Reflections on Self: Immunity and Beyond

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.

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).

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The SI (S) of Crucifers

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 (1). This locus behaves genetically as a single Mendelian locus, but it is in fact molecularly complex and contains two un-related 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 trans-membrane 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 ubiquit-ous 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 surveil-lance 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-
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, 25). 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-compati-
table 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
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 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-mega-base 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/non-self recognition genes and shape the structure of their controlling loci.

References and Notes
37. J. B. Nasrallah, data not shown.
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Self-Representative 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 non-conscious (3); and (iii) as the Scottish philosophe 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.

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

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To 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.

VIEWPOINT

Self-Representation in Nervous Systems

Patricia S. Churchland*

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