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20. Like physicists, who deduced the need for a new particle based on the behavior of the system, Bretscher and Cohn (*14*) and Lafferty and Cunningham (*15*) postulated cells and/or signals for which, at the time, there was no evidence. Later experiments showed resoundingly that they were correct. In a similar vein, Janeway postulated a new state for a previously known cell, the APC. Up to that time, APCs were thought to be constitutively active, but a seemingly small glitch in the behavior of the system (the need for adjuvant) led him to suggest that they were normally quiescent and needed to be activated. These insights showed that theoretical biology and physics may have more in common than is sometimes thought.
21. Allergy, for example, is a partial conundrum. Many allergens are dangerous substances. Der-p1, the major allergen in house dust mite, is a protease that attacks the surface of B cells and lung epithelium. Likewise, bee venom is not an innocuous substance. From the standpoint of the Danger model, it is not surprising that the immune system responds to allergens. What is not clear, however, is why some individuals make IgG whereas others make IgE (the antibody associated with allergy).
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53. The Network model, which proposed that "self" is defined in a positive way, also emphasized the idea of connectedness. The idea was that lymphocytes react against each other's antigen-specific receptors and maintain a balance of self-reactive and foreign-reactive cells (*55*). The proponents of the network have been arguing for years that the study of single lymphocytes is an inappropriate way to study the immune system, but that we should study the connectivity between cells (*56*) Finally, after years of finding the model intriguing, but narrow, I agree. However, I think that we should not limit the study to interactions between lymphocytes but expand it to include their conversations with all the bodily tissues, which have the ultimate say.
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VIEWPOINT

Recognition and Rejection of Self in Plant Reproduction

June B. Nasrallah

Plant self-incompatibility (SI) systems are unique among self/nonself recognition systems in being based on the recognition of self rather than nonself. SI in crucifer species is controlled by highly polymorphic and co-evolving genes linked in a complex. Self recognition is based on allele-specific interactions between stigma receptors and pollen ligands that result in the arrest of pollen tube development. Commonalities and differences between SI and other self/nonself discrimination systems are discussed.

The concept of self/nonself discrimination was elaborated by Burnet (*1*) as a way to describe specificity in the immune response and is most often associated with the field of immunology. It is perhaps less well known that, in the plant kingdom, sophisticated self-recognition systems have evolved that allow plants with perfect (hermaphroditic) flowers to avoid inbreeding. These intraspecific prefertilization mating barriers are collectively known as self-incompatibility (SI). This term encompasses several systems that are mechanistically distinct but have the same outcome, namely the inhibition of self-related pollen tube development and, consequently, the prevention of sperm cell delivery to the ovules.

SI systems are said to discriminate between self and nonself because they produce different outcomes in self- and cross-pollinations. Specificity in SI is typically controlled by one or more highly polymorphic genetic loci. In the context of SI, self and nonself mean, respectively, genetic identity and nonidentity at the SI locus (or loci) in pistils and pollen. The outcome of this discrimination is the converse of that of the immune response, in which case self has been classically defined as those elements that are tolerated and do not elicit a response. In SI, self is the condition that elicits the response and is inhibited, whereas nonself is the condition that is ignored and does not elicit a response.

Department of Plant Biology, Cornell University, Ithaca, NY 14853, USA. *E-mail: jbn2@cornell.edu

A Variety of Plant SI Systems

As an advantageous outbreeding device, SI is widely distributed in flowering plants (*2*). It evolved independently in several lineages, and the SI systems adopted by different plant families vary with respect to site and mechanism of self inhibition. In self-incompatible species of the crucifer family (e.g., *Brassica* species and close relatives of *Arabidopsis thaliana*), SI disrupts hydration and germination of a pollen grain on the stigma epidermis, thus preventing growth of pollen tubes into the subepidermal tissues of the pistil. In other families, SI acts after pollen germination and pollen tube ingress into the pistil, either within the stigmatic zone (as in the poppy family), or later, within the style (as in the tobacco, rose, and snapdragon families).

These differences are reflected in drastically different mechanisms of recognition and of pollen or pollen tube arrest. In the early-acting SI system of crucifers, recognition of pollen is mediated by a receptor/ligand system, with a signaling cascade being triggered within the stigma epidermis. In late-acting SI systems, the invading pollen tubes are actively destroyed. In the poppy, a glycoprotein secreted by cells of the stigma somehow induces within self pollen tubes a signal transduction cascade manifested by increases in cytosolic calcium, disruption of the cytoskeleton, and cessation of growth (*3*). In plant species with stylar inhibition, an RNase (*4*) secreted by cells of the style enters pollen tubes and degrades cytoplasmic RNA selectively in self tubes. Only in the SI system of crucifers has the molecule expressed in pollen that identifies it as self and invites destruction been identified.

The Self-Recognition Genes of Crucifers

The SI (*S*) locus of crucifers is highly polymorphic, with the number of variants estimated at more than 100 in some species (*5*). This locus behaves genetically as a single Mendelian locus, but it is in fact molecularly complex and contains two unrelated highly polymorphic recognition genes that are in tight genetic and physical linkage (Fig. 1). Transgenic (*6*–*9*) and biochemical (*10*, *11*) studies have shown that the products of these genes function as receptors and ligands that determine specificity in the stigma epidermis and pollen, respectively. The products of these genes also are the primary determinants of the outbreeding mating habit in crucifers. Deletion or inactivation of one or both genes is the principle mutation underlying the evolutionary switch from an outbreeding to an inbreeding mating system in this family (*12*).

In the stigma epidermis, the determinant of SI specificity is the *S*-locus receptor protein kinase (SRK), a single-pass transmembrane serine/threonine kinase (*13*). In pollen, SI specificity is determined by the *S*-locus cysteine-rich protein gene *SCR* [(*6*); also designated SP-11 (*7*, *11*, *14*)], which encodes small secreted hydrophilic and positively charged proteins of 50 to 59 amino acids. Both *SRK* and *SCR* are members of large families of genes that are expressed in a variety of plant tissues but have unknown functions, which suggests that they were recruited from genes for receptors and ligands that function in plant processes unrelated to reproduction. SRK is the prototypic member of a family of plant receptor-like protein kinases defined by a distinctive ectodomain (*15*). The SCR peptides exhibit some resemblance, but not sequence identity, to defensins, a ubiquitous class of small cysteine-rich antimicrobial peptides found in mammals, insects, and plants that function primarily in innate immunity, although some have functions unrelated to defense (*16*, *17*). Defensin-like proteins are grouped into highly diverged classes whose evolutionary relationships have been difficult to resolve (*16*), and it will be even more difficult to retrace the evolutionary path connecting the rapidly evolving *SCR* gene to defensins. Nevertheless, we speculate that a function directed at recognizing nonself patterns in microbial pathogens was co-opted for self recognition in the SI response.

Receptor/Ligand Interactions and Activation of the SI Response

Maturation of the flower in self-incompatible crucifers is accompanied by the insertion of SRK into the plasma membrane of stigma epidermal cells and of SCR into the pollen coat (*7*, *10*). By the time anthers release their pollen and the flower opens to receive pollinators laden with pollen, the stigma epidermal cell has its SRK sentinel and SI surveillance system in place and is poised to screen among pollen grains. For their part, mature pollen grains carry specific SCR variants that identify them as self or nonself, thus marking them for rejection or acceptance. SRK interacts with SCR (*10*, *11*), and this interaction occurs only between receptor and ligand vari-

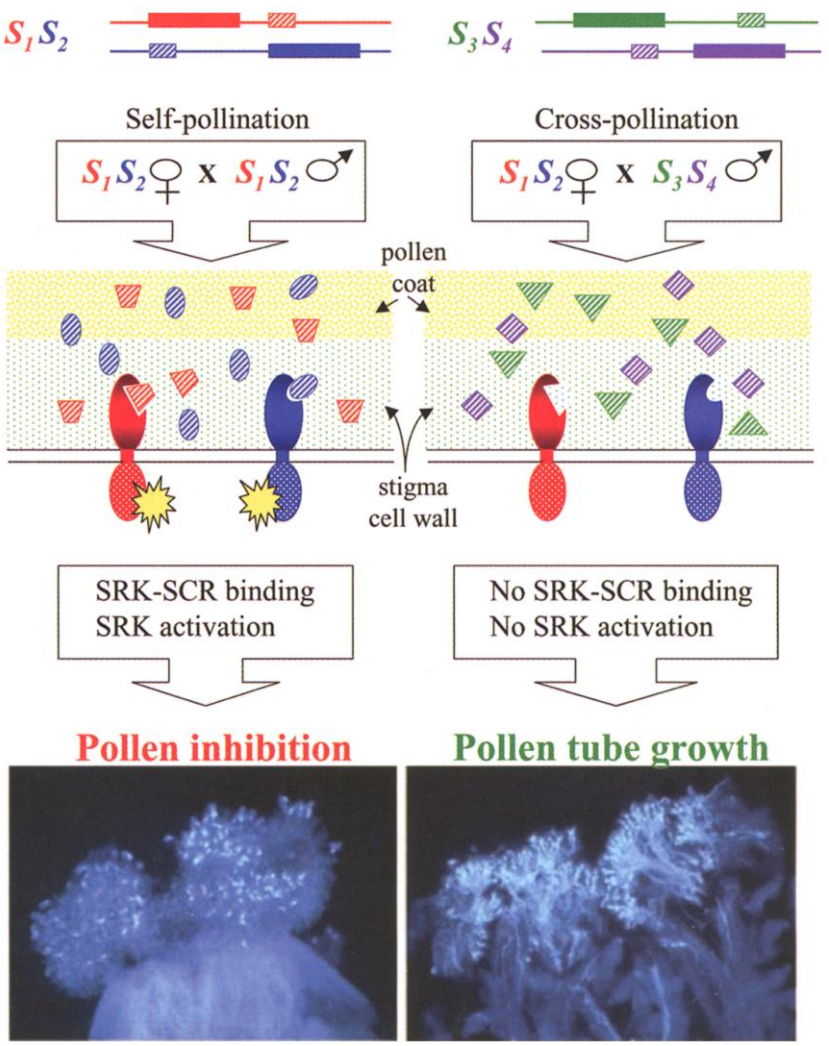

Fig. 1. Recognition and inhibition of self pollen in crucifers. The outcomes on an S_1S_2 stigma of self-pollination (left) and cross-pollination with pollen from an S_3S_4 heterozygote (right) are shown. At the top, the *S* haplotypes carried by each plant are shown with their *SRK* (closed rectangles) and *SCR* (crosshatched rectangles) genes. Variable distances and arrangements of the genes illustrate the structural heteromorphism of the *S* locus. *SRK* and *SCR* genes and gene products derived from the same *S* haplotype are drawn in the same color. Microscopic analysis shows inhibition of self pollen at the stigma surface as a result of the binding of the SCR ligand to its cognate SRK receptor, SRK activation, and phosphorylation of ARC1 (*37*). Nonself pollen forms pollen tubes, because nonself SCR neither binds nor activates SRK.

ants encoded by the same *S* haplotype (*10*).

The allele-specific binding of SCR to the SRK ectodomain explains the high degree of specificity in the SI response. After pollination, the SCR protein is delivered to the surface of a stigma epidermal cell as the pollen coat flows over the surface at the site of pollen contact (*18*). We believe it would then be rapidly translocated toward the plasma membrane within the region of the stigma epidermal cell wall subtending the zone of pollen contact. In a pollination with self pollen, SCR would interact with its cognate SRK, leading to receptor activation and the triggering within the stigma epidermal cell of a signaling cascade that culminates in the arrest of self pollen tube development (Fig. 1). In a cross-pollination, nonself SCR would not bind SRK, the signaling pathway would not be activated, and pollen tube development would proceed unhindered (Fig. 1). The SCR peptide is the only pollen factor required for SRK activation, because the SI response can be reproduced by addition to the stigma surface of self SCR expressed in bacteria or produced synthetically (*10*, *11*, *14*).

The binding of self SCR to the SRK ectodomain apparently causes oligomerization, transphosphorylation of the receptor (*19*, *20*), and phosphorylation of specific substrates. One such substrate is the arm repeat–containing protein ARC1 (*21*). A U-box motif in ARC1 (*22*) suggests a role for ubiquitination in the SI response, but the immediate cause of inhibition of self pollen remains unknown. Nor is it known if events downstream of SRK activation are mediated by components shared with other signaling pathways.

Receptor/Ligand Polymorphisms and the Evolution of New SI Specificities

The *S* haplotype specificity of SRK-SCR binding is not surprising given the extraordinarily high levels of allelic polymorphism attained by *SRK* and *SCR*. SRK ectodomains can diverge by as much as 35%. Alignment of SRK sequences reveals numerous base pair substitutions over the length of the domain as well as insertions and deletions and suggests that intragenic recombination has shuffled hypervariable regions among alleles (*13*, *23*). For their part, *SCR* alleles are so diverged (*6*, *12*, *24*) that unambiguous alignment of *SCR* DNA sequences is not possible. Only seven cysteine residues and one glycine residue are conserved among the 22 SCR sequences isolated to date, and the spacing between the cysteines is also variable. A challenge for the future is to sift through this variability and identify the specific residues or domains that form the points of contact between SRK and SCR and consequently determine specificity in receptor-ligand binding.

Another challenge is to explain how allelic polymorphisms in *SRK* and *SCR* translate into the puzzling interactions of co-dominance, dominance, incomplete dominance, or mutual weakening that are exhibited by different *S* haplotypes. These interactions occur not only in stigmas but also in pollen, because in crucifers the SI specificity of a pollen grain is determined by the diploid genotype of the plant that produced it rather than by its own genotype. Importantly, these allelic interactions can affect the distribution of SI alleles in populations. For example, recessiveness in pollen confers an advantage on an *S* haplotype by allowing pollen carrying it to evade the SRK-mediated stigmatic surveillance. *S* haplotypes are arranged in dominance hierarchies that can differ in stigma and pollen, consistent with the activity of distinct specificity determinants in stigma and pollen. As more *SRK* and *SCR* alleles are being isolated, investigations into mechanisms of dominance are becoming possible (*25*, *26*), and these studies are beginning to reveal the unusual ways in which SI alleles have diverged. In a study of a dominant-recessive interaction in pollen, recessiveness was ascribed to allelic differences in the pattern of *SCR* transcript accumulation and silencing of the recessive allele (*26*). Future studies of other allelic interactions are likely to uncover allelic differences in the relative affinities of different SCRs for their cognate SRKs or the relative efficiencies with which SRK variants recruit downstream targets.

An even more difficult issue to resolve is how multiple SI specificities evolve. In this two-gene system, SRK and SCR proteins encoded in one *S* haplotype must co-evolve to maintain their interaction. Therefore, a mutation in one component that disrupts their interaction will lead to the loss of SI, and a new specificity can arise only if a compensatory mutation in the second component within the same *S* haplotype restores the interaction. Schemes outlining how this process might have occurred repeatedly to evolve a multiplicity of SI specificities usually involve sequential mutations through a self-compatible intermediate (*27*). Evolution through a dual-specificity intermediate has also been proposed (*28*), but this scheme has been criticized because it requires at least three mutations in a single *S* haplotype for each new specificity (*29*).

Commonalities with Other Self/Nonself Recognition Phenomena

A unique feature of plant SI systems is that they are based on the recognition of self, whereas all other known recognition systems are based on the recognition of nonself. This distinction holds true, even in comparisons to other mate recognition systems that also prevent self-mating. For example, in basidiomycete fungi, multiallelic genes at two unlinked loci specify a large number of different mating types, and mating can only occur between individuals that differ at both loci (*30*). One of these loci contains genes for lipopeptide pheromone ligands and pheromone receptors and is therefore at least superficially analogous to the crucifer *S* locus (Fig. 2). A major difference, however, is that a given pheromone can only activate receptors encoded in a different haplotype and not a receptor encoded in the same haplotype (Fig. 2). Additionally, a pheromone can activate several different receptors, and one receptor can be activated by more than one pheromone. This relaxed specificity is essential in such a nonself recognition system, because a one-to-one correspondence between receptor and ligand, which maximizes the number of compatible mates in self-incompatible crucifer populations, would instead have the unfavorable effect of severely restricting flexibility in mate choice in the fungal system.

Despite their unique features, plant SI systems share important similarities with other eukaryotic self/nonself recognition systems, such as the vertebrate major histocompatibility complex (MHC), histocompatibility in colonial marine invertebrates, and mating type in *Chlamydomonas* and fungi. The striking parallels among these disparate systems, which have

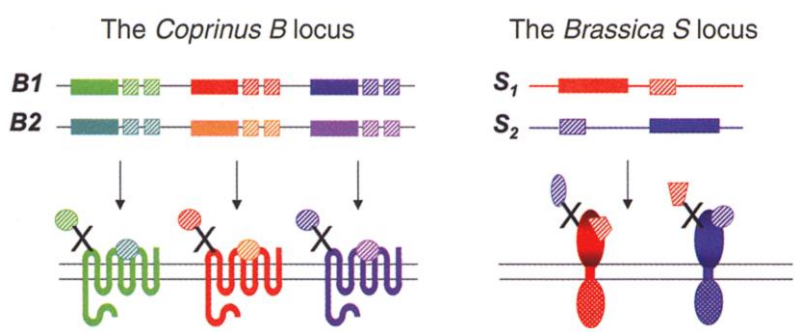

Fig. 2. Recognition of self in SI and of nonself in fungal mating systems. The left panel [adapted from (*30*)] shows the *B* locus of *Coprinus cinereus*, which contains three groups of genes, with each group encoding a G protein–coupled pheromone receptor (closed rectangles) and two pheromones (crosshatched rectangles). In contrast to crucifer SI (right) (Fig. 1), productive interactions occur only between receptors and pheromones encoded by genes in the same group but in different loci.

been noted by immunologists grappling with the origin of adaptive immunity (*1*, *31*), are a consequence of similar selective pressures for diversification and co-evolution of recognition functions to retain affinity between interaction partners.

A hallmark of these specific recognition systems is that their genes are subject to intense diversifying selection. Large numbers of alleles are commonly found, and extraordinarily high levels of intraspecific polymorphism are typically achieved, in some cases resulting from accelerated rates of evolution (*18*, *32*). Due to balancing selection, polymorphisms in these genes can persist for long periods of time and often predate species diversification. Trans-species polymorphisms have been described in the MHC (*33*) and in SI systems (*34*), and in both cases, divergence of some allelic lineages appears to have occurred at least 20 million years ago.

Another emerging commonality between recognition loci is their structural heteromorphism, which apparently reduces intralocus recombination events and prevents disruption of the co-adapted gene complex. The crucifer *S* locus has been extensively restructured by expansion or contraction of the physical distance between *SRK* and *SCR*, gene duplication, as well as rearrangement of these two genes relative to each other and to flanking markers (Fig. 1) (*18*, *35*). Similarly, the MHC has undergone frequent gene duplications and deletions during its evolution (*33*), and the mating-type locus of *Chlamydomonas* contains a highly rearranged region that causes suppression of recombination over a 1-megabase chromosomal region (*36*).

Thus, in many respects, the challenges facing research in the crucifer SI system are similar to those facing researchers of other recognition systems. Comparisons of these different systems should lead to insight into common selective pressures that drive the diversification and co-evolution of self/nonself recognition genes and shape the structure of their controlling loci.

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VIEWPOINT

Self-Representation in Nervous Systems

Patricia S. Churchland*

The brain's earliest self-representational capacities arose as evolution found neural network solutions for coordinating and regulating inner-body signals, thereby improving behavioral strategies. Additional flexibility in organizing coherent behavioral options emerges from neural models that represent some of the brain's inner states as states of its body, while representing other signals as perceptions of the external world. Brains manipulate inner models to predict the distinct consequences in the external world of distinct behavioral options. The self thus turns out to be identifiable not with a nonphysical soul, but rather with a set of representational capacities of the physical brain.

What Is "the Self"?

Descartes proposed that the self is not identical with one's body, or indeed, with any physical thing. Instead, he famously concluded that the essential self—the self one means when one thinks, "I exist"—is a nonphysical, conscious thing. At this stage of scientific development, the Cartesian approach is unsatisfactory for three reasons: (i) psychological functions generally, including conscious thoughts such as "I exist," are activities of the physical brain (*1*, *2*); (ii) aspects of self-regulation (e.g., inhibiting sexual inclinations), and self-cognition (e.g., knowing where I stand in my clan's dominance hierarchy), may be nonconscious (*3*); and (iii) as the Scottish philosopher David Hume (1711–1776) realized, there is in any case no introspective experience of the "self" as a distinct thing apart from the body (*4*). Introspection, Hume concluded, reveals only a continuously changing flux of visual perceptions, sounds, smells, emotions, memories, thoughts, feelings of fatigue, and so forth.

To identify the phenomenon that we want explained, it is useful to start with the idea that one's self-concept is a set of organizational tools for "coherencing" the brain's plans, decisions, and perceptions. Thus, if a brick falls on my foot, I know the pain is mine. I know without pausing to figure it out that "this body is my own," and that a decision to fight rather than flee is a decision affecting my body's painful encounter with the body of another. If I scold myself about jaywalking, I know that it is me talking to myself. We know that if we fail to plan for future contingencies, our future selves may suffer, and we care now about that future self. Sometimes we use "myself" to mean "my body," as when we say "I weighed myself." By contrast, when we say "I deceived myself," we are not referring to our physical bodies. We talk of our social and our private selves, of discovering and realizing ourselves, of self-control, self-improvement, and self-denial (*5*).

This remarkably diverse range of uses of the self-concept motivates recasting problems about "the self" in terms of self-representational capacities of the brain. Doing so deflates the temp-

Philosophy Department 0119, University of California, San Diego, La Jolla, CA 92093, USA.

*To whom correspondence should be addressed. E-mail pschurchland@ucsd.edu