CHICAGO JOURNALS

The University of Chicago

Histocompatibility as Adaptive Response to Discriminatory Within-Organism Conflict: A Historical Model.

Author(s): Owen M. Gilbert

Source: *The American Naturalist*, Vol. 185, No. 2 (February 2015), pp. 228-242

Published by: [The University of Chicago Press](#) for [The American Society of Naturalists](#)

Stable URL: <http://www.jstor.org/stable/10.1086/679442>

Accessed: 09/06/2015 10:34

Your use of the JSTOR archive indicates your acceptance of the Terms & Conditions of Use, available at <http://www.jstor.org/page/info/about/policies/terms.jsp>

JSTOR is a not-for-profit service that helps scholars, researchers, and students discover, use, and build upon a wide range of content in a trusted digital archive. We use information technology and tools to increase productivity and facilitate new forms of scholarship. For more information about JSTOR, please contact support@jstor.org.

The University of Chicago Press, The American Society of Naturalists, The University of Chicago are collaborating with JSTOR to digitize, preserve and extend access to *The American Naturalist*.

<http://www.jstor.org>

Histocompatibility as Adaptive Response to Discriminatory Within-Organism Conflict: A Historical Model

Owen M. Gilbert*

Department of Integrative Biology, University of Texas, Austin, Texas 78712

Submitted March 14, 2014; Accepted September 25, 2014; Electronically published January 8, 2015

Online enhancement: appendix.

ABSTRACT: Multicellular tissue compatibility, or histocompatibility, restricts fusion to close kin. Histocompatibility depends on hyper-variable cue genes, which often have more than 100 alleles in a population. To explain the evolution of histocompatibility, I here take a historical approach. I focus on the specific example of marine invertebrate histocompatibility. I use simple game-theoretical models to show that histocompatibility can evolve through five steps. These steps include the evolution of indiscriminate fusion, the evolution of discriminatory within-organism conflict, the evolution of minor histocompatibility, the evolution of major histocompatibility, and the evolution of major histocompatibility cue polymorphism. Allowing for gradual evolution reveals discriminatory within-organism conflict as a selective pressure for histocompatibility and associated cue polymorphism. Existing data from marine invertebrates and other organisms are consistent with this hypothesis.

Keywords: conflict, cooperation, chimera, kin recognition, game theory.

He who believes that some ancient form was transformed suddenly... will further be compelled to believe that many structures beautifully adapted to all the other parts of the same creature and to the surrounding conditions, have been suddenly produced; and of such complex and wonderful coadaptations, he will not be able to assign a shadow of an explanation. (Darwin 1872, p. 204)

Introduction

In the various independent evolutionary transitions to multicellular organisms and societies, entities that formerly existed as discrete and autonomous units became integrated into larger functional wholes (Buss 1987; Maynard Smith and Szathmáry 1995; Bourke 2011). Key and potentially adaptive features of these evolutionary tran-

sitions are behaviors that limit social associations to kin on the basis of polymorphic genes (Buss 1987; Grosberg 1988; Bourke 2011). Such behaviors are found in bacteria that form boundaries while swarming (Gibbs et al. 2008; Velicer and Vos 2009), in social amoebae that aggregate and segregate (Hirose et al. 2011), in plasmodial slime molds that discriminately fuse plasmodia (Clark and Haskins 2012), in fungi that discriminately fuse mycelia (Worrall 1997; Glass et al. 2000), and in clonal marine invertebrates and placental mammals that discriminately fuse somatic tissue (Burnet 1971; Buss 1982; Grosberg 1988; Rosengarten and Nicotra 2011). At another level, many arthropods and vertebrates preferentially associate with kin or reject non-kin from nests or territories on the basis of variable phenotypes (Fletcher and Michener 1987; Hepper 1991). A key challenge for evolutionary theory is to explain the adaptive significance of these complex behavioral systems.

Thus far, a primary theoretical emphasis has been on explaining the polymorphism of “tissue” or “histo-” compatibility cue genes (Grosberg 1988). When cue genes are highly variable, fusion is restricted to close kin (Grafen 1990). Population genetic theory suggests that extreme polymorphism, as viewed in natural populations (>100 alleles; e.g., Rinkevich et al. 1995; Gloria-Soria et al. 2012), can originate by negative frequency-dependent selection favoring rare alleles (Grosberg 1988). Two hypotheses have been offered to explain this negative frequency-dependent selection. The first states that rare alleles are favored for avoiding costs of within-organism conflict (Burnet 1973; Buss 1982). Models confirm that rare cue alleles can be favored if there are average costs of fusion with non-kin (Grosberg and Quinn 1988). However, it remains unclear why fusion is maintained in that case (Grosberg 1988; Aanen et al. 2008; Folse 2011). The second hypothesis states that rare cue alleles are favored through linkage disequilibrium with alleles for cooperation (Grafen 1990). However, the accumulation of polymorphism allows cooperation to fix, which reverses this selective pressure for

* E-mail: owen.gilbert@utexas.edu.

rare cue alleles (Rousset and Roze 2007). Some thus suggest that histocompatibility cue polymorphism must be maintained by “extrinsic” selection, as might be imposed by pathogen recognition or mate compatibility, rather than by histocompatibility itself (Rousset and Roze 2007; Holman et al. 2013).

Here, I challenge the idea that histocompatibility cue polymorphism must be maintained by extrinsic selection. I note that the models yielding this prediction assume that histocompatibility is a behavior that restricts cooperation to those sharing a cue (Rousset and Roze 2007; Holman et al. 2013). Because histocompatibility is a behavior that restricts fusion to those sharing a cue, these models assume that fusion is cooperation and that both evolve simultaneously. Given that fusion can result in conflict (Buss 1987) and that complex traits can evolve through multiple steps (Maynard Smith and Szathmáry 1995), I here relax these assumptions. I allow for the effects of fusion to vary, and I formulate a model that allows for gradual, multistep evolution. I ask whether a model that focuses on immediate selective pressures (*sensu* Darwin 1872) and allows the effects of fusion to vary on the basis of historical context can explain why histocompatibility evolves and why the associated cue genes are so polymorphic.

As a theoretical platform, I employ evolutionary game theory. Evolutionary game theory is useful for gradual models because of its value in identifying and comparing strategies possible at particular points in evolution (Maynard Smith 1982). Under this approach, it is possible to build a model that heeds evolutionary constraints and focuses on the historical context of adaptation. I here take an explicit focus on marine invertebrate histocompatibility because of the amount of data available (Grosberg 1988; Rosengarten and Nicotra 2011). To identify the strategies available at each stage, I adhere to Price’s dictum of including only those strategies “possible for the species without taking a major step” (quoted in Harman 2011, p. 3). Adhering to this simple dictum prevents the modeler from invoking saltation (Price 1968). It shifts the focus to slight favorable changes, of the sort more likely to arise by random mutation (Fisher [1930] 1999), and the particular biological context of adaptation. Employing this approach, I present this analysis as a series of simple models, each focused on a particular point in evolution and each solving a separate problem. Near the end, I combine the solutions into a cohesive analysis that solves the whole problem.

Model

Basic Approach

Throughout, I use simple analytic models based in evolutionary game theory. For each model, I begin by iden-

tifying the “strategy set,” a list of alternative behavioral programs that are biologically plausible and potentially favorable. I ask first whether the strategy might invade a resident strategy assumed to exist beforehand. If a strategy is capable of invading, I then ask whether it is an evolutionarily stable strategy (ESS) resistant to invasion by alternatives (Maynard Smith 1982). Next, I ask whether a strategy is capable of accumulating polymorphism of its cue locus. To do so, I first ask whether the strategy favors rare alleles of its cue locus under the same conditions required for its evolutionary stability. If it does, I ask whether the strategy is an ESS once cue polymorphism of its cue has accumulated to a high level. For each model, I give a brief summary of the results listed more fully in tables A7–A11 (tables A1–A15 available online).

Assumptions

I assume a life cycle that is an idealized caricature of that seen in some clonal marine invertebrates (fig. 1). In addition to what is shown in figure 1, I assume that the organism is haploid, the population is infinite, the organism has separate sexes, the sex ratio is even, and adults die after mating. I assume that each larva has a finite number of sexually produced kin n (e.g., siblings, cousins) and thus that the probability of settling near kin is equal to the frequency of kin encounters, $n/\infty \approx 0$. However, I assume that each colony fragments to produce two clone-mate colonies (fig. 1). Specifically, I assume that colonies encounter physically discrete clonemate colonies with probability K and nonclonemates with probability $1 - K$. Biologically, if fragmentation occurred only during great disturbances (e.g., violent storms) in which fragments are often swept away from each other on ocean currents, K would be low. If fragmentation occurred only by more subtle disturbances (e.g., substrate flexion, predation, or less violent storms) in which fragments settle near each other, K would be high.

Given my assumptions, colonies cannot mate with kin because clonemates are the same sex and there is an effectively zero chance of random encounter with sexually produced kin. Hence, the population is completely outbred, and alleles at unlinked loci assort independently. In all cases, I assume that behavioral strategies are employed by clonal colonies, whether those colonies are fused together or physically separate. I assume that interactions may occur within or between organisms, where by “organism” I mean a colony, connected by a common vasculature, within which resources are shared. Where discriminatory behaviors are based on phenotypes used as cues, discrete functional variants correspond to discrete alleles of a single gene. In all cases, I assume that the

Figure 1: Life cycle of a hypothetical marine invertebrate. *A*, Gametes fuse and begin to develop into a larva. *B*, Larvae disperse randomly. *C*, Each larva settles and fixes to a substrate. *D*, Each larva metamorphoses to produce a polyp. *E*, Polyps reproduce by clonal budding to produce a colony connected by a common vasculature. *F*, A disturbance causes colonies to fragment into two clonemate colonies, some of which may remain in the same vicinity. *G*, Growing across a substrate, each colony encounters one other, equally sized colony, which is either a clonemate (same shade) or nonrelative (different shade).

identity of a cue type does not directly correlate with differences in health, strength, or strategy.

In all models in which there is only one discriminatory behavior and cue, I assume that the cue gene has v alleles ($v \geq 1$) and that where $v > 1$, alleles are equally frequent. The probability of sharing a cue with a random colony is thus $P_i = 1/v$, and the probability of not sharing a cue with a random colony is $1 - P_i = P_j$. The letters i and j refer to the cue type of the encountered colony relative to the colony receiving the payoff (i for same, j for different). Clonemates always share cues. Moreover, at any given point in evolution where two genes vary simultaneously (e.g., a behavioral gene and a cue gene, or two cue genes), I assume that these different genes are unlinked and in linkage equilibrium. I introduce additional notation for a second cue where necessary below.

The Evolution of Fusion

I begin with the assumption that colonies do not fuse in the initial state. I allow for the following immediate fitness effects of fusion. First, fusion may entail an average benefit of belonging to an organism of larger size, s , as might arise from metabolic efficiencies of larger colonies. Second, fu-

sion may entail an average benefit of resource sharing, u , between otherwise disconnected parts of a colony. Third, fusion may entail an average benefit of avoiding overgrowth conflict or other types of aggression, ϕ , with a physically discrete neighbor. Fourth, fusion may entail a cost of parasite transmission, p , consequent on tissue mingling and blood exchange. I assume that these various "fitness effects" are the average effects on fecundity and that they combine additively to yield a net fecundity effect of fusion, $\varepsilon = s + u + \phi - p$.

I next outline a strategy set. The first strategy, which I assume is the resident strategy, simply fails to fuse: I call this strategy "Never Fuse." The second strategy, "Fuse Like," activates fusion only with conspecifics sharing an allelic variant of a particular gene, which I call the "fusion-activator" cue gene. The third strategy, "Always Fuse," activates fusion with any colony sharing the fusion-activator cue gene, independent of allelic identity. I assume that the fusion-activator cue gene is shared with all conspecifics, but not with other species, and that both colonies in an encounter must activate fusion for fusion to occur.

In summary of the results (table A7), Always Fuse can invade Never Fuse where $K\varepsilon > 0$. A nonzero clonemate encounter rate ($K > 0$) is necessary because Always Fuse

must encounter Always Fuse to fuse in a population dominated by Never Fuse. Moreover, Always Fuse is the ESS, given that both clonemates and non-kin are encountered ($1 > K > 0$) and that the net effect of fusion is positive ($\varepsilon > 0$). This result holds for any level of polymorphism of the fusion-activator cue locus (any $P_j > 0$). Because Always Fuse is an obligate strategy, it does not have a cue and thus cannot select for polymorphism of its cue. Thus, I conclude that fusion will evolve as an indiscriminate behavior where there is an immediate benefit of fusion and where colonies cannot discriminate on the basis of cues correlated with competitive ability before fusion.

The Evolution of Within-Organism Interactions

The previous model raises the question of why fusion would evolve to be a discriminatory behavior. One possibility is that strategies that discriminate on the basis of cues of competitive ability are possible, so that colonies avoid fusion with non-kin who are stronger. However, I see this as unlikely because it requires the ability to judge the outcome of fusion before fusion. Another possibility, which will remain obscure without additional considerations, is that fusion allows for the evolution of discriminatory within-organism interactions, which in turn affect the payoffs of fusion. In considering this possibility here, I do not assume that discriminatory interactions and histocompatibility evolve simultaneously. Rather, I keep with the assumption of gradual evolution and focus on slight changes that do not require a major leap.

To construct a model of discriminatory interactions, I assume that two types of actions are possible: help, which has positive effects on recipients, and harm, which has negative effects on recipients. To describe help, I use b to refer to the average benefit of help to the recipient and c to refer to the average cost of help to the actor. To model harm, I use b' to refer to the average cost of harm to the recipient and c' to refer to the average benefit of harm to the actor.

I note that the simplest strategy set for each type of behavior will include an obligate action, an obligate non-action, and a discriminatory action. For both help and harm, therefore, I allow for both obligate help ("Always Help") and obligate harm ("Always Harm"), obligate non-help ("Never Help") and obligate nonharm ("Never Harm"), and discriminatory help ("Help Like") and discriminatory harm ("Harm Different"). I assume that Help Like helps only those sharing a cue, while Harm Different harms only those not sharing a cue. More specifically, I assume that the cue is detectable after fusion of blood vessels and is not coded by the fusion-activator cue gene. I consider the evolution of help and that of harm separately,

assuming that the obligate nonactions are resident strategies.

In summary of the results (tables A8, A9), Help Like can invade and resist invasion by Never Help if $rb > c$, where $r = K/[K + (1 - K)P_j]$. Here, r increases with increasing K and decreasing P_j (or increasing v ; fig. A1; figs. A1, A2 available online). The benefit of Help Like, relative to that of Never Help, is that Help Like helps i colonies with probability above random r of sharing the Help Like allele. Moreover, Help Like will resist invasion by Always Help where $(1 - K)P_j c > 0$. The benefit of Help Like, relative to that of Always Help, is that Help Like accepts the benefits of help from Always Help and never reciprocates in random j encounters (table A2). When Help Like is fixed, rare alleles of its cue locus are disfavored where $(1 - K)(b - c) > 0$. Because it is necessary that $1 - K > 0$ for Help Like to resist invasion by Always Help and that $b - c > 0$ for Help Like to resist invasion by Never Help (because $0 \leq r \leq 1$), Help Like disfavors rare alleles of its cue locus where it is maintained by selection.

Moreover, Harm Different can invade and resist invasion by Always Harm if $rb' > c'$ (same definition of r). The benefit of Harm Different, relative to that of Always Harm, is that Harm Different avoids harming i colonies with probability above random r of sharing the Harm Different allele. Likewise, Harm Different will resist invasion by Never Harm where $(1 - K)P_j c' > 0$. The benefit of Harm Different, relative to that of Never Harm, is that Harm Different harms Never Harm in random j encounters and is never harmed in return. When Harm Different is fixed, rare alleles of its cue locus are disfavored where $(1 - K)(b' - c') > 0$. Because it is necessary that $1 - K > 0$ for Harm Different to resist invasion by Never Harm and that $b' - c' > 0$ for Harm Different to resist invasion by Always Harm, Harm Different disfavors rare alleles of its cue locus where it is maintained by selection.

The Evolution of Minor Histocompatibility

I assume now that Help Like and Harm Different are both fixed and based on the same cue (the "interaction" cue). Consequently, fusion with clonemates and random i colonies results in a payoff $\varepsilon + B$, where $B = b - c$, while fusion with random j colonies results in a payoff $\varepsilon - C$, where $C = b' - c'$ (B is the net benefit of cooperation and C is the net cost of conflict). If Help Like and Harm Different are ESSs, then $B > 0$ and $C > 0$. Thus, the payoffs of fusion have changed from those assumed by the first model above.

What type of histocompatibility behavior might be advantageous and biologically plausible? One strategy would permit fusion with i colonies but not with j colonies, because $\varepsilon + B > 0$ and it is possible that $\varepsilon - C < 0$. Because

the interaction cue must be detectable only after fusion, however, I assume that histocompatibility functions by means of discriminatory rejection after initial fusion. Thus, colonies will reject only those differing in a cue (j), and this rejection leads to colony separation. Moreover, I include parameters δ_1 and δ_2 , which represent the fraction of the life span spent in fusion when one (δ_1) or both (δ_2) colonies in a pairwise encounter reject on the basis of the interaction cue ($0 \geq \delta_1 \geq 1$ and $\delta_2 \leq \delta_1$). If two colonies fuse for δ_1 of the life span, then δ_1 of the payoff of the interaction occurs. Biologically speaking, a greater δ_1 or δ_2 may be reflective of a situation where rejection occurs only after vascular fusion and substantial cell exchange. I assume that once rejection is complete, each colony is dominated exclusively by a single clone and within-organism conflict ceases (fig. 2).

Because this histocompatibility behavior operates by means of discriminatory rejection, I assume that it is coded by a gene separate from that coding Always Fuse. I include as the resident strategy a null behavior that does not reject, "Never Reject." Where Never Reject is fixed, fusion always occurs, because Always Fuse is fixed at a separate locus. An additional strategy rejects when the fusion-activator cue gene is shared. I call this strategy "Always Reject" and assume that when activated it triggers immediate rejection that prevents fusion completely. Finally, I include a discriminatory strategy, "Minor Histocompatibility," that rejects j colonies but not i colonies, subject to the constraints mentioned above (fig. 2).

In summary of the results (table A10), Minor Histocompatibility can invade and resist invasion by Never Reject for the benefit of rejecting random j colonies. Minor Histocompatibility can resist invasion by Always Reject for the benefit of allowing fusion with clonemates and random i colonies. When Minor Histocompatibility is maintained by selection, selection against rare interaction cue alleles imposed by Harm Different is alleviated where $1 > \delta_2 > 0$ and eliminated where $\delta_2 = 0$. However, Minor Histo-

compatibility has no effect on the alleviating selection against rare interaction cues imposed by Help Like, which persists for any value of δ_2 . Thus, Minor Histocompatibility does not itself favor rare cue alleles.

The Evolution of Major Histocompatibility

The previous model demonstrated a condition under which a histocompatibility behavior can evolve. We are still left with the question of how a histocompatibility behavior can select for polymorphism of its cue. I here assume that at some point in evolutionary time, a different phenotype becomes available for use as a cue. This phenotype is detectable before fusion, and the rejection based on it allows a colony to avoid fusion completely. I here examine the conditions under which a histocompatibility behavior that utilizes this cue, which I call "Major Histocompatibility," can be favored. I also ask whether such a behavior selects for polymorphism of its cue (the "major-histocompatibility" cue).

I assume the same set of behavioral strategies as in the previous model, with one addition: Major Histocompatibility. Major Histocompatibility activates rejection when the fusion-activator cue gene is shared, like Always Reject, but it inhibits rejection when an allele of the major-histocompatibility cue is shared. Thus, rejection with colonies sharing a major-histocompatibility cue will be quickly suppressed, leading to fusion, while rejection with colonies not sharing a major-histocompatibility cue will not be suppressed (fig. 3). In addition, Major Histocompatibility also carries out the Minor Histocompatibility function. Thus, if the major-histocompatibility cue is shared but the interaction cue is not, rejection occurs as if it were carried out by Minor Histocompatibility (e_1 in fig. 3).

To allow for two cue genes, I list the major-histocompatibility cue first and the interaction cue second. An ij colony thus shares the major-histocompatibility cue ($i \cdot$) and differs in the interaction cue ($\cdot j$). I assume that the

Figure 2: Minor Histocompatibility rejection based on the interaction cue can result in rejection before the possibility for within-organism conflict ($\delta_1 = 0$; A); delayed rejection, resulting in some within-organism conflict ($\delta_1 > \delta_2 > 0$; B); or no rejection ($\delta_1 = \delta_2 = 1$; C), resulting in conflict. When one colony rejects on the basis of the interaction cue, a payoff $\delta_1(\epsilon - C)$ results. When both colonies reject on the basis of the interaction cue, a payoff $\delta_2(\epsilon - C)$ results. Here, circles represent colonies. Different shades represent different genotypes. Costs of conflict are represented by a decrease in colony size.

Figure 3: Scenario for the genetics of Major Histocompatibility. A, The ability to recognize an activator of fusion is innate, indicated by the presence of a template (a) of the fusion-activator, cue-template pair in developing embryos and larvae. B, The ability to recognize an inhibitor of rejection is present once the template (b) of the rejection-inhibitor, cue-template pair is developed by cell education. Rejection is also based on the fusion-activator cue and becomes active once the rejection-inhibition capacity is mature. C, Clonemates sharing an allelic variant of the rejection-inhibitor cue (major-histocompatibility cue) fuse. D, Non-kin not sharing an allelic variant of the major-histocompatibility cue reject. E, Non-kin sharing an allelic variant of the major-histocompatibility cue fuse and either conflict and undergo delayed rejection because they do not share the within-organism interaction cue (e_1) or cooperate and form a stable chimera because they share the within-organism interaction cue (e_2).

major-histocompatibility cue gene has x alleles ($x \geq 1$) and that where $x > 1$, alleles are equally frequent ($P_i = 1/x$). As above, v is the number of interaction cue alleles ($P_i = 1/v$). A dot ($\cdot$) leaves a position unspecified; that is, $(\cdot)$ means “ i or j .” Thus, $P_{ii} = P_i \times P_{\cdot i}$.

Summarizing the results of this model (table A12), Major Histocompatibility can invade and resist invasion by Minor Histocompatibility only if the cost of fusion with random colonies, $P_{\cdot j} \delta_2 (C - \varepsilon)$, is greater than the benefit of fusion with random colonies, $P_{\cdot i} (B + \varepsilon)$. Moreover, Major Histocompatibility will resist invasion by Never Reject for avoiding fusion with non-kin and by Always Reject for allowing fusion with clonemates. When Major Histocompatibility is maintained as an ESS, a novel histocompatibility cue allele will have fitness higher than the population mean only if $P_{\cdot j} \delta_2 (C - \varepsilon) > P_{\cdot i} (B + \varepsilon)$. Because this is a necessary condition for Major Histocompatibility

to be an ESS, Major Histocompatibility will select for polymorphism of its cue (given, also, that $K < 1$). Moreover, once polymorphism has accumulated to a high level ($P_{\cdot i} \approx 0$), the conditions for Major Histocompatibility to be an ESS hold (table A11). The caveat is that encounters with colonies sharing the major-histocompatibility cue ($i \cdot$) must sometimes occur ($P_{\cdot i} > 0$). This ensures that Harm Different is maintained as an ESS and thus that the payoffs of fusion do not change.

This selective pressure for major histocompatibility cue polymorphism depends on the assumption that there is some interaction cue polymorphism. This raises the question of how much interaction cue polymorphism is necessary to select for polymorphism of the major-histocompatibility cue. To answer this question, I take the expression $P_{\cdot j} \delta_2 (C - \varepsilon) > P_{\cdot i} (B + \varepsilon)$, necessary for rare major-histocompatibility cue alleles to be favored, and substitute

$1/v$ for $P_{\cdot j}$ and $1 - 1/v$ for $P_{\cdot j}$. With rearrangement, this expression becomes

$$v > 1 + \frac{B + \varepsilon}{C - \varepsilon} \times \frac{1}{\delta_2}. \quad (1)$$

Inequality (1) shows that, where δ_2 is greater than $1/2$ and C is large relative to ε and B , only 2–7 interaction cue alleles are required to select for polymorphism of the major-histocompatibility cue locus (fig. 4). Even for lower values of δ_2 , there are conditions in which only 2–10 interaction cue alleles are required (fig. 4). A mildly polymorphic interaction cue can thus provide selection for extreme polymorphism of the major-histocompatibility cue locus.

A Cohesive Model

Thus far, I have divided a complex problem into simpler components and solved each in isolation. Now I will combine these solutions, using a particular set of parameter values, to solve the whole problem. To do so, I note that the only parameter that has been measured is x , the number of major-histocompatibility cue alleles in the population. I here assume that after polymorphism has accumulated, $x = 200$, which is similar to the number found in several species (Rinkevich et al. 1995; Gloria-Soria et al. 2012). Moreover, I assume that the major-histocompatibility cue initially has five alleles ($x = 5$) and that the interaction cue maintains at seven alleles ($v = 7$). For values of δ_1 and δ_2 , I assume a simple relationship such that dual rejection (δ_2) is increasingly effective relative to single rejection (δ_1) as the efficacy of single rejection increases, $\delta_2 = \delta_1^2$; specifically, $\delta_1 = 0.70$ and $\delta_2 = 0.49$.

To choose values of c , b , c' , and b' , I consider two situations, one where $c/b > c'/b'$ and another where $c/b = c'/b'$. To determine parameter values in the former case, I derive an argument based on consideration of the energetics of interactions (see “Derivation of Terms” in the appendix). This argument results in $c = 1.2$, $b = 1.3$, $c' = 0.80$, and $b' = 1.3$. I assume a value of K such that $c/b > K/[K + (1 - K)P_i] > c'/b'$; in particular, $K = 0.25$. For the latter case, I assume the same values except $b = b' = 0.80$ and $c = c' = 0.30$. Finally, I choose a value of ε such that $\varepsilon < C$, where $C = b' - c' = 0.50$; in both cases, $\varepsilon = 0.15$.

Examining each step of this evolutionary process in the former case demonstrates that histocompatibility can evolve in response to Harm Different, increase relatedness, and allow Help Like to evolve where it otherwise would not (fig. 5). In the latter case, Help Like and Harm Different both evolve immediately after the initial evolution

Figure 4: Minimum number of interaction-cue alleles (v) required to select for polymorphism of the major-histocompatibility cue locus, as a function of the fraction of conflict that occurs when both colonies reject on the basis of the interaction cue (δ_2) and the $(B + \varepsilon)/(C - \varepsilon)$ ratio (inequality [1]). Here, $(B + \varepsilon)/(C - \varepsilon)$ is $1/2$ for the long-dashed line, 1 for the short-dashed line, 2 for the dotted line, and 3 for the solid line; B is the average benefit of cooperation, ε is the net automatic benefit of fusion, and C is the average cost of conflict.

of fusion. Histocompatibility evolves nevertheless (table A15).

Discussion

By allowing for gradual evolution, I identified five steps in the origin of a complex histocompatibility system (fig. 5A–5F). My model predicts that histocompatibility evolves to avoid discriminatory within-organism conflict with non-kin. The selective advantage of rare major-histocompatibility cue alleles is also in avoiding conflict with non-kin. Major Histocompatibility is distinguished from Minor Histocompatibility in that it utilizes a separate cue for histocompatibility, as for within-organism conflict. Such behavior can be favored where the cue for conflict is detectable only after vascular fusion. I showed also that a relatively low level of polymorphism of a within-organism interaction cue can select for extreme polymorphism of a major-histocompatibility cue. This selective pressure is evolutionarily stable as polymorphism accumulates. I found that histocompatibility, evolving in response to discriminatory conflict, can incidentally promote the evolution of cooperation (fig. 5F, 5G). However, this is an incidental effect of adaptation and not the driving cause.

Model Assumptions

I here attempt to gauge the sensitivity of my model's outcome to some of its assumptions. A first assumption is

Figure 5: Gradual evolution of histocompatibility. A, Initially, colonies never fuse. B, Evolution of indiscriminate fusion (Always Fuse) leads to widespread fusion and immediate benefits, ε . C, Evolution of discriminatory within-organism conflict (Harm Different) decreases $\bar{W}$. D, Evolution of discriminatory rejection based on the conflict cue (Minor Histocompatibility) avoids some conflict and increases $\bar{W}$. E, Evolution of histocompatibility based on a separate cue (Major Histocompatibility) further avoids conflict and increases $\bar{W}$ and r . F, Evolution of major-histocompatibility cue polymorphism avoids conflict and increases $\bar{W}$ and r . G, Evolution of discriminatory within-organism cooperation (Help Like) increases $\bar{W}$. In the sample populations, circles represent colonies. Fitness effects of fusion are indicated by change in average colony size. Shades in sample populations, histograms, and pie charts indicate outcomes. Pie charts summarize outcomes. Parameter values for all panels are $K = 0.25$, $\varepsilon = 0.15$, $b = 1.3$, $c = 1.2$, $b' = 1.3$, $c' = 0.80$, $v = 7$, $\delta_1 = 0.70$, and $\delta_2 = 0.49$. For panels A–E, $x = 5$; for F, G, $x = 200$. See tables A13, A14, fig. A2, and the appendix for details.

that non-kin share alleles randomly. This assumption could be violated if dispersal and mating are nonrandom, such that the population is divided into genetically distinct demes. Whether this genetic structure could lead to a different evolutionary outcome may depend on the situation. In a first situation, there is little genetic variability within demes. Histocompatibility would be less likely to evolve because the type of colonies that normally encounter each other, those from the same deme, would tend to share genetic cues independent of relatedness (preventing the evolution of discriminatory behaviors such as Harm Different). In a second situation, there is substantial genetic variation within demes but occasional migration between demes. The effect of interdemic encounters would be to raise the probability that colonies differing in major-histocompatibility cue alleles also differ in interaction cue alleles. This would favor rare major-histocompatibility cue alleles. Other factors that could lead to nonrandom allele sharing with non-kin include strong selection, major mutational events leading to genetic linkage (e.g., chromosomal inversions), and long-term maintenance of clones in a population. If such factors led to very strong genetic correlations between the interaction cue and the major-histocompatibility cue, then Major Histocompatibility could exert a selective pressure on its cue locus similar to that of Minor Histocompatibility where $\delta_2 = 0$. Weaker genetic correlations might reduce, but not remove, selection favoring rare major-histocompatibility cue alleles. More-specific models will be necessary to gauge the effects of nonrandom allele sharing with non-kin on evolutionary outcomes.

Another assumption of my model is that the only kin encountered are fragmented clonemates. I did not here allow for encounters with self, as might occur if colonies wrap around three-dimensional substrates (Feldgarden and Yund 1992). I also did not consider the effects of encounters with sexually produced categories of kin (e.g., siblings, parents), as may result from nonrandom larval dispersal. Organisms that encounter self or sexual kin may still encounter non-kin, so it is possible that histocompatibility is still favored for avoiding fusion with non-kin. However, it is important to mention two discrepancies. First, where histocompatibility mediates self-fusion and not fusion with physically discrete colonies, the cost of parasite transmission caused by fusion, p , would be limited to fusion with nonself. Thus, parasite transmission could provide a differential selective pressure for histocompatibility that complements discriminatory within-organism conflict. In the case of nonrandom dispersal of larvae, an additional question is whether strategies that permit fusion with nonclonemate kin can be favored (e.g., allele-sharing recognition; Grosberg 1988).

I also made a number of assumptions for the genetic

basis of histocompatibility. The first assumption was that help and harm are not based on the fusion-activator cue gene. My defense for this assumption is that there are many possible genes coding for phenotypes that could be used as cues for within-organism interactions (e.g., detectable within the blood), of which the fusion-activator cue gene is but one. Moreover, the fusion-activator cue need not be polymorphic, while various factors in the blood could be (e.g., cellular components involved with immunity). The second assumption was that there is only one cue gene for within-organism interactions. The presence of multiple such genes would increase the probability of conflict in fusion events with non-kin, which would favor histocompatibility. Third, I assumed that within-organism cooperation and conflict are based on the same cue. The use of separate cues would not drastically alter the outcome if cues are variable, because non-kin would be unlikely to share cues.

I also assumed that histocompatibility functions by means of discriminatory rejection rather than discriminatory fusion. For Minor Histocompatibility, this assumption can be justified by the argument that the fusion-activator cue will not directly correlate with the interaction cue unless the two genes are linked. For Major Histocompatibility, however, this assumption is more tenuous, because histocompatibility could work by discriminatory fusion (e.g., Fuse Like). In botryllid ascidians, histocompatibility functions by means of discriminatory rejection, as evidenced by the occurrence of some fusion before rejection in most species (Saito et al. 1994). In the star ascidian *Botryllus schlosseri*, genetic experiments suggest that the same gene, *fester*, encodes a receptor that activates both fusion and rejection (Nyholm et al. 2006), as assumed here (fig. 3). In an alternative model, one would ask whether a Fuse Like strategy can be favored in a population where Minor Histocompatibility is fixed at a separate locus. In that case, Fuse Like would have the same payoffs when encountering Always Fuse and Never Fuse as Major Histocompatibility has when encountering Never Reject and Always Reject here (table A5). Thus, Fuse Like would be favored under the same conditions, and which behavior evolves in practice would likely depend on historical constraints.

Three other assumptions of my model related to cue genes. In the first, I assumed that cue alleles of each locus are equally frequent. I made this assumption for mathematical simplicity, and it is unlikely to alter the main conclusion. Indeed, parameters P_i , P_p , P_j , and P_{ij} can also be calculated by summing across alleles of variable frequencies (sensu Grosberg and Quinn 1989). Also, the assumption of equally frequent cue alleles is not unrealistic, especially for the major-histocompatibility cue: it will likely hold approximately in equilibrium where negative fre-

quency-dependent selection maintains cue allele diversity (Grosberg 1988). Second, I assumed that a novel cue allele allows effective discrimination. This is possible where the cue type is learned, for example, by cell-level “education” (McKittrick et al. 2011). With innate recognition, complementary mutations in linked cue-template pairs may be required before novel cue alleles can function as such (Boehm 2006). Nevertheless, novel cue-template pairs originate by gradual divergence in binding affinities (Chookajorn et al. 2004). In such a case, polymorphism would be likely to accumulate more slowly and could have limits imposed by physical constraints of cue-template allelic matching. Third, to make a specific prediction for the number of alleles maintained in a population, it would be important to account for the effects of genetic drift (Grosberg 1988) or, in the case of innate recognition, physical constraints of cue-template allelic matching.

A final assumption of my model was that each colony encounters only one other colony. In some species that live in high-density situations, colonies might have the opportunity to fuse with more than one colony (e.g., Westerman et al. 2009). Assuming a simple situation where a second colony will be encountered if the first is rejected, rare cue alleles can be favored for allowing fusion with clonemates on a second encounter if the first encounter is with non-kin (see appendix, eq. [A2]). Thus, under high density, the selective pressure to cooperate with clonemates may complement the pressure to avoid conflict with non-kin in favoring rare cue alleles.

Evidence for Conflict in Marine Invertebrates

The primary hypothesis generated from this work is that discriminatory within-organism conflict selects for histocompatibility and associated cue polymorphism. If this hypothesis is correct, then discriminatory conflict should exist in organisms with histocompatibility. For an organism such as that envisioned here, however, encounters with non-kin would almost always lead to immediate rejection once a major-histocompatibility system is in place (fig. 5G). Thus, even if discriminatory conflict exists and selects for histocompatibility, there is no reason to expect that it will have been described in detail.

Nevertheless, there are two studies of the colonial ascidian *B. schlosseri* that report data on fusion between non-kin. In the first, Rinkevich and Weissman (1992) collected wild, fertilized, egg-bearing colonies of *B. schlosseri* from Monterey Bay and Santa Barbara, California (>200 miles apart). The offspring from Monterey and Santa Barbara colonies were paired (almost certainly unrelated), and five fusion events were described. Out of the five chimeric organisms, the four surviving ones had less than one-half the average size of the seven colonies that rejected. In

another study, Chadwick-Furman and Weissman (2003) examined the outcome of encounters between nonsibling colonies derived from separate wild parent colonies at Monterey Bay. They found that six of eight fused colonies and 16 of 28 rejecting colonies died before breeding (N. E. Chadwick, unpublished data). This corresponds to a 75% versus a 57% death rate in fusing versus rejecting nonsibling colonies.

There are more data on the outcome of fusion between sexually produced kin in *B. schlosseri*. Fusion between sexual kin is expected to lead to conflict because sexual kin will often not share both alleles of a diploid locus. If conflict is triggered when at least one allele of a diploid locus is not shared, then conflict will be relatively common. In *B. schlosseri*, kin fusion often leads to delayed rejection, decreased colony growth rates, and the death of one or both partners in a chimera (Rinkevich and Weissman 1987, 1989, 1992). In one striking example, Rinkevich and Weissman (1989) found that out of nine pairs of colonies that fused, both partners died in six (in at least one replicate) and none died in the control replicates (relatedness was not reported). Rinkevich and Weissman (1989) concluded that there was a noxious interaction between fused partners.

Evidence of Gradual Evolution

A molecular phylogeny of botryllid ascidians shows that a lack of fusion is the ancestral state, rejection after vascular fusion is the intermediate state, and rejection before vascular fusion is the most derived state (fig. 6). Moreover, only blood cells are involved in the rejection reaction of species that reject after vascular fusion, while both blood and tunic cells are involved in many species that reject before vascular fusion (Hirose 2003). These data are consistent with Major Histocompatibility supplanting Minor Histocompatibility, as my model predicts. It is also worth note that the colonial aplousobranch ascidian *Diplosoma listerianum* (Didemnidae) fuses tunic indiscriminately, suggesting that in addition to the strategies in figure 6, an Always Fuse strategy can also be stable in the long term in colonial ascidians. It seems as though the likely reason an Always Fuse strategy is stable in *D. listerianum* is that this species does not fuse blood vessels, which reduces the opportunities for conflict (Bishop and Sommerfeldt 1999).

Comparison of Marine Invertebrates and Multinucleate Organisms

If one were to make a direct comparison between fungal heterokaryon incompatibility and marine invertebrate histocompatibility, one would be perplexed by the fact that heterokaryon incompatibility systems involve multiple, mildly polymorphic cue genes (Cortesi and Milgroom

Figure 6: Evidence for the gradual evolution of histocompatibility in colonial ascidians. Species with Minor Histocompatibility reject after vascular fusion, while those with Major Histocompatibility reject before vascular fusion. Character state for *Botrylloides leachi* from Zaniolo et al. (2006). The character state for *Styela plicata* I label “ambiguous” because it is unclear how common fusion is, and there is no direct evidence of rejection separating individuals (Kingsley et al. 1989). Phylogeny is based on 18S ribosomal DNA sequence; numbers at nodes represent percent of bootstraps that support the node. Redrawn from Cohen et al. (1998).

1998; Glass et al. 2000). In contrast, marine invertebrate histocompatibility usually has one or two highly polymorphic cue genes (Rosengarten and Nicotra 2011). Moreover, some fungal heterokaryon incompatibility genes are also involved in mate compatibility (Cortesi and Milgroom 1998; Glass et al. 2000), in contrast to marine invertebrate histocompatibility genes (Grosberg and Hart 2000). According to my model, this discrepancy can be explained if heterokaryon incompatibility genes trigger within-organism conflict and minor histocompatibility-like behavior. This would explain why these genes are only mildly polymorphic, why they are active only following hyphal fusion (Saupe 2000), why they lead to apparent conflict (e.g., slow growth and aberrant morphology), and why they are sometimes found to have pleiotropic functions that may balance their polymorphism (e.g., functions in mate compatibility).

If fungal heterokaryon incompatibility genes are the analogues of conflict/minor-histocompatibility cue genes, what are the analogues of major-histocompatibility cue

genes? To answer this question, it is important to recognize that the analogue of major-histocompatibility behavior would be rejection before hyphal fusion. An example of such behavior is found in the ascomycete fungus *Rossellinia necatrix* (Inoue et al. 2011), and it appears to be triggered by a single Mendelian factor (Ikeda et al. 2011). Although there is increasing evidence of similar behavior across fungi (Ford et al. 1995; Giovannetti et al. 2003; Micali and Smith 2003; Iotti et al. 2012; Smith and Lafontaine 2013), there is only one example where a gene has been isolated. This example is the *vic4* gene of the chestnut blight fungus *Cryphonectria parasitica* (Ascomycota). When two strains that differ in *vic4* encounter each other, the result is the formation of a boundary, or “barrage,” that prevents fusion (Smith et al. 2006). However, when strains differing in *vic4* are forced to fuse, there is no sign of heterokaryon incompatibility (Smith et al. 2006). Thus, *vic4* may be the fungal analogue of a major-histocompatibility cue gene. This argument is consistent with the finding of frequent barrage formation between

distinct isolates of *C. parasitica* in nature (Liu and Milgroom 2007).

If fungal heterokaryon incompatibility genes are the functional equivalents of within-organism interaction cue genes, then why are they so well studied in fungi but not in marine invertebrates? One reason is that fungal geneticists have invented methods for creating chimeras using auxotrophic mutants that must form a chimera to survive (Leslie 1993). This method leads to a chimera in which one clone will not be lost because of sampling error or an effect of genetic background: only discrimination based on differences in a heterokaryon incompatibility gene will lead to altered clonal proportions. Thus, the method allows inference of within-organism discrimination and isolation of the genes involved. This method also allowed Smith et al. (2006) to force chimerism between clones that differ in a mycelial compatibility gene. No comparable methods exist for carefully distinguishing within-organism discrimination in marine invertebrates or for forcing chimerism between colonies differing in major-histocompatibility alleles.

An additional informative comparison can be made between the colonial hydroid *Hydractinia symbiolongicarpus* and the plasmodial slime mold *Physarum polycephalum*. In many respects, encounters between *P. polycephalum* plasmodia and between *H. symbiolongicarpus* colonies look superficially the same (Carlile 1972; Buss et al. 2012). Both organisms have vascular systems, and fusion leads to anastomoses. A difference is what happens when unrelated colonies that share major-histocompatibility genes fuse. In *H. symbiolongicarpus*, the consequence is minor tissue degradation and delayed rejection (Powell et al. 2007). In *P. polycephalum*, the consequence is extreme conflict and no sign of delayed rejection (Carlile 1972). One possible explanation for this discrepancy is that *H. symbiolongicarpus* is a multicellular organism with blood cells. If blood cells can play a role in minor-histocompatibility rejection reaction, as shown in *Botryllus scalaris* (fig. 6; Shirae et al. 1999), the resulting minor-histocompatibility reaction could be more effective in separating colonies. In contrast, *P. polycephalum* lacks blood cells, and it is unknown whether nuclei carry out the same complex functions. Moreover, the rapid protoplasmic streaming (Carlile and Dee 1967) could result in a situation where any fusion in *P. polycephalum* leads quickly to conflict (equivalent to $\delta_1 = \delta_2 = 1$).

Other Comparisons

There is no evidence of histocompatibility in plants that naturally fuse roots and stems (Linhart and Tomback 1985; Carsey and Tomback 1994; Jelínková et al. 2009; McIntire and Fajardo 2011). Plants generally fuse indiscriminately when artificially grafted, and any exceptions can be ex-

plained as consequences of response to injury (Moore 1984; Garner and Bradley 2013). Why is histocompatibility absent in plants? Buss (1987) proposed that plants lack histocompatibility because plant cells are immobile, which prevents germline parasitism (see also Brusini et al. 2013). Germline parasitism occurs when one genotype in a chimera usurps the gonads or reproductive cells of the other. Other forms of conflict, however, are also possible. Plants could potentially rob each other of water and nutrients via the use of specialized structures, haustoria, that facilitate penetration of tissue, prying, and sucking (Moss 1926; Heckard 1962). This potential for conflict seems to be limited, however, to interspecific parasitism (Westwood et al. 2010). Thus, the lack of histocompatibility in plants can be explained by a relative lack of potential for conflict, discriminatory or otherwise, with possible benefits of fusion being prevalent (Tarroux and DesRochers 2011).

It may also be asked how histocompatibility compares to nestmate recognition in social insects. Here, it is important to note three distinctions. First, without nestmate recognition, the members of neighboring colonies are free to interact. Social insects lack the equivalent ectodermal tissue at the colony level, and there is no need for specific mechanisms allowing between-colony fusion. Second, social insects can use spatial cues for discriminatory harming behaviors such as brood raiding and nest robbery (Fletcher and Michener 1987). Third, where spatial cues are used for harming behaviors, it is impossible to use the same cue for nonnestmate rejection. One cannot discriminate individuals at one location by using “location” as a cue. Thus, nestmate recognition would likely involve three evolutionary steps: the evolution of discriminatory conflict based on spatial cues, the evolution of nonnestmate rejection based on colony odor cues, and the evolution of colony odor cue diversity. There would be no separate step for the evolution of fusion or the evolution of minor histocompatibility-like behavior. Nestmate recognition would necessarily evolve as a major histocompatibility-like behavior, based on a cue separate from that use for harming behavior. Any subsequent conflict between nests would be analogous to “between-organism” conflict, in the sense that it could rely on variable odor cues that distinguish nests (Fletcher and Michener 1987), while the former types of “within-organism” conflict—for example, brood raiding and nest robbery—would be possible only at times of year before nestmate recognition systems become functional (Klahn 1988; Tschinkel 1992).

Another question is how the results of this model apply to vertebrate animals, where fusion is restricted to viviparous taxa and occurs only among kin in the context of pregnancy. Here, vascular connection between mother and fetus leads to potential conflict: the fetus genome would benefit by usurping the germline of the mother, and vice

versa (Buss 1982). Thus, within-organism conflict between mother and fetus is expectable, and there is some evidence of germline parasitism (Mayr et al. 1979) and various tissue disorders associated with chimerism in humans (Bianchi 2000; Voskoboynik 2009; Fugazzola et al. 2011). There is also evidence that major histoincompatibility can prevent maternal-fetal chimerism in house mice *Mus musculus* (Kaplan and Land 2005). Thus, it remains possible that vertebrate major-histocompatibility polymorphism is favored, in part, for limiting the degree of chimerism (see also Naugler 2011).

A final question is why there has been so much evidence of inbreeding depression (Keller and Waller 2002; Charlesworth and Willis 2009) and well-developed theory of self-incompatibility invoking inbreeding depression as a selective pressure (Barrett 2002; Charlesworth 2006) but so little evidence of discriminatory within-organism conflict and no theory of histocompatibility invoking discriminatory within-organism conflict as a selective pressure until now. One possible answer is that a trait leading to the evolution of histocompatibility, organismal fusion, is a prerequisite for the evolution of discriminatory within-organism conflict (fig. 5), but a trait leading to the evolution of self-incompatibility, hermaphroditism, is not a prerequisite for the evolution of inbreeding depression (Lande and Schemske 1985). Indeed, inbreeding depression is even more severe where mechanisms promoting inbreeding, such as hermaphroditism, are not present (Keller and Waller 2002). Thus, inbreeding depression can be easily studied in organisms lacking self-incompatibility, but discriminatory within-organism conflict cannot easily be studied in organisms lacking histocompatibility. This difficulty can be surmounted by finding organisms with low costs of conflict and large immediate benefits of fusion. Such organisms may exhibit discriminatory conflict but not histocompatibility. A possible example of such an organism is the cellular slime mold *Dictyostelium discoideum*, which exhibits some evidence of discriminatory within-organism conflict (Buttery et al. 2009; Li et al. 2014) but weak histocompatibility-like behavior (Gilbert et al. 2012).

Conclusion

My model predicts that discriminatory within-organism conflict is a common selective pressure for histocompatibility and associated cue polymorphism. The difficulty in testing this hypothesis is that histocompatibility is expected to prevent the expression of conflict. One way to circumvent this difficulty is to find unrelated genotypes that share major-histocompatibility cues. Fusion between such genotypes should lead to conflict and delayed rejection. Examination of fusion between sexually reproduced kin should also afford observations of conflict and delayed

rejection. Discriminatory within-organism conflict may also be studied by forcing chimerism or by examining organisms that fuse and lack strong histocompatibility. If the theory here is correct, further elucidating the nature of discriminatory within-organism conflict will be the first step toward a more complete understanding of the adaptive basis of histocompatibility.

Acknowledgments

I thank T. Day, A. Gardner, and two anonymous referees for comments. I thank G. Balázs, J. Gilbert, L. Gilbert, D. Kapan, T. Miller, D. Queller, R. Rosengarten, G. Saxer, J. Smith, and J. Strassmann for comments on early versions of the manuscript. I thank N. Chadwick, M. Fagan, O. Harman, B. Rinkevich, and E. Westerman for discussions. I express gratitude to the Kavli Institute for Theoretical Physics at the University of California, Santa Barbara, for support, and to the participants of the 2013 program on cooperation and the evolution of multicellularity. This work was supported in part by the National Science Foundation under grant DEB 0816690 to D. Queller and J. Strassmann, in part by a Wray-Todd graduate fellowship to the author, and in part by the National Science Foundation under grant NSF PHY11-25915. I also thank L. Gilbert, C. Hawkes, and C. Sauer for encouragement and support.

Literature Cited

- Aanen, D. K., A. J. M. Debets, J. de Visser, and R. F. Hoekstra. 2008. The social evolution of somatic fusion. *BioEssays* 30:1193–1203.
- Barrett, S. C. H. 2002. The evolution of plant sexual diversity. *Nature Reviews Genetics* 3:274–284.
- Bianchi, D. W. 2000. Fetomaternal cell trafficking: a new cause of disease? *American Journal of Medical Genetics* 91:22–28.
- Bishop, J. D., and A. D. Sommerfeldt. 1999. Not like *Botryllus*: indiscriminate post-metamorphic fusion in a compound ascidian. *Proceedings of the Royal Society B: Biological Sciences* 266:241–248.
- Boehm, T. 2006. Quality control in self/nonself discrimination. *Cell* 125:845–858.
- Bourke, A. F. G. 2011. *Principles of social evolution*. Oxford University Press, Oxford.
- Brusini, J., C. Robin, and A. Franc. 2013. To fuse or not to fuse: an evolutionary view of self-recognition systems. *Journal of Phylogenetics and Evolutionary Biology* 1:103. doi:10.4172/2329-9002.1000103.
- Burnet, F. M. 1971. "Self-recognition" in colonial marine forms and flowering plants in relation to the evolution of immunity. *Nature* 232:230–235.
- . 1973. Multiple polymorphism in relation to histocompatibility antigens. *Nature* 245:359–361.
- Buss, L. W. 1982. Somatic cell parasitism and the evolution of somatic tissue compatibility. *Proceedings of the National Academy of Sciences of the USA* 79:5337–5341.

- . 1987. The evolution of individuality. Princeton University Press, Princeton, NJ.
- Buss, L. W., C. Anderson, E. Westerman, C. Kritzberger, M. Poudyal, M. A. Moreno, and F. G. Lakkis. 2012. Allorecognition triggers autophagy and subsequent necrosis in the cnidarian *Hydractinia symbiolongicarpus*. PLoS ONE 7:e48914. doi:10.1371/journal.pone.0048914.
- Buttery, N. J., D. E. Rozen, J. B. Wolf, and C. R. L. Thompson. 2009. Quantification of social behavior in *D. discoideum* reveals complex fixed and facultative strategies. Current Biology 19:1373–1377.
- Carlile, M. J. 1972. The lethal interaction following plasmodial fusion between two strains of the myxomycete *Physarum polycephalum*. Journal of General Microbiology 71:581–590.
- Carlile, M. J., and J. Dee. 1967. Plasmodial fusion and lethal interaction between strains of a myxomycete. Nature 215:832–834.
- Chadwick-Furman, N. E., and I. L. Weissman. 2003. Effects of allogeneic contact on life-history traits of the colonial ascidian *Botryllus schlosseri* in Monterey Bay. Biological Bulletin 205:133–143.
- Charlesworth, D. 2006. Evolution of plant breeding systems. Current Biology 16:R726–R735.
- Charlesworth, D., and J. H. Willis. 2009. The genetics of inbreeding depression. Nature Reviews Genetics 10:783–796.
- Chookajorn, T., A. Kachroo, D. R. Ripoll, A. G. Clark, and J. B. Nasrallah. 2004. Specificity determinants and diversification of the *Brassica* self-incompatibility pollen ligand. Proceedings of the National Academy of Sciences of the USA 101:911–917.
- Clark, J., and E. F. Haskins. 2012. Plasmodial incompatibility in the myxomycetes: a review. Mycosphere 3:143–155.
- Cohen, C. S., Y. Saito, and I. L. Weissman. 1998. Evolution of allorecognition in botryllid ascidians inferred from a molecular phylogeny. Evolution 52:746–756.
- Cortesi, P., and M. G. Milgroom. 1998. Genetics of vegetative incompatibility in *Cryphonectria parasitica*. Applied and Environmental Microbiology 64:2988–2994.
- Darwin, C. D. 1872. The origin of species. 6th ed. J. Murray, London.
- Feldgarden, M., and P. O. Yund. 1992. Allorecognition in colonial marine invertebrates: does selection favor fusion with kin or fusion with self? Biological Bulletin 182:155–158.
- Fisher, R. A. (1930) 1999. The genetical theory of natural selection: a complete variorum edition. Oxford University Press, Oxford.
- Fletcher, D. C., and C. D. Michener. 1987. Kin recognition in animals. Wiley, New York.
- Folse, H. J., III. 2011. Weighing benefits of large size, costs of genetic interference, and risks of germ cell parasitism: modeling the decision to fuse or reject in a colonial ascidian. Pages 86–141 in Evolution and individuality: beyond the genetically homogeneous organism. PhD diss. Stanford University.
- Ford, E. J., R. V. Miller, H. Gray, and J. E. Sherwood. 1995. Heterokaryon formation and vegetative compatibility in *Sclerotinia sclerotiorum*. Mycological Research 99:241–247.
- Fugazzola, L., V. Cirello, and P. Beck-Peccoz. 2011. Fetal microchimerism as an explanation of disease. Nature Reviews Endocrinology 7:89–97.
- Garner, R. J., and S. Bradley. 2013. The grafter's handbook. Chelsea Green, White River Junction, VT.
- Gibbs, K. A., M. L. Urbanowski, and E. P. Greenberg. 2008. Genetic determinants of self identity and social recognition in bacteria. Science 321:256–259.
- Gilbert, O. M., J. E. Strassmann, and D. C. Queller. 2012. High relatedness in a social amoeba: the role of kin-discriminatory segregation. Proceedings of the Royal Society B: Biological Sciences 279:2619–2624.
- Giovannetti, M., C. Sbrana, P. Strani, M. Agnolucci, V. Rinaudo, and L. Avio. 2003. Genetic diversity of isolates of *Glomus mosseae* from different geographic areas detected by vegetative compatibility testing and biochemical and molecular analysis. Applied and Environmental Microbiology 69:616–624.
- Glass, N. L., D. J. Jacobson, and P. K. T. Shiu. 2000. The genetics of hyphal fusion and vegetative incompatibility in filamentous ascomycete fungi. Annual Review of Genetics 34:165–186.
- Gloria-Soria, A., M. A. Moreno, P. O. Yund, F. G. Lakkis, S. L. Dellaporta, and L. W. Buss. 2012. Evolutionary genetics of the hydroid alldeterminant *alr2*. Molecular Biology and Evolution 29:3921–3932.
- Grafen, A. 1990. Do animals really recognize kin? Animal Behaviour 39:42–54.
- Grosberg, R. K. 1988. The evolution of allorecognition specificity in clonal invertebrates. Quarterly Review of Biology 63:377–412.
- Grosberg, R. K., and M. W. Hart. 2000. Mate selection and the evolution of highly polymorphic self/nonself recognition genes. Science 289:2111–2114.
- Grosberg, R. K., and J. F. Quinn. 1988. The evolution of allorecognition specificity. Pages 157–167 in R. K. Grosberg, D. Hedgecock, and K. Nelson, eds. Invertebrate historecognition. Plenum, New York.
- . 1989. The evolution of selective aggression conditioned on allorecognition specificity. Evolution 43:504–515.
- Harman, O. 2011. Birth of the first ESS: George Price, John Maynard Smith, and the discovery of the lost “Antlers” paper. Journal of Experimental Zoology B 316:1–9.
- Heckard, L. R. 1962. Root parasitism in *Castilleja*. Botanical Gazette 124:21–29.
- Hepper, P. G. 1991. Kin recognition. Cambridge University Press, Cambridge.
- Hirose, E. 2003. Colonial allorecognition, hemolytic rejection, and viviparity in botryllid ascidians. Zoological Science 20:387–394.
- Hirose, S., R. Benabentos, H. Ho, A. Kuspa, and G. Shaulsky. 2011. Self-recognition in social amoebae is mediated by allelic pairs of *tiger* genes. Science 333:467–470.
- Holman, L., J. S. van Zweden, T. A. Linksvayer, and P. d'Ettorre. 2013. Crozier's paradox revisited: maintenance of genetic recognition systems by disassortative mating. BMC Evolutionary Biology 13:211. doi:10.1186/1471-2148-13-211.
- Ikeda, K., K. Inoue, H. Nakamura, T. Hamanaka, T. Ohta, H. Kitazawa, C. Kida, S. Kanematsu, and P. Park. 2011. Genetic analysis of barrage line formation during mycelial incompatibility in *Rosellinia necatrix*. Fungal Biology 115:80–86.
- Inoue, K., S. Kanematsu, P. Park, and K. Ikeda. 2011. Cytological analysis of mycelial incompatibility in *Rosellinia necatrix*. Fungal Biology 115:87–95.
- Iotti, M., A. Rubini, E. Tisserant, A. Kholer, F. Paolocci, and A. Zambonelli. 2012. Self/nonself recognition in *Tuber melanosporum* is not mediated by a heterokaryon incompatibility system. Fungal Biology 116:261–275.
- Jelinková, H., F. Tremblay, and A. DesRochers. 2009. Molecular and dendrochronological analysis of natural root grafting in *Populus tremuloides* (Salicaceae). American Journal of Botany 96:1500–1505.
- Kaplan, J., and S. Land. 2005. Influence of maternal-fetal histocom-

- patibility and MHC zygosity on maternal microchimerism. *Journal of Immunology* 174:7123–7128.
- Keller, L. F., and D. M. Waller. 2002. Inbreeding effects in wild populations. *Trends in Ecology and Evolution* 17:230–241.
- Kingsley, E. A., D. A. Briscoe, and D. A. Raftos. 1989. Correlation of histocompatibility reactions with fusion between conspecifics in the solitary urochordate *Styela plicata*. *Biological Bulletin* 176:282–289.
- Klahn, J. 1988. Intraspecific comb usurpation in the social wasp *Polistes fuscatus*. *Behavioral Ecology and Sociobiology* 23:1–8.
- Lande, R., and D. W. Schemske. 1985. The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. *Evolution* 39:24–40.
- Leslie, J. F. 1993. Fungal vegetative compatibility. *Annual Review of Phytopathology* 31:127–150.
- Li, S. I., N. J. Buttery, C. R. L. Thompson, and M. D. Purugganan. 2014. Sociogenomics of self vs. non-self cooperation during development of *Dictyostelium discoideum*. *BMC Genomics* 15:616. doi:10.1186/1471-2164-15-616.
- Linhart, Y. B., and D. F. Tomback. 1985. Seed dispersal by nutcrackers causes multi-trunk growth form in pines. *Oecologia (Berlin)* 67:107–110.
- Liu, Y., and M. G. Milgroom. 2007. High diversity of vegetative compatibility types in *Cryphonectria parasitica* in Japan and China. *Mycologia* 99:279–284.
- Maynard Smith, J. 1982. *Evolution and the theory of games*. Cambridge University Press, Cambridge.
- Maynard Smith, J., and E. Szathmáry. 1995. *The major transitions in evolution*. W. H. Freeman, Oxford.
- Mayr, W. R., V. Pausch, and W. Schnedl. 1979. Human chimaera detectable only by investigation of her progeny. *Nature* 277:210–211.
- McIntire, E. J., and A. Fajardo. 2011. Facilitation within species: a possible origin of group-selected superorganisms. *American Naturalist* 178:88–97.
- McKittrick, T. R., C. C. Muscat, J. D. Pierce, D. Bhattacharya, and A. W. De Tomaso. 2011. Allorecognition in a basal chordate consists of independent activating and inhibitory pathways. *Immunity* 34:616–626.
- Micali, C. O., and M. L. Smith. 2003. On the independence of barrage formation and heterokaryon incompatibility in *Neurospora crassa*. *Fungal Genetics and Biology* 38:209–219.
- Moore, R. 1984. A model for graft compatibility-incompatibility in higher plants. *American Journal of Botany* 71:752–758.
- Moss, E. H. 1926. Parasitism in the genus *Comandra*. *New Phytologist* 25:264–276.
- Naugler, C. 2011. Immune recognition of transplacentally acquired lymphoid allografts selects for increased major histocompatibility polymorphism. *Medical Hypotheses* 77:323–325.
- Nyholm, S. V., E. Passegue, W. B. Ludington, A. Voskoboynik, K. Mitchel, I. L. Weissman, and A. W. De Tomaso. 2006. *fester*, a candidate allorecognition receptor from a primitive chordate. *Immunity* 25:163–173.
- Powell, A. E., M. L. Nicotra, M. A. Moreno, F. G. Lakkis, S. L. Dellaporta, and L. W. Buss. 2007. Differential effect of allorecognition loci on phenotype in *Hydractinia symbiolongicarpus* (Cnidaria: Hydrozoa). *Genetics* 177:2101–2107.
- Price, G. R. 1968. Antlers, intraspecific combat, and altruism. *George Price Papers*. British Library, London.
- Rinkevich, B., R. Porat, and M. Goren. 1995. Allorecognition elements on a urochordate histocompatibility locus indicate unprecedented extensive polymorphism. *Proceedings of the Royal Society B: Biological Sciences* 259:319–324.
- Rinkevich, B., and I. L. Weissman. 1987. A long-term study on fused subclones in the ascidian *Botryllus schlosseri*: the resorption phenomenon (Protochordata, Tunicata). *Journal of Zoology* 213:717–733.
- . 1989. Variation in the outcomes following chimera formation in the colonial tunicate *Botryllus schlosseri*. *Bulletin of Marine Science* 45:213–227.
- . 1992. Chimeras vs genetically homogeneous individuals: potential fitness costs and benefits. *Oikos* 63:119–124.
- Rosengarten, R. D., and M. L. Nicotra. 2011. Model systems of invertebrate allorecognition. *Current Biology* 21:R82–R92.
- Rousset, F., and D. Roze. 2007. Constraints on the origin and maintenance of genetic kin recognition. *Evolution* 61:2320–2330.
- Saito, Y., E. Hirose, and H. Watanabe. 1994. Allorecognition in compound ascidians. *International Journal of Developmental Biology* 38:237–247.
- Saupe, S. J. 2000. Molecular genetics of heterokaryon incompatibility in filamentous ascomycetes. *Microbiology and Molecular Biology Reviews* 64:489–502.
- Shirae, M., E. Hirose, and Y. Saito. 1999. Behavior of hemocytes in the allojection reaction in two compound ascidians, *Botryllus scalaris* and *Symplesma reptans*. *Biological Bulletin* 197:188–197.
- Smith, M. L., C. C. Gibbs, and M. G. Milgroom. 2006. Heterokaryon incompatibility function of barrage-associated vegetative incompatibility genes (*vic*) in *Cryphonectria parasitica*. *Mycologia* 98:43–50.
- Smith, M. L., and D. L. Lafontaine. 2013. The fungal sense of non-self. Pages 9–21 in D. P. Kasbekar and K. McCluskey, eds. *Neurospora: genomics and molecular biology*. Caister Academic, Norfolk.
- Tarroux, E., and A. DesRochers. 2011. Effect of natural root grafting on growth response of jack pine (*Pinus banksiana*; Pinaceae). *American Journal of Botany* 98:967–974.
- Tschinkel, W. R. 1992. Brood raiding and the population dynamics of founding and incipient colonies of the fire ant, *Solenopsis invicta*. *Ecological Entomology* 17:179–188.
- Velicer, G. J., and M. Vos. 2009. Sociobiology of the myxobacteria. *Annual Review of Microbiology* 63:599–623.
- Voskoboynik, A. 2009. Chimerism and a natural ability to tolerate kin, evolutionary traits connecting mammalian and protochordates. *Invertebrate Survival Journal* 6:S9–S20.
- Westerman, E. L., J. A. Dijkstra, and L. G. Harris. 2009. High natural fusion rates in a botryllid ascidian. *Marine Biology* 156:2613–2619.
- Westwood, J. H., J. I. Yoder, M. P. Timko, and C. W. dePamphilis. 2010. The evolution of parasitism in plants. *Trends in Plant Science* 15:227–235.
- Worrall, J. J. 1997. Somatic incompatibility in basidiomycetes. *Mycologia* 89:24–36.
- Zaniolo, G. L., L. Manni, and L. Ballarin. 2006. Colony specificity in *Botrylloides leachi*. I. Morphological aspects. *Invertebrate Survival Journal* 3:125–136.

Associate Editor: Andy Gardner
Editor: Troy Day