

The Microbiota Regulates Immunity and Immunologic Diseases in Dogs and Cats

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KEYWORDS

- Microbiota • Dysbiosis • Hygiene hypothesis • Atopic dermatitis • Allergies
- Autoimmunity

KEY POINTS

- It is now possible, by the use of modern sequencing techniques, to determine the composition of the microbiota on body surfaces, especially the skin and gastrointestinal tract.
- The microbiota influences the development and functions of the immune system.
- In healthy animals, the microbiota and the immune system maintain a balance so that excessive immune and inflammatory responses are avoided.
- Disturbances in the composition of the microbiota (dysbiosis) permit the development of inflammatory and allergic diseases (the hygiene hypothesis).
- Important diseases triggered in dogs and cats by dysbiosis include respiratory allergies, atopic dermatitis, and inflammatory bowel disease.

Animals are obliged to develop a relationship with the microbes that live on their surfaces. The enormous and diverse population of microorganisms living on the skin and within the respiratory and digestive tracts directly influences the development, regulation, and function of the immune system. Conversely, the immune system regulates the composition and behavior of these microbial populations. Immune responses are therefore profoundly influenced by the microbiota.

Body surfaces constitute stable, nutrient-rich ecosystems where microbes thrive. As a result, they are densely populated by bacteria, archaea, fungi, and viruses, collectively termed the microbiota. It is estimated that in an animal body at least half of all the cells are microbial. These microbes release a complex mixture of metabolites, vitamins, and nutrients that signal to the host's immune system and influence the immune

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system development, function, and behavior.¹ This is reflected in profound effects on the development of immunologic and allergic diseases. These microbial effects must be considered while treating such complex diseases and they provide possible routes to new innovative treatments.

The body's surface defenses are faced with the task of coexisting with the microbiota while simultaneously preventing any invasion of pathogens through breaks in the epithelial barriers. Nutrients and microbial metabolites are continually released into the body by the microbiota where they influence immune cell and inflammatory functions. These products, detected by the cells of the immune system, ensure that the immune system is prepared to respond promptly to microbial invasion.² In fact, the body's response to the microbiota involves 2 opposing processes. Stimulation by microbial products serves to activate the immune system. However, to ensure that inflammation and other immune processes are not excessive, this stimulatory response must be counterbalanced by regulatory processes.

For many years, it was believed that the role of the immune system was simply to ensure exclusion of all invading microbes by distinguishing between self and not-self and eliminating foreign antigens. It is now known, however, that the immune system must also determine the degree and nature of the threat posed by the microbes it encounters and adjust its responses accordingly. It must tolerate the microbiota and food antigens while simultaneously be highly responsive to invading pathogens. It must decide, when necessary, whether to mount a cell-mediated or an antibody-mediated response. This discrimination is determined both by how the antigens are processed and by signals from the microbiota. The presence of the microbiota must either be tolerated or ignored if an animal is to remain healthy. An animal cannot afford to act aggressively toward its own microbiota. The presence of all these bacterial products has the potential to trigger massive acute inflammation; however, this inflammation must not happen unless absolutely required to defend the body.

Therefore, in a normal, healthy animal, 2 opposing responses are in balance. The body, although not responding aggressively to the microbiota, must be prepared to respond rapidly and effectively at any time. The body must refrain from overresponding aggressively to the microbiota while being ready to respond rapidly and effectively when necessary.

If this equilibrium between the proinflammatory and antiinflammatory processes is disturbed, this will be reflected in changes in the level of activation of the immune and inflammatory systems.

HOW THE MICROBIOTA IS ANALYZED

The existence of the microbiota has been known since the invention of the microscope. Its importance, however, has been generally underappreciated until recently. Advances in technology have allowed for a deeper understanding of the complex ecosystem of the microbiome and its interactions with the host immune system.

In the past, intestinal bacteria were identified by growing them in culture; however, this only allowed a small proportion of the highly diverse microbial ecosystem to be identified. The anaerobic nature and restricted cultural conditions of most gut bacteria in cats and dogs, as well as limited knowledge of appropriate media for many bacterial species, prevent culturing them.³⁻⁶ However, prokaryotes can now be identified and classified within complex mixtures by sequencing their specific DNA. As a result, much of the characterization of the gastrointestinal microbiota has focused on the

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