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Holoimmunity Revisited

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Commensal and pathogenic organisms employ camouflage and mimicry to mediate mutualistic interactions and predator escape. However, the immune mechanisms accounting for the establishment and maintenance of symbiotic bacterial populations are poorly understood. A promising hypothesis suggests that molecular mimicry, a condition in which different organisms share common antigens, is a mechanism of establishing tolerance between commensals and their hosts.[1] On this view, certain bacteria may mimic the structural features of some of their host's T-cell receptors (TCRs), namely those that survive thymic selection due to their lack of complementarity to self-antigens. With such "holoimmunity" the mimicking micro-organisms avoid immune recognition as the copied TCRs become mirror images of an extended super-organismal self, consisting of symbiotic and host antigens. Accordingly, analysis of genomic and metagenomic data suggests a tripartite mimicry between TCRs, self-antigens, and commensal antigens that would serve as the basis for immune tolerance between these populations. And conversely, in an autoimmune scenario, both symbiotic microbes and the mimicked host tissue would be targeted for immune destruction.[1]

A recent report offers support for a large shared antigen pool: Calculations of the putative number of combinations of amino acids that TCRs can bind is 3.2 million, and 75.4% of these possible combinations are present in the human proteome and as many as 91.4% of them can be found on commensal bacteria as well.[2] This assessment has possible significance inasmuch as microbial peptides similar to human peptides are generally less immunogenic than other microbial molecules[3] and thus peripheral immune-modulation is likely. Indeed, the functional relevance of a large shared antigen pool is suggested by a study of the role of T-cell-exposed integrase motifs expressed by *Bacteroides* commensals in non-obese diabetic mice.[4] These motifs, almost identical in sequence to human pancreatic β cell autoantigens, are presented by intestinal pro-inflammatory dendritic cells (DCs) to CD8+ T-cells, which, after being activated, prevent intestinal inflammation by destroying these DCs.[4] Hence, peptide mimics can actively suppress destructive responses and, furthermore, instead of just increasing risk of pathological autoimmunity the mimicry may also promote tolerance as Root-Bernstein originally proposed.

These early findings support the notion that mimicry may play an important role in the induction of tolerance to commensals through active suppressive mechanisms. However, despite the major overlap between human and commensal motifs and suggestive evidence of functional corollaries, it is not clear whether antigen-sharing alone could account for immune tolerance employed by mimicking microbes. After all, commensals also express unique bacterial epitopes absent in the human proteome. So a fundamental question remains: How does antigenic mimicry between commensals and their hosts contribute to an induction of tolerance if antigens structurally distinct from mammalian antigens remain present on microorganisms? Apart from evident cases of camouflage, like that of hyaluronic-acid-covered streptococci, most bacteria express exclusive microbe-associated molecular patterns along with motifs they share with their hosts. In this regard, the larger context in which the immune encounter occurs may well determine immunity, whether destructive or tolerant. Indeed, that mimetic peptides can activate autoreactive TCRs highlights the context-sensitivity of induced tolerance.[5] Thus to establish the causal relationship of bacterial mimicry and immune tolerance, in vivo studies will be required that can control for context-dependent effects. While difficult to design, such studies promise to provide deep insights into the dynamics of immunity.

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