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Editorial

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Golden Age of Immunotherapy: Challenges and Opportunities

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The history of immunotherapy can be traced back to the 1700s when Benjamin Jesty and Edward Jenner noticed that milkmaids who previously caught cowpox were protected from contracting smallpox (1). Then in the late 1800s, Emil von Behring, Shibasaburo Kitasato and Paul Ehrlich invented serum therapy that contained neutralizing antibodies to toxins (2). As such, active and passive immunotherapies have been effectively exploited to save human lives for centuries and even led to near eradication of some fatal infectious diseases.

In addition to infectious diseases, significant progress in the development of immunotherapy has been demonstrated in other areas such as cancer, autoimmune diseases and allergy. While immunotherapies of the past rely on the generation or adoptive transfer of antibodies against target pathogens, recent approaches aim to harness multiple components of immune regulations; i.e. genetic engineering (DNA/RNA), recombinant proteins (antigens, cytokines, antibodies, extracellular vesicles) and cells (T cells, myeloid-derived suppressor cells, stem cells). Multi-target approach used in conjunction with combination therapy broadens the scope for innovation in immunotherapy.

In the current issue of *Immune Network*, a series of review articles discusses up-to-date findings of immunotherapies for cancer, autoimmune and allergic diseases. For instance, strategies to overcome limitations of immune checkpoint blockers (ICBs) are frequently conferred (3). One of these strategies is to use specific microbes, as commensal microbiota is shown to be required for successful cancer immunotherapy (4). Furthermore, encouraged by the positive treatment outcomes of ICBs, bispecific antibodies that target two cell surface proteins simultaneously are designed in hopes of improving efficacy while reducing undesired side-effects. Particularly, T cell-engaging bispecific antibodies designed to link tumor cells and T cells are thought to be promising next generation cancer therapeutics (5). In addition to ICBs, recombinant cytokines have been evaluated as anti-cancer biologics that increases the survival, expansion and differentiation of CD8 T cells and NK cells. Namely, it is discussed how immunotherapy with cytokines of common gamma has been modified to overcome the limitations of initial trials (6). Moreover, the reviews evaluate the profound therapeutic efficacy of chimeric antigen receptor (CAR) T cells in blood cancers and discuss how next generation CAR T therapy can be applied to solid tumors, infectious disease and autoimmune diseases (7).

Cytokines such as IL-17 and IL-23 have been recently shown to be pathogenic in psoriasis. On the other hand, autoantibodies and CD8 T cells are known to mediate blistering skin

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disease and alopecia areata, respectively. The latest understanding of the pathogenesis and immunotherapies of skin inflammatory diseases are reviewed (8). TNF blockers are widely used for the treatment of rheumatic diseases. Approaches to target cytokines other than TNF, JAK inhibitors, co-stimulatory blockers, B cell antibodies and B cell survival factors have been developed for the treatment of rheumatoid arthritis, ankylosing spondylitis and lupus in humans. Two review papers comprehensively discuss the current immunotherapies and future perspectives of these autoimmune diseases (9,10). In addition to antibodies and small molecules, several cellular approaches using mesenchymal stem cells, Treg cells, myeloid-derived suppressor cells have been proposed as novel immunotherapies for autoimmune diseases. The rationales and recent pre-clinical/clinical data are provided to discuss the challenges and limitations of these cell therapies (11).

Unnecessary allergen-specific type 2 immunity and IgE production cause allergic diseases including atopic dermatitis, chronic rhinosinusitis, allergic asthma and food allergy. Antibodies to classical type 2 cytokines such as IL-4, IL-5 and IL-13, and small molecules targeting their signaling pathway in atopic dermatitis are reviewed (8). In addition to the classical type 2 cytokines, innate type 2 cytokines such as IL-25, IL-33 and TSLP produced by epithelial cells, act as "alarmin" in allergic diseases to regulate innate and adaptive immune cells as well as non-immune cells including epithelial cells and sensory neuron. Latest understanding on the role of these epithelium-derived cytokines and findings from recent clinical trials targeting IL-33 and TSLP pathway are reviewed (12). To overcome drawbacks of the current allergen-specific immunotherapy, clinical trials have been conducted to verify whether alternative routes of allergen administration would be more effective in inhibiting allergic responses. The limitation and opportunities of the clinical trials are discussed (13). We hope this review series provides comprehensive and up-to-date information on immunotherapies for diverse immune disorders and hence prompts translational research for next generation immunotherapies.

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