

Antibiotics as Anti-inflammatory and Immunomodulatory Agents

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When I first came to the National Institutes of Health in 1965 as a postdoctoral fellow in immunology, research on the induction and expression of antibody responses *in vitro* was in an early stage of development. Most investigators felt compelled to add one or more antibiotic(s) to their spleen or lymph node cell cultures to reduce the incidence of bacterial contamination. This was believed to be essential, because laminar-flow hoods did not exist in those days. However, one colleague down the hall adamantly resisted the use of antibiotics because he believed they would have an adverse effect on one or more type(s) of cells that play a key role in generating an immune response. Although his studies did not progress as rapidly as he had hoped due to problems with contamination, his arduous efforts were rewarded by obtaining antibody responses 100–1000 times greater in magnitude than those reported by others who used antibiotics. I have never forgotten this experience and have often wondered about the extent to which antibiotics may have influenced the outcome of the many published studies on *in vitro* immune responses. Consequently, when asked to review this monograph, I eagerly agreed to do so.

The take-home message of this book, which reviews anti-inflammatory and immunomodulatory effects of antibiotics

since 2004, is that antibiotics—in addition to their well-known bactericidal and bacteriostatic effects—have many other biological, physiological, and immunological properties that could have a significant impact on various host defense mechanisms. These include their ability (1) to suppress the expression of virulence factors (e.g., quorum sensing mechanisms, as well as the production of exotoxins, exopolysaccharides, pili, flagellin, and lipopolysaccharides); (2) to accumulate in inflammatory cells in high concentration, thereby providing more efficient delivery of antibiotic to sites of infection; (3) to downregulate the molecular expression of integrins known to influence leukocyte adhesion and the accumulation of macrophages and neutrophils at sites of infection; (4) to inhibit the maturation and proliferation of subsets of T lymphocytes, as well as to influence immunoglobulin secretion and isotype class switching by B lymphocytes; (5) to protect the respiratory ciliated epithelium from bacterial injury by interfering with bacterial adherence and colonization; (6) to inhibit neutrophil migration; (7) to modulate the expression of adhesion molecules and to reduce the production of chemotactic factors at the site of inflammation; (8) to increase the production of various inflammatory cytokines (IL-8, IL-1 β , and TNF- α) that are potent activators of neutrophils; (9) to increase the production of IL-2, colony stimulating factor, and other cytokines that modulate the induction of TH1 and TH2 lymphocyte activity; and (10) to cause significant reductions in the number of lymphocytes and the ratio of CD4⁺CD8⁺ T lymphocytes.

The clinical implications of some of these effects are discussed with reference to which antibiotics are used as mucoregulatory agents for treating diffuse pan-bronchiolitis, cystic fibrosis, various upper airway diseases, chronic asthma, and lung

injury, as well as which antibiotics are used for the development of more precise therapies to prevent biofilm diseases or chronic inflammation without increasing the risk of antimicrobial resistance to macrolides. The implications of these findings with respect to protracted antibiotic therapy remain to be fully assessed. If one also considers the results of a recent study [1] that indicates that as many as 15 different β -lactam antibiotics, including penicillin and its derivatives, exert profound neuroprotective effects, it, indeed, may be difficult at times to attribute the beneficial effects antibiotic therapy to any particular mechanism.

This concise and well-illustrated monograph contains much information of value to clinical immunologists and microbiologists engaged in research on the management and treatment of infectious diseases. I was disappointed that it did not go into more detail and focus more directly on how antibiotics might influence the qualitative and quantitative features of the immune response, *per se*, as well as the mechanisms involved. I hope it will inspire others to conduct more detailed and long overdue studies addressing those issues.

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