

Preface

The immune system is a complex network whose primary functions are to protect the host from external threats such as bacteria and viruses as well as internal threats, namely, allergic responses and malignant transformation. Immune cells produce various biological products that allow them to communicate with one another and orchestrate immune responses. Cytokines, which are secreted by immune cells in response to microbes and other antigens, are soluble protein mediators that are important in such intercellular communication. Different cytokines stimulate diverse responses in various phases of inflammation and immunity, including the innate immune response, the generation of cytotoxic T cells, and the development of antibodies by the humoral immune system. Cytokines have pleiotropic effects and functional redundancy, and the combination of cytokines produced in response to various stimuli determines the kind of immune response that is activated. In addition, cytokines operate in a complex network, in which one cytokine can affect the production of many other cytokines as well as modulate the responses to them.

Historically, cytokine identification has undergone several stages of development. Initially, cytokines were purified by several biochemical processes and identified simply according to their biological activities. Subsequently, cytokines were identified through expression cloning following their biological activities or by using specific antibodies. Cytokine identification then entered the most recent stage, which was primarily driven by the Human Genome Project in the late 1990s to the early 2000s. Identification of the complete sequence of human genes made it possible to assign a function to each member of the huge database of previously unrecognized proteins through sequence comparison with previously named genes. Thus, numerous candidate cytokines were identified based on their homology to known cytokines. The most important means of assessing the biological function of these newly identified cytokines has been to evaluate the phenotype of mice genetically engineered to either knock out a particular gene or overexpress it. Thus far, more than 100 cytokines and their cell-surface receptors have been analyzed, including the most recently assigned interleukin (IL), IL-38.

It is now also clear that the pathophysiology of many infectious, autoimmune, allergic, and malignant diseases can be largely explained by which cytokines are induced and subsequently regulate the cellular responses. In clinical medicine, cytokines are involved in a wide spectrum of diseases; cytokines are therefore considered important as therapeutic targets for specific agonists or antagonists in numerous immune and inflammatory diseases. For instance, ample basic and clinical evidence indicates that excess tumor necrosis factor (TNF)- α underlies the pathogenesis of chronic inflammatory diseases, such as rheumatoid arthritis. The therapeutic effectiveness of TNF- α inhibitors has subsequently been demonstrated in the treatment of this disease. The success of anti-TNF- α therapy has led to recognition of the importance of cytokines as therapeutic targets in disease.

Although this field has undergone enormous expansion, insufficient understanding of cytokine biology and its complicated network continues to be the rate-limiting step in developing cytokine therapeutics. The present book thus aims to provide the reader not only with information about the original properties of cytokines, but also with up-to-date findings on their roles under physiological and pathological conditions—with the ultimate goal of helping to create strategies for therapeutic treatment.

This book is not a survey of individual cytokines; rather, it guides the reader through the latest research on the cytokine network, covering signaling pathways, control of the immune response, and potential therapeutics. Among various important cytokines, we selected 15 key examples whose profiles we believed would stimulate the reader's interest. In this book, these cytokines are divided into three groups based on their physiological roles in the immune system. The first group includes cytokines associated with inflammatory disorders, proinflammatory cytokines, and the recently identified new helper T (Th) subset, Th17 cells. The second group is associated with allergic disorders, including Th2 responses and recently identified types of innate cells. The third group of cytokines is associated with immunological tolerance and anti-inflammation, including regulatory T (Treg) cells, IL-10-producing Treg (Tr1) cells, and inducible IL-35-producing Treg (iTr35) cells.

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