Cultivating Our “Frienemies”: Viewing Immunity as Microbiome Management

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ABSTRACT

Immunology has been studied and understood in the context of the compelling problems of infectious disease. But our rapidly growing knowledge of immune interactions with our healthy microbiota, and the many benefits it confers, suggests there may be value to an alternative view: that mechanisms of defense against pathogens are one aspect of a complex system with the broader purpose of managing our healthy microbiome. From this perspective, adaptive immunity may be viewed as a flexible system for simultaneously recruiting and managing a near limitless number of potential symbionts. This perspective can allow for reinterpretation of many observations and can suggest new experiments to help us better understand our complex interactions with the microbes that surround us.

OPINION/HYPOTHESIS

Our ability to study the microbial world around us has historically been limited by our ability to culture them *in vitro*. Infectious disease research, guided by Koch’s postulates, generally begins with the need to culture the microorganism to purity. Importantly, we can culture many pathogens on medium that contains blood or serum, nutrients many of the most dangerous pathogens are well adapted to utilize. We have had much less success in the culture and, therefore, the study of the many commensal or symbiotic organisms of our microbiota that do not directly parasitize us. They do not eat our blood but have more complex and/or specific needs that are harder to mimic in the lab, and they are therefore generally more fastidious and difficult to culture. Thus, our great interest in human disease and our relative success in the culture of pathogens have converged to keep our focus on adversarial interactions between complex, multicellular organisms like ourselves and the pathogens, rather than the broader microbial world around us. However, our rapidly growing knowledge of the predominance of nonpathogens in our microbiome allows for a reevaluation of this adversarial view.

LUNCH WITH OUR “FRIENEMIES”

All multicellular animals have to deal with the complex microbiota that surrounds them. We humans anthropocentrically view our immune system as a supreme accomplishment of evolution. And the great complexity of genomic rearrangements that can generate molecules, such as antibodies, with a seemingly infinite ability to recognize and defend against any newly encountered pathogens is so impressive that it supports this view. However, animals with such “adaptive immunity” are not free of pathogens and parasites. Insects and plants that lack adaptive immunity (as we know it) are no less successful and

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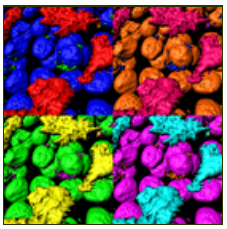

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suffer no more predation by pathogens and parasites. So what does adaptive immunity really get us? The “Red Queen” hypothesis (1) offers the morose perspective that the constant pressure of pathogens and parasites leads to the generation of more and more complex immune responses. These provide selective advantage to the host in competition against other hosts but cannot provide ultimate escape from predation by pathogens for the simple reason that the pathogens evolve more rapidly. As Lewis Carroll’s Red Queen says, “It takes all the running you can do, to keep in the same place.”

Here, I describe an alternative to the rather defeatist Red Queen hypothesis. Viewing everything currently considered “immunity” (including both resistance and tolerance) as aspects of a complex microbiome management system that mediates interactions with the sea of microbes that surround us, many of which are beneficial, can provide a much more positive outlook and different valuable perspectives. After all, a host cannot rid its surroundings of microorganisms, but it can affect them in many ways. There could be a strong selective advantage to the maintenance of a positive microbiota of commensals and symbionts. This reasoning leads to the alternative view of all the host functions that resist and repel pathogens, previously considered the “immune system,” as but one aspect of a system that also encourages commensals and symbionts, many of which contribute important beneficial functions for the host.

RESOURCE UTILIZATION: OLD FRIENDS ARE SILVER, NEW FRIENDS ARE GOLDEN OPPORTUNITIES

Mice and men spend vast resources on immunity. In a resting, healthy state, in the absence of known pathogens or parasites, the body produces huge numbers of immune cells and secretes large amounts of antibodies every day. It may be argued that these resources must be spent on an ongoing basis so that the body is optimally prepared for the next onslaught of pathogens. However, there could clearly be a strong selective advantage to conserving the resources spent on immunity. There are many examples of important functions with much less ongoing cost, including vision and flight, being lost in the absence of constant selective pressure, allowing flightless birds and sightless animals to thrive. In contrast, the many costly aspects of immunity appear to be highly conserved irrespective of the relative rate of predation by various pathogens, suggesting other potential selective pressures could be at work even in the relative absence of major pathogens.

Let us consider the alternative view that many of the known and unknown mechanisms that can protect against pathogens, and are therefore considered aspects of immunity, might be part of a system that maintains a healthy microbiome in close association with the host. From this perspective, it is not surprising that antibodies protect critical systems, but the predominant isotype, IgA, has less antimicrobial activity. Secreting massive amounts of a large protein like IgA, which targets but has little effect on resident flora, does not make much sense from a classical immunology viewpoint. It can make sense, however, if IgA contributes to the positive management of a complex and varying set of beneficial organisms. Maintaining and encouraging a healthy microbial flora that can vary over time could have many advantages for the host. These include physical and biochemical barriers to pathogen entry and intense competition for limiting nutrients on most body surfaces. But they could also include the ability to detoxify and digest some foods.

We introduce many new microorganisms into our gastrointestinal system with every bite of food we ingest and therefore have many opportunities to add new genes and functions to our microbiome. Just as grapes are naturally covered by yeast that can ferment them, all the leaves, fruits, nuts, etc., of our diet contain microorganisms that can detoxify their antimicrobials and utilize them as a nutrient source. Furthermore, other herbivores, such as insects, leave behind samples of their own intestinal flora on our shared food, including bacteria that are well adapted to live in their guts and digest that particular leaf’s or fruit’s nutrients. By eating shared foods and thereby introducing such microorganisms to our own gastrointestinal system, we have the opportunity to recruit new genes into our microbiome, including some that can help detoxify and/or digest a new food source, but only if we can rapidly adapt to the introduction of new

microbiota. It takes evolutionary time scales to incorporate gene-for-gene bacterial recognition systems into a host genome, as has been observed in insects or plants. But, viewing immunology as microbiome management provides the perspective that our adaptive recognition (immune) system allows such an organism to be “acquired” as a new, long-term resident of the gastrointestinal tract much more rapidly.

Thus, our microbiome management system provides the ability to accommodate new symbionts, adding new genes and functions that could allow flexibility of diet, a huge advantage to the host. This view explains the vast resources expended by the immune system as offset by the many benefits our friendly commensals provide. It also leads to the prediction that the ability to accommodate new symbionts into a flexible microbiome should correlate with a more complex and/or changing diet. Significantly, organisms that lack adaptive immunity, such as insects, can adapt and evolve relatively quickly in other ways but may be highly specific in their diet, eating only a single species of plant, for example.

APPLYING THE FLEXIBLE MICROBIOME VIEW OF IMMUNOLOGY

Interpreting unexplained phenomena from an alternative viewpoint can often reveal bias in current approaches and/or generate new testable hypotheses. For example, there is growing understanding that aspects of mammalian immunity are altered by changes in abundance of vitamin D. But vitamin D is not a coenzyme or building block for other molecules required for any immunological function. Rather, it is generated from a precursor in the skin upon exposure to sunlight and detected by receptors that can affect a transcriptional response, allowing the body to sense and respond to sunlight exposure. Why would the immune system need to respond to changes in sunlight? The current, pathogen-focused view of immunity would lead to speculation that there could be advantage to seasonal changes in the response to pathogens, although it is difficult to imagine what seasonal pathogen pressures could be strong and sustained across all the wide range of animals that use vitamin D. Viewing immunology as microbiome management offers a different interpretation. For most animals there is strong seasonality to food sources. Sensing and responding to changing seasons via vitamin D could allow for changes in the management of the microbiome involved in the digestion of seasonally changing foods. Importantly, the view of immunity as microbiome management suggests new experimental approaches: manipulation of vitamin D and diet in conjunction with metagenomic analysis of the microbiome of the gut. By extension, this view also suggests similar experimental approaches to examine the many mouse strains with engineered mutations in cytokines or immune functions but no observable defect in control of pathogens. One prediction might be that many such mutant strains have altered microbiomes.

THE RISK OF LOOKING DOWN ON “LOWER ORGANISMS”

Our pride in the complexity of adaptive immunity, whether we view its primary function to be combating pathogens or microbiome management, should not blind us to the similarly advanced analogous systems in other multicellular organisms. They are likely to have evolved as rapidly under similar selective pressures and to have acquired different but similarly effective mechanisms to mediate interactions with the surrounding microbiota. Lacking genomic rearrangement to generate novel specificities (hallmarks of our adaptive immune system), they are likely to have alternative, but similarly complex, mechanisms encoded in their genome, allowing such interactions to be heritable. We can explore our alternative views of immunity in the context of the unexplained phenomena, most notable in plants, of “hybrid vigor”: the observation that the offspring of different lineages are often superior to the parental lines by a variety of measures. In the traditional view of immunity, it is easy to predict that the offspring could be resistant/tolerant to a larger set of pathogens and therefore suffer less disease than the parents, but that does not lead to an expectation of many improved traits in the absence of pathogen damage. In contrast, viewing immunity as but one aspect of a system that manages microbiota with diverse positive effects leads directly to an expectation of increased vigor of the hybrid offspring. Organisms that inherit specific “gene-for-gene” (2) symbiosis

mechanisms from their parents should benefit from diverse parentage, since more diverse parents, coevolved with a different set of microorganisms, provide a larger combined set of symbionts to their hybrid offspring. In contrast, hybrid vigor should be less pronounced in organisms with a flexible microbiome that can generate specificity to any newly introduced organism, since the set of microorganisms that can be accommodated would not be affected. Consistent with this view is the example of plants, which have “gene-for-gene” relationships with bacterial commensals and pathogens and display pronounced hybrid vigor. It will be interesting to look for a correlation between hybrid vigor and vertical inheritance of mechanisms of microbiome management in diverse organisms. But the selective advantages of positive interactions with the microbial world are so great that we should be cautious to conclude that multicellular organisms do not have a sophisticated microbiome management system just because they do not have one that is recognizably similar to those we are beginning to understand. One of the most far-reaching implications of the microbiome management viewpoint is that the strong selective advantage to accommodating new commensals, and the challenge of the rapid evolution of those microorganisms, should result in the genes involved in microbiome management being among the most rapidly evolving of any in the genomes of multicellular organisms. Perhaps this is how we will find and describe the microbiome management systems of “lower organisms,” by comparing sets of genes that are most rapidly evolving. The mechanisms of microbiome management in diverse hosts are likely to have important applications to our ongoing efforts to manipulate microbiota to our advantage.

CONCLUSION

The prevailing view of interactions between complex, multicellular hosts and the microbes that surround them is skewed by a historical focus on pathogens. But in our rapidly accelerating exploration of the microbial world around us, there may be advantages to taking the broader view of immunity to pathogens as one aspect of a microbiome management system that regulates interactions with intimately associated microbiota, the great majority of which may be beneficial. From an evolutionary standpoint, there is little justification for the presumption that mammalian microbiome management is more complex or effective than that of other multicellular organisms. To understand how microbiome management works in other multicellular organisms, it may be illuminating to define its function in terms of aspects of its microbiota, such as complexity, diversity, plasticity, and stability. Undoubtedly, the highly evolved mechanisms used by other organisms to manage their microbiota will be an important source of new tools to manipulate our own.

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FOOTNOTES

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