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Molecular mimicry
Good artists copy, great artists steal

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Over the course of evolution, microorganisms have developed innovative survival strategies to thrive in their hosts.[1] The human body is home to many species of bacteria, viruses, fungi, and other invertebrate parasites. Some of these organisms that live and thrive in humans are commensals and are harmless. They may be also beneficial to the host as they provide certain nutrients or compete with pathogenic organisms for space and recourses.[2] However, there is also a myriad of organisms that are pathogenic to the hosts. One of the mechanisms that empower pathogenic organisms to avert or subvert the host's surveillance and defense mechanisms is molecular mimicry.[3-5] The pressure to evolve molecular mimics may have arisen when the primordial free-living organisms "chose" to parasitize other organisms.

Molecular mimicry is the sequence or structural resemblance of molecules of the host and the microbe.[1,3] Classically, the phenomenon of molecular mimicry is associated with autoimmune reactions.[3,5] Immunological central tolerance mechanisms involve clonally deleting the populations of T cells and B cells that react to self-antigens. However this mechanism is not foolproof, as a considerable number of cells can escape deletion.[6] T cells and B cells mount their response to certain portions of a pathogen's molecule, popularly called antigenic determinants or epitopes. If the antigenic determinants of pathogens are similar to host proteins as a result of mimicry, then the immune system reacts against its own cells and tissues, expressing that epitope resulting in autoimmune reactions. One of the classical examples of bacterial molecular mimics that elicit autoimmune reactions is the M protein of *Streptococcus pyogenes* that elicits autoantibodies that cross-react with heart myosin leading to heart damage.[7] Viral infections may also provoke autoimmune reactions through molecular mimicry. Cross reactive T cell response to islet antigens GAD65 or proinsulin aftermath of herpes, rubella, and coxsackie B viral infections may result in type I diabetes.[3]

Besides autoimmune reactions, molecular mimicry also influences the subversion of the host surveillance mechanisms and may help promote the survival of parasites or pathogens. Indeed, many parasites and pathogens, including plant pathogens, show evidence of molecular mimicry.[1,8-10] In these cases, structural mimicry is usually involved.[1] Viruses produce their "own" versions of cytokines or decoy receptors of host's cytokines, which results in immunomodulation of the host's response to the advantage of the virus.[4] For instance, Human cytomegalovirus produces the immunosuppressive cytokine IL-10 and orthopoxviruses produce decoy receptors for the antiviral cytokines interferon-γ and IL-1.[11-13] Another example is the vaccinia virus protein A49 that interferes with NFκB.[14] The transcription factor NFκB, which is central to the activation of the host's immune response, is normally retained in the cytoplasm as an inactive form bound to its inhibitor IκBα. Upon stimulation, IκBα is degraded and NFκB moves in to the nucleus to turn on an array of genes. A49, a mimic of IκBα, binds to the ubiquitin ligase thus preventing IκBα degradation, thus promoting cytoplasmic retention of NFκB.[14] Similarly, bacteria produce structural mimics to gain entry in to the host cell. *Yersinia pseudotuberculosis* produces invasin to bind the host β1 integrin surface receptors to enable attachment and entry.[1,15] Invasin out-competes the natural β1 integrin ligand fibronectin, with which it shares structural similarity without any sequence homology. Further, structural mimicry can be also witnessed in pathogens and commensal bacteria mimicking the host's sialylation patterns to masquerade as "self" to avoid, subvert, or inhibit host innate immunity.[16] Many human pathogens coat their surface with sialic acid N-acetylneuraminic acid (Neu5Ac) that enables them to recruit inhibitory siglecs (sialic acid recognizing Ig-superfamily lectins) or to bind to factor H (a serum protein which restricts the alternative complement pathway) thus dampen innate immune response.[17,18] Indeed, molecular mimicry in host–pathogen interactions typifies the Picasso quote: "Good artists copy, great artists steal."

Thus, identification of molecular mimics may provide important insights to the understanding of pathogenesis. Although high throughput genome-wide analysis has been used in the past to discover candidate molecular mimics in several different parasites, such studies for bacteria have largely been lacking.[9] In this issue, Doxey and McConkey attempt to fill this void.[19] Employing in silico tools for high throughput analyses, they have identified almost a

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hundred of such candidates by screening a total of 128 bacterial proteomes.[19] The authors have classified the bacteria analyzed in the study into two broad groups—pathogenic and non-pathogenic species. They matched the whole proteomes of the selected bacteria against the human proteome. Molecular mimicry candidates were observed in both pathogenic species and non-pathogenic species of bacteria. The authors then compared all the candidates to select the unique set of mimics that may aid in pathogen virulence. They do this by applying the criteria of mimics that are specific or enriched in pathogens and either absent or not enriched in non-pathogenic species. Finally, they arrive at a list of 95 such candidates that show unique relationships. Importantly, almost third of the selected candidates could be correlated with published experimental data as possible virulence factors. Molecular mimics that affect host lipid metabolism, phagocytosis, apoptotic pathways of host cells, which enables to destroy the engulfed bacteria, could be readily identified. Finally, the authors also try to uncover the evolutionary origins and relationships of the mimics using collagen mimics and leucine-rich repeat proteins as examples. Both mimics stand out as representatives of independent evolutionary origins yet achieving convergent functions, which is not unusual in pathogenic bacteria.[8]

An arbitrary classification of pathogenic vs. non-pathogenic bacterial species has been used in the study. However, the work succeeds in identifying putative candidates of virulence and manipulators of host function, which was the primary objective of the study. Nevertheless, one has to remember that this approach may not be sufficient to identify mimics that are not necessarily involved in virulence. For example, selection pressure to evolve mimics that aid in colonizing the host would be similar in both commensal non-pathogenic bacteria as well as pathogens.[1,2] Further, mimics may share structural similarity but need not have a similar sequence.[1,15] Furthermore, this approach may not also effectively identify mimicry candidates in pathogens that may elicit autoimmunity. Even small regions of similarity, not necessarily the complete sequence of a protein, are sufficient to trigger such autoimmune reactions.[3,5] However, this study clearly demonstrates the utility of high-throughput approach to identify virulence factors. It also provides a platform for further research in scrutinizing the identified candidates that may eventually open avenues for better comprehension of pathogenesis and therapeutic interventions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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