oral myelin basic protein (MBP) or intraveneous MBP8298, result in the presentation of these self antigens (which resemble human MBP) to lymphocytes in the absence of costimulatory molecules. This results in partial activation of the corresponding self-reactive lymphocytes which then undergo apoptosis owing to the lack of full activation (Lopez-Diego and Weiner 2008). The effect of these

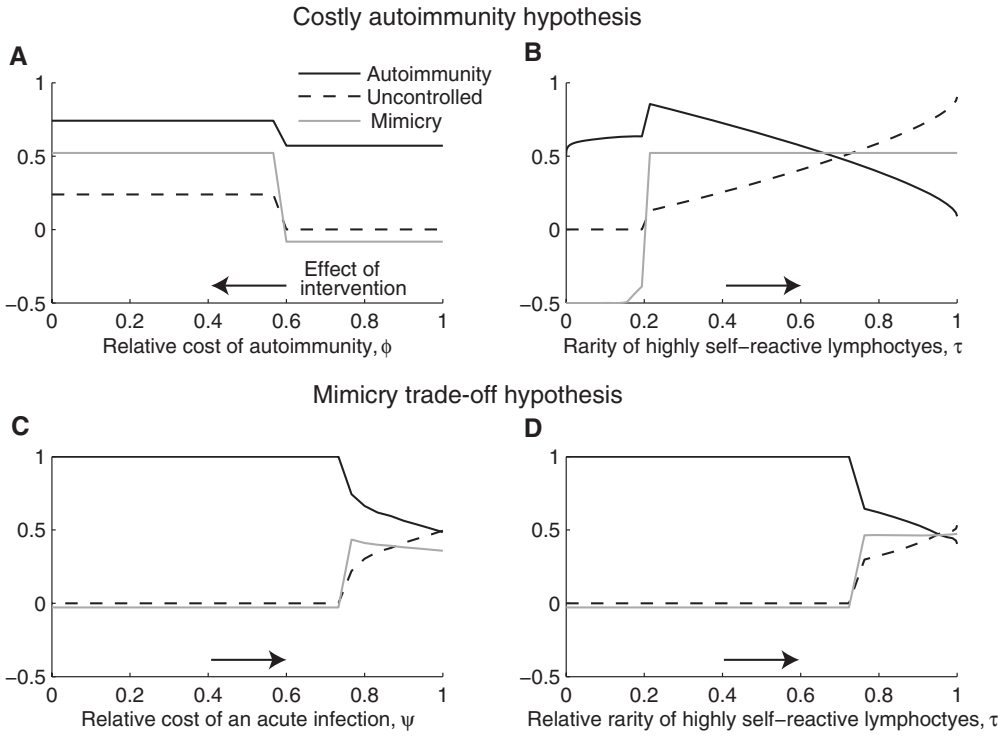

Figure 5. The probability of an uncontrolled infection and infection-induced autoimmunity under the costly autoimmunity hypothesis and the mimicry trade-off hypothesis for two different medical interventions: one which decreases ϕ or increases ψ; and one which increases τ (the direction of the arrows indicate the direction of the effect of the medical intervention). In all cases, when mimicry evolves (gray line) there is an increased risk of an uncontrolled infection (dashed line). For the mimicry trade-off hypothesis (*C*, *D*), when mimicry evolves the risk of infection-induced autoimmunity decreases (solid line), while under the costly autoimmunity hypothesis, this risk may increase (*A*,*B*). For *B*, the risk of infection-induced autoimmunity increases for intermediate τ, but then decreases for large τ. The parameters used are the same as for Fig. 4.

therapies on the immune system is that some highly self-reactive lymphocytes are destroyed. The second type of medical intervention that we consider is therefore one that decreases the frequency of highly self-reactive lymphocytes, thereby increasing τ.

The effect of both of these interventions is to select for molecular mimicry (Fig. 5, recall that the effect of the interventions are to decrease ϕ (A), to increase ψ (C), and to increase τ (B,D)). In all cases, selection for mimicry results in an increase in the probability that the infecting parasite induces an uncontrolled infection. A difference between the costly autoimmunity hypothesis and the mimicry trade-off hypothesis is that under the mimicry trade-off hypothesis the parasite ESS continues to change after a threshold value of ψ is exceeded, but for the costly autoimmunity hypothesis, apart from the one major shift, there is little change in the parasite ESS (Fig. 4A,B and E,F; note the correspondence between Figs. 4 and 5). In particular, under the mimicry trade-off hypothesis, the antigenicity of the ESS phenotype (proportional to the total number of $\alpha_j^* = 1$, see eq. (11)) continues to evolve; this is in contrast with the costly autoimmunity hypothesis, which requires that antigenicity is fixed. This change in antigenicity determines whether evolved mimicry also implies a higher probability of infection-induced autoimmunity. Consider a parasite strategy which is to activate all lymphocytes ($\alpha_j = 1$ for all j) versus one which is to activate only the most self-reactive lymphocyte (only $\alpha_k = 1$): the latter strategy has high mimicry, but the former has a greater chance of inducing autoimmunity, solely because more antigens are expressed. In Figure 5A, under the costly autoimmunity hypothesis, antigenicity is fixed, and so when mimicry evolves uncontrolled infections and infection-induced autoimmunity are both more likely (Fig. 5A). In Figure 5C, under the mimicry trade-off hypothesis lower levels of antigenicity, and higher levels of mimicry evolve concurrently (Fig. 4E), and the net effect is that the probability of autoimmunity given an infection decreases as a result of the intervention (increasing ψ).

When τ changes, the probability of infection-induced autoimmunity in-and-of-itself changes, even if there is no parasite evolution. This can be seen in Figure 5B. Under the costly autoimmunity hypothesis, for $0.25 < \tau < 1$ the parasite ESS changes very little (Fig. 4B), however, the probability of autoimmunity given an infection steadily decreases in this same range (Fig. 5B). This is owing to the effect of the intervention; that highly

self-reactive lymphocytes are destroyed to reduce the chance that infections lead to autoimmunity. Under the costly autoimmunity hypothesis, given the effect of both parasite evolution and the effect of increasing τ itself, there is a range of τ values ($0.2 < \tau < 0.5$ in Fig. 5B) where the effect of the intervention is insufficient to offset the increased chance of autoimmunity arising from the evolution of mimicry.

Returning to the initial question of how these two medical interventions will impact the chance of the two most serious types of human pathologies, the answer depends on which factors are affecting parasite evolution (i.e., the costly autoimmunity hypothesis or the mimicry trade-off hypothesis), and also which interventions are initiated. In all cases, these interventions increase the risk of an uncontrolled infection, and so they should only be considered if the risk of autoimmunity is reduced (i.e., the second most serious type of human infection). For the intervention that reduces the number of new infections generated by hosts with acute infections only; this intervention should be considered if the mimicry trade-off hypothesis is the trade-off that affects the evolution of mimicry. For the intervention that increases the rarity of highly self-reactive lymphocytes, this intervention could be considered under either hypothesis, but under the costly autoimmunity hypothesis, only when highly self-reactive lymphocytes are made extremely rare should this intervention be considered (Fig. 5B). In noting that the rationale for implementing an intervention that eliminates highly self-reactive lymphocytes was to decrease the risk of autoimmunity given an infection, we determined that the evolution of mimicry can potentially undermine this intended effect if not all types of highly self-reactive lymphocytes are eradicated, or if eradication is only partially successful (i.e., if $\tau < 0.6$).

Discussion

A general problem in evolutionary epidemiology is to understand the evolution of parasite transmission. A more specific version of this problem is to understand why immune evasion is not more common. To understand how selection acts to prevent the evolution of mimicry, our analysis considers two hypotheses that may explain why immune evasion via molecular mimicry is not ubiquitous among parasite species. Under the costly autoimmunity hypothesis, parasites that are molecular mimics are both more likely to evade the immune response and to induce autoimmunity in their hosts, and hosts with autoimmunity generate fewer new infections relative to hosts with other types of infections (Damain 1964; Graham et al. 2005). Under the mimicry trade-off hypothesis, trade-offs on the structure of proteins mean that proteins may either mimic host cells, or contribute to parasite replication resulting in more new infections, but not both. We showed that the parasite ESS (Fig. 4) and two different medical interventions have different impacts on human health (Fig. 5) depending on which of these two trade-offs explain selection against mimicry in a particular parasite.

A difference between the parasite ESSs for each of the two hypotheses is that, under the costly autoimmunity hypothesis, intermediately self-reactive lymphocytes are never activated (eq. (14); Appendix B of Supporting Information, Lemma 1), whereas under the mimicry trade-off hypothesis, intermediately self-reactive lymphocytes can be activated (eq. (16)). The reason that intermediately self-reactive lymphocytes are not activated under the costly autoimmunity hypothesis is that these lymphocytes are neither rare nor unreactive to self antigens, and therefore pose the greatest risk of inducing autoimmunity in the host. The risk of inducing autoimmunity for each lymphocyte is $\Delta_j \omega_j$, and for most reasonable choices of ω_j, the risk of inducing autoimmunity is highest for intermediate values of j. Some empirical evidence supports the conclusion that intermediately self-reactive lymphocytes do indeed pose the greatest risk of inducing autoimmunity. Qa-1-restricted CD8+ T cells protect mice against autoimmunity and this protection occurs because these Qa-1-restricted CD8+ T cells destroy intermediately self-reactive lymphocytes (Chen et al. 2007). Therefore, although both the costly autoimmunity hypothesis and the mimicry trade-off hypothesis are plausible, unique hallmarks of protein expression can be used to distinguish between each of these to understand which selective force is affecting parasite evolution.

The differences in the parasite ESSs given the different selective forces also results in differences in how parasites will evolve in response to changes due to medical interventions. Given our focus on the evolution of molecular mimicry, we reported these results in terms of the changes in the types of infections that are induced *given an infection*; however, the number of individuals that are infected may also change as a result of parasite evolution, although we have not considered this in the current analysis. In addition to gene therapies and the targeted elimination of self-reactive lymphocytes (discussed in section "The effect of medical interventions on the evolutionarily stable parasite phenotype and the types of infections that are induced in the host"), other proposed treatments for autoimmune disease include immunosuppressive therapies, such as B-cell depletion agents that destroy both self-reactive and non-self-reactive lymphocytes. In that B-cell depletion agents affect lymphocytes of all specificities there is no reason that mimics or any other parasite phenotype would have a particular selective advantage. Therefore, B-cell depletion agents are not expected to affect the evolution of mimicry in parasites.

In addition to these contributions, our model derivation provides mathematical definitions for the terms mimicry, immunogenicity and antigenicity. The definition of mimicry that we

derive (eq. (12)) avoids anthropocentric biases and instead defines mimicry from the point of view of the lymphocyte. Quantification of mimicry from our definition requires estimating the probabilities of lymphocyte activation by self and parasite antigens. Past work has shown that approximately 5% of 800 monoclonal antibodies that reacted with one of 15 viruses cross-reacted with normal tissues (Shrinivasappa et al. 1986; Bahmanyar et al. 1987). The different measures of sequence homology, the relationship between primary and quaternary protein structure, and the complexity of antigen processing and presentation, make it difficult for general links to be established between amino acid sequence homology and the probability of lymphocyte activation. We suggest bypassing these complications by defining mimicry using the lymphocyte reaction probability. Therefore, we have developed a definition of mimicry that is simple and meaningful, because our definition reflects the functional significance of mimicry.

Several aspects of our model formulation warrant further discussion. In suggesting that molecular mimicry may facilitate immune evasion, we have assumed that when parasites express only proteins that correspond to very highly self-reactive lymphocytes, an uncontrolled infection is very likely. This follows from the theory of clonal deletion: that highly self-reactive lymphocytes undergo apoptosis to prevent autoimmunity. Given this effect of clonal selection, the only lymphocytes with the specificity to the parasite are also highly self-reactive and may not exist, resulting in an uncontrolled infection. Previous work states that parasites that are mimics are more likely to evade the immune system, however, in most cases this statement is made without any supporting evidence (Damain 1964; Young et al. 2002; Elde and Malik 2009). In fact, we are aware of only one study that has directly shown that immune evasion can arise from mimicry (Wölfl and Rutebemberwa 2008).

Our model refers to infection-induced autoimmunity only, and we note that autoimmunity is caused by many genetic and environmental factors, and only a subset of observed autoimmune disease is caused by cross-reacting lymphocytes activated by parasites that are molecular mimics. The immunological details of why some individuals develop autoimmunity and others do not are not well known (Arnold 2002). If parasites activate cross-reactive lymphocytes that are suppressed, or do not lead to a clinical form of disease, it may be difficult to accurately estimate the prevalence of molecular mimicry in parasites.

Parasite evolution has practical consequences in terms of evolutionary medicine, and the nature of these implications depend on the constraints and life history trade-offs that act on the parasite. In that the immune system aims to destroy parasites, characteristics of the immune system strongly impact parasite evolution. Evolutionary biologists (Nesse and Williams 1995; Graham et al. 2005) have suggested that autoimmunity is an unavoidable cost of an immune system that is able to respond to a wide range of parasites, and as such, autoimmunity is a relevant consideration for understanding how the immune system shapes parasite evolution. Now that several broadly immunosuppressive therapies are promising treatments for autoimmune diseases (Lopez-Diego and Weiner 2008), a timely consideration is to understand how these therapies would impact parasite evolution, and ultimately, what the consequences would be for human health.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix A. The proof that the evolutionarily stable parasite strategy maximizes R_0.

Appendix B. The proof that eq. (14) is the evolutionarily stable parasite strategy under the costly autoimmunity hypothesis.

Appendix C. The numerical methods used to generate Figs. 3–5.