Epilogue

The idea that utilization of host immunity for prevention and/or treatment of cancer patients has been very attractive, thus massive efforts were put into this field for more than half a century without much success. However, in 1991, the identification of the first human tumor antigens was reported by Boon's group. Thereafter, many tumor antigens were reported and the nature of these antigens have been elucidated. In the 1990s and 2000s, some of those antigens were utilized for immunization as antigenic proteins and/or peptides mostly with incomplete Freund adjuvant in clinical trials, but in general the response rate was found to be very low. These results are certainly disappointing but were not unexpected, since it is conceivable that the immunogenicity of most tumor antigens is much weaker than that of non-self microorganisms, as will be described below. More importantly, by vaccination alone it is more difficult to induce growth suppression of tumors, which had once escaped from the host immune surveillance, than to prevent infection in healthy donors. During the course of these clinical studies, fortunately rapid progress has been made in the field in basic immunology, which now can be employed for improvement of cancer immunotherapy.

By the technique of X-ray crystallization, the study of "antigen presentation" entered the age of structure analysis of MHC molecules and antigenic peptides. Since then the biology of dendritic cells has been extensively studied, together with research advances in clonal selection, development of methods for identification of antigen peptides, epitope/agretope analysis, and the genetic mechanism of the diversity of T cell receptors.

It was also argued in connection with autoimmunity that MHC class I presents an auto-antigen, and that peptides of self-origin do not always induce an intense immune response like the non-self peptide shown in the case of infection. Concepts such as cryptic antigen (non-recognizing antigen below a threshold value) and tolerance (like immune tolerance) were introduced, in part explaining immunologic unresponsiveness to self-origin antigens including tumor antigens. It needs to be studied, however, whether cancer antigens can trigger initiation of specific immunity against cancer without causing autoimmune diseases.

T. Seya et al. (eds.), *Inflammation and Immunity in Cancer*,
DOI 10.1007/978-4-431-55327-4

It also became clear from recent studies on microbial infection that immune activation was not started even if a "non-self" antigen is present apart from other microbial factors, namely, pattern molecules. Systematic understanding of the innate immune system (TLR, NLR, RLR, CLR, and others) and immuno-regulatory systems (regulatory T cells, Treg, and checkpoint inhibitors PD-1/PDL-1) suggests that antigen uptake and the immune-activating (or -suppressing) mechanism are caused by different machinery. Surprisingly, the recent success of anti-PD-1/PD-L1 antibody therapy for patients with progressive cancer unequivocally revealed that the immune system has a potential to look out for growing tumors when it is awakened. There would be differential ways for immunological waking, which we should select depending on the nature of the tumors to be targeted for immunotherapy. I believe that vaccine immunotherapy will contribute to the future eradication of cancer.

As described above, to date a number of tumor antigens have been defined and a part of them have been or are ready for clinical use. In contrast, as for immune adjuvants, a relatively small number of them have been used, thus only a small amount of information is available. Based on new findings and concepts described above, now is the time to study the next generation of immune adjuvants and to find a suitable way to select proper adjuvants to potentiate immunogenicity of tumor antigens in the interest of inducing antitumor immunity in cancer patients.

This book overviewed cancer immunity from broad scientific fields, based on the concept that cancer is a sort of by-product of infection, inflammation, and host–immune response. In this book, authors actively involved in the field of antitumor immunity study in Japan and Taiwan were invited to contribute. We do hope that the knowledge summarized in the book will encourage readers to understand and satisfy patient's urgent wishes, that is, we believe in the establishment of immunotherapy that brings high QOL to patients with cancer.

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