Creation and maintenance of variation in allorecognition loci: molecular analysis in various model systems

Marie L. Nydam* and Anthony W. De Tomaso

Department of Molecular, Cellular and Developmental Biology, University of California Santa Barbara, Santa Barbara, CA, USA

INTRODUCTION

Allorecognition is the ability of an organism to differentiate self or close relatives from unrelated conspecifics, occurs throughout the tree of life (Buss, 1982), in anemones (Mercier et al., 2011), angiosperms (Allen and Hiscock, 2008), ascidians (Raitos, 1994; Saito et al., 1994; Harada et al., 2008), bacteria (Gibbs et al., 2008), bryozoans (Hughes et al., 2004), cellular slime molds (Shaulsky and Kessin, 2007), corals (Hidaka et al., 1997), fungi (Glass et al., 2000), gymnosperms (Pandey, 1960; Runions and Owens, 1998), hydroids (Grosberg et al., 1996), plasmodial slime molds (Clark, 2003), and sponges (Fernandez-Busquets and Burger, 1999).

Effective allorecognition systems are critical to the survival of organisms: the SI loci prevent inbreeding depression in plants, and in many colonial organisms, fusing to a closely related individual can provide competitive and reproductive advantages where space is limited and reproductive output is based on the size of the organism (Buss, 1982).

Despite decades of research, the genetic basis of allorecognition remains hidden in many groups, including bryozoans, corals, and sponges. Many marine invertebrate species are difficult to culture and breed, which limits the crossing experiments necessary to pinpoint genomic locations involved in allorecognition (Grosberg and Plachetzkii, 2010).

However, researchers have been studying the SI (self-incompatibility) loci in angiosperms for some time. And allorecognition genes have recently been identified in ascidians (Fusion Histocompatibility, FuHC in Botryllus schlosseri and s-themis/v-themis in Ciona intestinalis; De Tomaso et al., 2005; Harada et al., 2008, reviewed in Ben-Shlomo, 2008), bacteria (Gibbs et al., 2008), cellular slime molds [tgrB1 and tgrC1 in Dictyostelium discoideum (Shaulsky and Kessin, 2007)], hydroids [alr1 and alr2 in Hydractinia symbiologicarpus (Nicotra et al., 2009)], and fungi [het or vic loci (Glass et al., 2000)]. In this review we will focus only on organisms where the genetic basis of allorecognition has been identified, and where the polymorphism in these loci has been studied. Although the loci governing self-incompatibility have recently been identified in the ascidian C. intestinalis (Harada et al., 2008) and the bacterium Proteus mirabilis (Gibbs et al., 2008), no evolutionary studies have yet been published.

In the systems where the loci governing allorecognition outcomes have been identified, the corresponding proteins have often exhibited exceptional polymorphism. In the clover Trifolium pratense, up to 193 S-alleles in the SI system were identified (Lawrence, 1996), and 13–16 S-alleles were identified from 20 Arabidopsis lyrata plants (Mable et al., 2003). In the colonial hydroid H. symbiologicarpus, 35 alleles of the alr2 allorecognition locus were sequenced from 18 colonies (Rosengarten et al., 2010).

Because allelic variation forms the basis of allorecognition, evolutionary studies of self/non-self recognition focus on this variation. If we can understand the evolutionary forces underlying the remarkable polymorphism in allorecognition loci, we gain valuable insights into the evolution and mechanisms of allorecognition systems. Two important questions about this polymorphism remain to be solved: how is it created and how is it maintained? We will address each question by summarizing and interpreting the available data.

CREATION OF POLYMORPHISM

Mutation and recombination are the two processes that commonly create variation in allorecognition loci. These forces have been examined in several systems: het/vic loci in fungi, FuHC in B. schlosseri, SI loci in the Brassicaceae (Arabidopsis and Brassica) and Solanaceae (Lycium, Petunia, Physalis, Solanum), and alr2 in Hydractinia.

In the fungus Podospora anserina, the het-d and het-e loci belong to a 10-member gene family; diversity is created by sharing...
of WD-repeats through recombinational processes within and between loci in this family. Because het-d and het-e have a large copy number of repeats, mutations arise frequently in the WD-domains, also creating diversity. So polymorphism is created by plentiful mutations, which are then exchanged within and between loci, creating even more polymorphism. An accelerated mutational process called repeat induced polymorphism (RIP) that targets repeat sequences in fungi is thought to further generate variation (Paolletti et al., 2007). Recombination does not often occur within the A-mating type locus of the basidiomycete fungus Coprinus cinereus (Day, 1963). But infrequent recombination events have created diversity in this locus; this is unusually in sex-determining loci (May and Matzke, 1995). Researchers found reduced recombination near the mating type locus (MAT) in the chestnut blight fungus, Cryptonecctria parasitica (Kubisiak and Milgroom, 2006).

In B. schlosseri, FuHC experiences a substantial amount of intragenic recombination, based on three independent measures: \( R_m \), the correlation between physical distance and three measures of linkage disequilibrium, and levels of recombination across the protein (Nydam, Taylor and De Tomas unpublished data). Six populations were examined, 112 alleles and 77 individuals for Exons 1–14, 111 alleles and 76 individuals for Exons 18–31. This data set was used for all Botryllus analyses discussed in this paper. The relative contributions of mutation and recombination in generating polymorphism in FuHC were determined by calculating \( \theta \) and \( R \) in DnaSP 5.10.01 (Librado and Rozas, 2009). \( \theta = 4N^*\mu \), where \( N^* \) is the effective population size and \( \mu \) is the mutation rate per DNA sequence per generation. \( R = 4N^*r \) (Hudson, 1987), where \( N \) is the population size and \( r \) is the recombination rate per sequence. \( R \) is estimated from the variance of the average number of nucleotide differences between pairs of sequences (Hudson, 1987). All values were estimated using DnaSP. A ratio of \( \theta/R = 1 \) signifies an equal contribution of mutation and recombination, \( >1 \) a larger role for mutation, and \( <1 \) a larger role for recombination. \( \theta/R \) was much less than one, so recombination clearly plays a larger role in the creation of FuHC than mutation.

When discussing the creation of variation in plant self-incompatibility (SI) loci, we must make a distinction between gametophytic and sporophytic SI systems. In gametophytic SI, the most common type of SI, the haploid self-incompatibility genotype of the pollen dictates its self-incompatibility phenotype. In sporophytic SI, the diploid self-incompatibility genotype of the plant dictates the self-incompatibility phenotype of the pollen produced by that plant (Newbigin et al., 1993).

Mutation plays a larger role than recombination in both gametophytic and sporophytic systems. Recombination would break up the association between pollen and pistil self-incompatibility loci, and thus is predicted to be suppressed around SI loci (Stein et al., 1991). Little evidence for recombination exists in gametophytic systems (Schierup et al., 2001), but this result may be due to the lack of power of recombination-detecting statistics, caused by the extraordinarily high polymorphism at these loci. Several successive mutations have occurred at the majority of segregating sites in these loci; this shows that mutation creates variation, but it also obscures the role of recombination. Recombination does play a substantial role in the creation of polymorphism in one species with gametophytic SI: Petunia inflata (Wang et al., 2001).

The authors state that recombination events must be rare, and that recombinant alleles causing a reduction in fitness are removed by natural selection.

Numerous tests in Arabidopsis sporophytic SI systems have yielded scant evidence for recombination (Kamau and Charlesworth, 2005; Charlesworth et al., 2006; Hagenblad et al., 2006; Edh et al., 2009). Recombination has been detected in SI loci of Brassica species (Kusaba et al., 1997; Awadalla and Charlesworth, 1999; Takuno et al., 2007) but only in genes or gene domains that do not play a direct role in self-incompatibility specificity (Takuno et al., 2007; Edh et al., 2009). Mutation must create the majority of variation at SI loci; multiple mutations at variable sites are well documented (Edh et al., 2009).

Recombination likely contributes to alr2 polymorphism in Hydractinia, based on the discovery of chimeric alleles having regions characteristic of two distinct types of structural polymorphism (Rosengarten et al., 2010), but the relative contribution of mutation and recombination to allelic diversity has not been assessed.

Except in the cases of sex-determining loci and SI loci in plants (where recombination is suppressed), mutation and recombination interact in allorecognition systems to create polymorphism.

**MAINTENANCE OF POLYMORPHISM**

**DISTRIBUTION OF POLYMORPHISM WITHIN AND AMONG POPULATIONS**

Using the Analysis of Molecular Variance (AMOVA), evolutionary biologists routinely partition the total molecular variation in a particular gene into three mutually exclusive groups: among geographical regions, among populations within geographical regions, and within populations. For example, geographical regions could be Europe and North America: how much of the variation is found when comparing the Valencia (Spain), Bergen (Norway), and Lucerne (Switzerland) populations? And finally, how much variation is found when populations are examined individually? If a large portion of the variation is found within populations, this means there is little genetic differentiation between populations (e.g., the same alleles would be found in Valencia, Bergen, and Lucerne). Fst is a related statistic; a statistically significant Fst signifies genetic differentiation between populations in the data set, pairwise Fst statistics are used to determine whether any pair of populations is significantly differentiated.

AMOVA and Fst calculations can inform us about the evolutionary forces operating on the allorecognition loci, allowing us to understand how polymorphism is maintained. Comparing allorecognition loci to neutral loci (usually microsatellites) with respect to Fst values and percentage of polymorphism within vs. among populations (AMOVA) allows one to test whether selection is occurring. Loci experiencing balancing selection (which maintains variation) should have larger amounts of polymorphism within populations and smaller amounts among populations than neutral loci (assuming selection pressures are similar between populations), whereas the opposite pattern is expected for loci experiencing directional selection (Schierup et al., 2000). Similar
genetic differentiation between allorecognition loci and neutral loci is taken as evidence for neutral evolution (e.g., genetic drift).

One might assume directional selection is acting when significant population structure is recovered, but allelic variation at allorecognition loci is likely older than current population structure. Limited gene flow between populations (conserving ancient variation), rather than selection, could lead to differentiation between contemporary populations (Richman et al., 2003). Because of this, strong inferences of selection on allorecognition loci should only be made from AMOVA and Fst values when these values are compared to other loci not presumed to be under balancing or directional selection.

AMOVA and Fst analyses have been completed in three allorecognition systems: het/vic loci in fungi, FuHC in *B. schlosseri*, and SI loci in the Asteraceae (*Guizotia abyssinica*), and Brassicaceae (*Arabidopsis* and *Brassica*). In both the chestnut blight fungus (C. parasitica) and the dry rot fungus (Serpula lacrymans), het/vic loci lack significant genetic differentiation among populations (Milgroom and Cortesi, 1999; Kauserved et al., 2006). In the ascidian *B. schlosseri*, >90% of the variation in the FuHC gene is found within populations, and Fst is not statistically significant (Nydam, Taylor, and De Tomaso unpublished data). This is in direct contrast to values obtained from two *B. schlosseri* genes not presumed to be under directional or balancing selection: mitochondrial cytochrome oxidase I and vasa. Both of these genes have less variation within populations than FuHC (81.2 and 27.16%, respectively), and both have highly significant Fst values (p < 0.001).

Patterns at SI loci are similar to those at *het/vic* and FuHC. In *G. abyssinica* (niger), 97% of the SI locus variation was found within populations, and Fst values were very low (although statistically significant; Geleta and Bryngelson, 2010). Fst values are significantly lower when compared to neutral loci, in all cases (A. lyrata: Kamau et al., 2007; A. halleri: Ruggiero et al., 2008; Brassica cretica: Edh et al., 2009; B. insularis: Glemin et al., 2005). These results provide strong evidence for balancing selection driving the evolution of SI loci.

*Het/vic*, FuHC, and SI loci show similar patterns: a large percentage of the variation at these loci is found within populations, Fst values are not often statistically significant, and Fst values are significantly lower when compared with neutral loci. These patterns are consistent with a straightforward model of balancing selection, where selection pressures are similar in all environments.

**TESTS OF SELECTION: POLYMORPHISM AND DIVERGENCE STATISTICS**

Tests of selection using polymorphism (e.g., Tajima’s *D*) and divergence (e.g., *dS*/d*G*) statistics commonly find evidence for selection at allorecognition loci. In fact, one of the earliest and most cited examples of *dS*/d*G* > 1 (non-synonymous substitution rate greater than synonymous substitution rate) comes from the peptide-binding region (PBR) in mouse and human MHC (Hughes and Nei, 1988). For polymorphism statistics such as Tajima’s *D* and Fu and Li’s *D* *a* and *F* *s*, values statistically greater than zero are evidence for balancing selection, and less than zero for directional selection (Tajima, 1989; Fu and Li, 1993). A pattern of *dS*/d*G* > 1 could indicate either directional or balancing selection (Garrigan and Hedrick, 2003); other data must be examined to determine which type of selection is occurring.

We will describe all the available data from the less well-studied loci (*tgrB1* and *tgrC1* in *D. discoideum*, *alr2* in *H. symbiolongicarpus*, mating-compatibility genes and *het/vic* loci in fungus, and FuHC in *B. schlosseri*). A complete description of all relevant studies in the SI literature is beyond the scope of this review; we instead highlight several recent studies from this allorecognition system.

In the cellular slime mold *D. discoideum*, the genes *tgrB1* and *tgrC1* are involved in kin recognition. Certain sections of these genes have *dS*/d*G* ratios > 1; the authors conclude that balancing selection is causing this pattern, given the extensive polymorphism at these loci (Benabentos et al., 2009). Nine codons in *alr2* of *H. symbiolongicarpus* have elevated *dS*/d*G* ratios; the majority are found in exon 2 (Rosengarten et al., 2010). The presence of 35 *alr2* alleles recovered from 36 individuals led the authors to conclude that negative frequency-dependent selection (a type of balancing selection where rare alleles are favored by selection) is occurring. At equilibrium, the alleles of a single locus subject to frequency-dependent selection are expected to be equally frequent (Grosberg, 1988).

Neither of two mating-compatibility genes examined in fungus species showed *dS*/d*G* > 1 (May et al., 1999; Rau et al., 2007), but the *b1* mating type gene in the mushroom fungus *C. cinereus* was shown to be experiencing balancing selection by comparing the topologies of gene genealogies under balancing selection and neutral scenarios (May et al., 1999). *Het-c* in *Neurospora crassa* was determined to be evolving under balancing selection; evidence included trans-species polymorphisms and an increase in non-synonymous substitutions in and around the specificity region of *het-c* (Wu et al., 1998). Four codon positions of the WD-40 repeats in *het-d* and *het-c* of *P. anserina* have *dS*/d*G* > 1. The authors conclude that balancing selection, rather than directional selection, is operating, because of the high number of amino acid combinations at the four codons of interest (Paoletti et al., 2007).

FuHC in *B. schlosseri* experiences selection, based on both polymorphism and *dS*/d*G* statistics (Nydam, Taylor, and De Tomaso unpublished data). Values of polymorphism statistics (Tajima’s *D*, Fu and Li’s *D* *a* and *F* *s*) were significantly negative in all East Coast populations, as well as Monterey, CA, USA on the West Coast, consistent with directional selection. But negative polymorphism statistics could be due to selective or demographic processes (e.g., recent population growth). In the case of FuHC, the pattern is likely due to selection rather than demography, given that none of the polymorphism statistics were significantly negative for a housekeeping gene (vasa). 11 additional housekeeping genes are currently being sequenced, to confirm that demographic processes are not causing this pattern. Omega statistics pinpointed 24 codons throughout the protein have a greater than 95% probability of *dS*/d*G* > 1. Four exon groups contained clusters of these positively selected sites: Exons 5, 6, 20, and 27. Exons 5, 6, and 20 had significantly higher omega values than the rest of the gene for a subset of populations; these exons will be targeted in future functional studies. Other tests are being conducted to determine whether this pattern is due to balancing or directional selection.

Inference of selection at SI loci in plants begins with Sewall Wright, who wrote, “It also fairly obvious that selection would tend
to increase the frequency of any additional alleles that may appear.” (Wright, 1939). Because fertilization is aborted when pollen and pistil S-alleles are identical, rare S-alleles have a selective advantage. As negative frequency-dependent selection is a type of balancing selection, researchers have spent considerable effort determining whether SI loci are evolving under balancing selection.

Data from numerous plant groups provide considerable support for balancing selection on SI loci. As in other allorecognition systems, the majority of these data are $d_s/d_S$ ratios $> 1$. However, $d_S/d_S$ ratios $> 1$ are consistent with directional and balancing selection, so additional data are needed to determine which of these scenarios is occurring. $d_S/d_S$ ratios $> 1$ have been found in many plant families, both in gametophytic and sporophytic SI systems (Clark and Kao, 1991; Ishimizu et al., 1998; Sato et al., 2002; Takebayashi et al., 2003; Igic et al., 2007; Guo et al., 2011). $d_S/d_S$ ratios $> 1$ were corroborated with additional data to infer the action of balancing selection: significantly positive Tajima's $D$ values, little population structure compared to neutral markers, and low recombination for SRK and SCR in B. cretica (Edh et al., 2009), trans-species polymorphisms in SRK and SCR in several Arabidopsis species (Sato et al., 2002; Guo et al., 2011).

**CONCLUSION**

Unusually high polymorphism is a hallmark of allorecognition loci; how this polymorphism is created and maintained has interested biologists since Sewall Wright. From the studies presented in this review, we can conclude that polymorphism is created by an interaction between mutation and recombination, except in the cases of sex-determining loci and SI loci in plants (where recombination is suppressed).

AMOVA/Fst studies examining the distribution of polymorphism within and among populations in Het/vic, FuHC, and SI loci generally provide support for the role of balancing selection in maintaining polymorphism.

Divergence statistics often show patterns of $d_S/d_S$ ratios $> 1$ for allorecognition loci; these values are consistent with both directional and balancing selection. In many cases, additional evidence such as significantly positive polymorphism statistics and/or identification of trans-species polymorphisms provide support for balancing over directional selection in the maintenance of variation in allorecognition loci.

**REFERENCES**

Allen, A. M., and Hiscock, S. J. (2008). "Evolution and phylogeny of self-incompatibility systems in angiosperms," in Self-Incompatibility in Flowering Plants – Evolution, Diversity and Mechanisms, ed. V. E. Franklin-Tong (Berlin: Springer-Verlag), 73–101.

Awadalla, P., and Charlesworth, D. (1999). Recombination and selection at Brassica self-incompatibility loci. Genetics 152, 413–425.

Benabentos, R., Hirose, S., Sugaw, R., Cukir, T., Kato, M., Ostrowski, E., Strassmann, J., Queller, D., Zupan, B., Shaulsky, G., and Kuupa, A. (2009). Polymorphic members of the lag-gene family mediate kin-discrimination in Dicyostelium. Curr. Biol. 19, 567–572.

Ben-Shlomo, R. (2008). The molecular basis of allorecognition in ascidians. Bioessays 30, 1048–1051.

Buss, L. (1982). Somatic cell parasitism and the evolution of somatic tissue compatibility. Proc. Natl. Acad. Sci. U.S.A. 79, 5337–5341.

Charlesworth, D., Kamau, E., Hagenblad, J., and Tang, T. L. (2006). Trans-specificity at loci near the self-incompatibility locus in Arabidopsis. Genetics 172, 2699–2707.

Clark, A. G., and Kao, T.-H. (1991). Excess non synonymous substitution at shared polymorphic sites among self-incompatibility alleles of Solanaceae. Proc. Natl. Acad. Sci. U.S.A. 88, 9823–9827.

Clark, J. (2003). Plasmoidal incompatibility in the myxomycete Didymium squamosum. Mycolologia 95, 24–26.

Day, P. R. (1963). The structure of the A mating-type factor in Coprinus lagopus: wild alleles. Genet. Res. 4, 323–325.

De Tomas, A. W., Nyholm, S. V., Palmeri, K. J., Ishizu K. J., Luddenon, W. B., Mitchell, K., and Weissman, I. L. (2005). Isolation and characterization of a protochordate histocompatibility locus. Nature 438, 454–459.

Edh, K., Widen, B., and Cepeitis, A. (2009). Molecular population genetics of the SRK and SCR Self-Incompatibility genes in the wild plant species Brassica cretica (Brassicaceae). Genetics 181, 985–995.

Fernandez-Busquets, X., and Burger, M. M. (1999). Cell adhesion and histocompatibility in sponges. Microsc. Res. Tech. 44, 204–218.

Fu, Y. X., and Li, W. H. (1993). Statistical tests of neutrality of mutations. Genetics 133, 693–709.

Garrigan, D., and Hedrick, P. W. (2003). Detecting adaptive molecular polymorphism: lessons from the MHC. Evolution 57, 1707–1722.
Geleta, M., and Bryngelson, T. (2010). Population genetics of self-incompatibility and developing self-compatible genotypes in niger (Guizotia abyssinica). Euphytica 176, 417–430.

Gibbs, K. A., Urbanowski, M. L., and Greenberg, E. P. (2008). Genetic determinants of self identity and social recognition in bacteria. Science 321, 256–259.

Glass, N. L., Jacobson, D. J., and Shiu, P. K. (2000). The genetics of hyphal fusion and vegetative incompatibility in filamentous ascomycete fungi. Annu. Rev. Genet. 34, 165–186.

Glemm, S., Gaude, T., Guillemin, M.-L., Lourmans, M., Olivieri, E., and Migo, F. (2005). Balancing selection in the wild: testing population genetics theory of self-incompatibility in the rare species Brassica insularis. Genetics 171, 279–289.

Grosberg, R. K. (1988). The evolution of allorecognition specificity in clonal invertebrates. Q. Rev. Biol. 63, 377–412.

Grosberg, R. K., Levitan, D. R., and Cameron, B. B. (1996). Evolutionary genetics of allorecognition in the colonial hyroid Hydractinia symbiolongicarpus. Evolution 50, 2221–2240.

Grosberg, R. K., and Plachetzi, D. (2010). “Marine invertebrates: genetics of colony recognition,” in Encyclopedia of Animal Behavior, eds M. D. Breed and J. Moore (Oxford: Academic Press), 381–388.

Guo, Y.-L., Zhao, X., Lanza, C., and Weigel, D. (2011). Evolution of the S-locus region in Arabidopsis thaliana.as relatives. Plant Physiol. 157, 937–946.

Hagenblad, J., Bechsgaard, J., and Charlesworth, D. (2006). Linkage disequilibrium between incompatibility locus region genes in the plant Arabidopsis lyrata. Genetics 173, 1057–1073.

Harada, Y., Takagaki, Y., Sunagawa, M., Saito, H., Yamaeda, L., Taniguchi, H., Shoguchi, E., and Sawada, H. (2008). Mechanism of self sterility in a hermaphroditic chordate. Science 320, 548–550.

Hidakà, M., Yurugi, K., Sunagawa, S., and Kinze, R.A. III (1997). Contact reactions between young colonies of the coral Pocillopora damicornis. Coral Reefs 16, 13–20.

Hudson, R. R. (1987). Estimating the recombination parameter of a finite population model without selection. Genet. Res. 50, 245–250.

Hughes, A. L., and Nei, M. (1988). Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals over-dominant selection. Nature 335, 167–170.

Hughes, R. N., Manriquez, P. H., Morley, S., Craig, S. F., and Bishop, J. D. D. (2004). Kin or self-recognition? Colonial fusibility of the bryozoan Celleporella hyalina. Evol. Dev. 6, 431–437.

Igic, B., Smith, W. A., Robertson, K. A., Schaal, B. A., and Kohn, J. R. (2007). Studies of self-incompatibility in wild tomatoes: I. S-allele diversity of Solanum chilense Don. (Solanaceae). Heredity 99, 553–561.

Ishahara, T., Endo, T., Yamaguchi-Kabata, Y., Nakamura, K. T., Sakiyama, F., and Norioka, S. (1998). Identification of regions in which positive selection may operate in S-RNase of Rosaceae: implication for S-allele-specific recognition sites in S-RNase. FEBS Lett. 440, 337–342.

Kamau, E., Charlesworth, B., and Charlesworth, D. (2007). Linkage disequilibrium and recombination rate estimates in the self-incompatibility region of Arabidopsis lyrata. Genetics 176, 2537–2539.

Kamau, E., and Charlesworth, D. (2005). Balancing selection and low recombination affect diversity near the self-incompatibility loci of the plant Arabidopsis lyrata. Proc. Biol. Sci. 15, 1773–1778.

Kassuerud, H., Sætre, G.-P., Schmidt, O., Decock, C., and Schumacher, T. (2006). Genetics of self/nonself recognition in Serpula lacrymans. Fungal Genet. Biol. 43, 503–510.

Kubisiak, T. L., and Milgroom, M. G. (2004). Kin or self-recognition? Evolution rate estimates in the S-locus region of Arabidopsis lyrata. Mol. Biol. Evol. 21, 1315–1324.

Nicotra, M. L., Powell, A. E., Rosen, D. R., Moreno, M., Grimwood, J., Lakkis, E. G., Dellaporta, S. L., and Buss, L. W. (2009). A hypervariable invertebrate alldeterminant. Curr. Biol. 19, 583–589.

Pandey, K. K. (1960). Incompatibility in Arabidopsis thaliana. Genet. Res. 51, 377–392.

Paolotti, M., Sapea, S. J., and Clave, C. (2007). Genesis of a fungal non-self recognition repertoire. PLoS ONE 3, e283. doi:10.1371/journal.pone.0000283

Raftos, D. (1994). Allorecognition and humoral immunity and tunicates. Ann. N. Y. Acad. Sci. 712, 227–244.

Rau, D., Attene, G., Brown, A. H. D., Nanni, L., Maier, F. J., Balmas, V., Saba, E., Schafer, W., and Papa, R. (2007). Phylogeny and evolution of mating-type genes from Pyrenophora teres, the causal agent of barley “net blotch” disease. Curr. Genet. 51, 377–392.

Rosengarten, R. D., Moreno, M. A., Lakkis, E. G., Buss, L. W., and Dellaporta, S. L. (2010). Genetic diversity of the alldeterminant slr2 in Hydractinia symbiolongicarpus. Mol. Biol. Evol. 28, 933–947.

Richman, A. D., Gerardo Herrera, L., Nish, D., and Schierup, M. K. (2003). Relative roles of mutation and recombination in generating allelic polymorphism at an MHC class II locus in Peromyscus maniculatus. Genet. Res. 82, 89–99.

Ruggiero, M. V., Jacquemyn, B., Castric, V., and Vekemans, X. (2008). Hitchhiking to a locus under balancing selection: high sequence diversity and low population subdivision at the S-locus genomic region in Arabidopsis halleri. Genet. Res. 90, 37–46.

Runions, C. J., and Owens, J. N. (1998). “Evidence of pre-zygotic self incompatibility in a grasshopper,” in Reproductive Biology, eds S. J. Owens and P. J. R. Rudall (Kew: Royal Botanic Gardens), 255–264.

Saito, Y., Hirose, E., and Watanabe, H. (1994). Allorecognition in compound asciidians. Int. J. Dev. Biol. 38, 237–247.

Sato, K., Nishio, T., Kimura, R., Kusaba, M., Suzuki, T., Hatakeyama, K., Okedon, D. J., and Satta, Y. (2002). Coevolution of the S-Locus genes SRK, SLG, and SP11/SCR in Brassaia oleracea and B. rapa. Genetics 162, 931–940.

Schierup, M. H., Mikkelsen, A. M., and Hejn, J. (2001). Recombination, balancing selection, and phylogenies in MHC and self-incompatibility genes. Genetics 159, 1833–1844.

Schierup, M. H., Vekemans, X., and Charlesworth, D. (2000). The effect of subdivision on variation at multi-allelic loci under balancing selection. Genet. Res. 76, 51–62.

Shaulsky, G., and Kessin, R. (2007). The cold war of the social amoeba. Curr. Biol. 17, 684–692.

Stein, J., Howlett, B., Boyes, D. C., Nasrallah, M. E., and Nasrallah, J. B. (1991). Molecular cloning of a putative receptor protein kinase gene encoded at the self-incompatibility locus of Brassaia oleracea. Proc. Natl. Acad. Sci. U.S.A. 88, 8816–8820.

Tajima, F. (1989). Statistical method for testing the neutral mutation hypothesis by DNA polymorphism. Genet. 123, 585–595.

Takebayashi, N., Brewer, P. B., Newbiggin, E., and Uyenoyama, M. K. (2003). Patterns of variation within self-incompatibility loci. Mol. Biol. Evol. 20, 1778–1794.

Takuno, S., Fujimoto, R., Sugimura, T., Sato, K., Okamoto, S., Zhang, S.-L., and Nishio, T. (2007). Effects of recombination on hitchhiking self-incompatibility in Arabidopsis thaliana.
diversity in the *Brassica* self-incompatibility locus complex. *Genetics* 177, 949–958.

Wang, X., Hughes, A. L., Tsukamoto, T., Ando, T., and Kao, T.-H. (2001). Evidence that intragenic recombination contributes to allelic diversity of the S-RNase gene at the self-incompatibility (S) locus in *Petunia inflata*. *Plant Physiol.* 125, 1012–1022.

Wright, S. (1939). The distribution of self-sterility alleles in populations. *Genetics* 24, 538–552.

Wu, J., Saupe, S. J., and Glass, N. L. (1998). Evidence for balancing selection operating at the het-c heterokaryon incompatibility locus in a group of filamentous fungi. *Proc. Natl. Acad. Sci. U.S.A.* 95, 12398–12403.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 18 October 2011; paper pending published: 14 November 2011; accepted: 02 December 2011; published online: 27 December 2011.

Citation: Nydam ML and De Tomaso AW. (2011) Creation and maintenance of variation in allorecognition loci: molecular analysis in various model systems. *Front. Immun.* 2:79. doi: 10.3389/fimmu.2011.00079

This article was submitted to Frontiers in Molecular Innate Immunity, a specialty of Frontiers in Immunology.

Copyright © 2011 Nydam and De Tomaso. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.