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Toll-like receptors and diseases

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By the end of the 19th century, Dr. Elie Metchnikof proposed the theory of “microbial recognition” by innate immunity and phagocytosis through his pioneering research into this field, for which he was awarded the Nobel Prize in 1908. In the late 1980s, Dr. Charles Janeway emphasized the importance of pathogen recognition as the first line of host defense. This established the concept of recognition of pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) of the host. The past decade has witnessed a booming in the scope of studies of the mechanisms of naturally occurring innate immunity. The discovery of Toll-like receptors (TLRs) in the mid-1990s clearly showed that pathogen recognition by innate immune system is, in contrast to the traditional belief in its non-specificity, a precisely regulated and specific process mediated by germline-encoded PRRs that have evolved to detect PAMPs of foreign pathogens. Although TLRs have been implicated as the first line defense in human for anti-microbial responses, they are also involved in the development of many inflammatory and immune diseases not directly caused by bacterial or viral infection. Such properties of TLRs are attributed to their capacity to recognize host-derived agonists mostly released by damaged cells or tissues during the progression of diseases. The development of the research of TLRs in diseases has reached to the stage that a collection of comprehensive reviews of the progress should provide a platform for further discussion of the beneficial versus detrimental roles of these PRRs. Thus, this Special Issue contains articles contributed by investigators directly involved in the studies of TLRs during the past years. We hope the experiences and perspectives of the authors of various backgrounds will stimulate more in-depth studies by our readers both in or ready to be in the relevant field.

Concerning TLRs as major portals for entry of microorganisms and allergens, Dr. K. Chen and co-workers [1] discuss the involvement of TLRs in the pathological processes of allergic airway inflammation in which dendritic cells (DCs) are preferential targets of PAMPs and TLR signaling in DCs determines the balance of Th1/Th2 polarization. In addition to DCs, airway epithelial cells, eosinophils and mast cells also express a variety of TLRs and

contribute to allergic airway inflammation. For instance, activation of TLRs in mast cells and airway epithelial cells increase the release of proallergic Th2 cytokines. On the other hand, stimulation of TLR9 induces Th1 responses that may limit Th2-dependent allergy. Moreover, activation of TLR4, TLR3 and TLR9 promotes DCs to release factors that skew a Th17 differentiation, which, while paradoxically, may exacerbate allergic airway inflammation, also could inhibit the production of Th2 cytokines in the airway, thus limiting the severity of the disease.

Drs. Kovach and Standiford [2] provide an overview of the participation of TLRs in both infectious and non-infectious lung diseases. The lung is in contact with numerous infectious agents, foreign antigens, and host-derived danger signals. Resident myeloid and stromal/structural cells of the lung express all mammalian TLRs, most abundantly TLR2, TLR3, TLR4, TLR5, and TLR6, which recognize PAMPs and endogenous danger-associated molecular patterns (DAMPs). TLRs play a prominent role in host defense in the lung against extracellular and intracellular pathogens, including *Mycobacterium tuberculosis*, fungi and respiratory viruses. In addition, new evidence suggests that TLRs may be involved in the development of non-infectious lung diseases, such as acute injury and interstitial disease. Therefore, TLRs may represent promising targets for therapeutic intervention of acute and chronic lung disease.

The article by Dr. Kong and Le [3] focuses on the recent developments in the role of TLRs in inflammation of the central nervous system (CNS). TLRs are expressed by various cell types in the CNS, including microglia, astrocytes, neurons, and vascular cells. Activated microglia promote inflammatory responses that serve to further engage the immune system and initiate tissue repair. Activation of TLRs in CNS cells enhances the production of proinflammatory cytokines that mobilizes immune responses but may also cause neuronal damage. The article highlights the role of TLRs in neuroinflammation related disorders, including ischemia/stroke, brain trauma/hemorrhage, pathogen infection and autoimmune diseases.

Dr. Arroyo et al. [4] discuss the participation of TLRs in neurodegenerative diseases. Pro-inflammatory molecules elevated in neurodegenerative diseases increase the expression of TLRs in CNS cells and upon activation, TLRs in turn promote the release of pro-inflammatory cytokines in the brain. Therefore, TLRs may participate in the progression of neurodegenerative diseases, such as Alzheimer's disease (AD) with persistent glial activation and multiple sclerosis (MS) caused by abnormal immune responses. In AD, in addition interacting with cognate ligands, TLR2 and TLR4 may also cooperate with other cell surface receptors such as CD36, $\alpha 6 \beta 1$ integrin, CD47 and scavenger receptor A (SR-A) to recognize fibrillar amyloid β ($A\beta$) peptides on the cell surface, which leads to the activation of microglial cells to increase endocytosis and the release of pro-inflammatory molecules. The article also reviews the capacity of TLR2, TLR4 and TLR9 ligands to promote the expression of a chemoattractant receptor FPR2 in microglial cells that mediates cell migration in response to $A\beta 42$ peptides, a pathogenic factor in AD. FPR2 also mediates the up-take of $A\beta 42$ by TLR ligand activated microglial cells. For MS, new number of publications relating TLRs to the pathogenesis is growing and interestingly, some TLR members may be protective for the host.

TLRs recognize a wide variety of putative host-derived agonists that have emerged as key mediators of innate immunity. TLR signaling also plays an important role in the activation of the adaptive immune system by inducing pro-inflammatory cytokines and up-regulating costimulatory molecules of antigen presenting cells (APCs). Inappropriate activation of TLRs by endogenous ligands released by damaged tissues may result in sterile inflammation. The review article by Dr. Su and colleagues [5] discusses the contribution of TLR signaling to the initiation and progression of sterile inflammation, such as ischemia/reperfusion injury, tissue repair/regeneration and autoimmune diseases.

In the liver, TLRs are widely expressed by parenchymal and nonparenchymal cells. Recent studies indicate that TLRs are involved in almost all liver diseases such as acute/chronic hepatitis, fibrosis/cirrhosis, alcoholic/non-alcoholic disease, ischemia/reperfusion injury, regeneration and hepatocellular carcinoma. Drs. Chen and Sun [6] review the expression patterns of TLRs in liver cell populations including hepatocytes, sinusoid endothelial cells, Kupffer cells, lymphocytes, DCs, biliary epithelial cells and stellate cells. By interacting with a plethora of ligands readily available in the liver, TLRs are pivotal in mediating acute injury as well as regeneration. Therefore, TLRs as key regulators of liver diseases are considered as promising therapeutic targets.

An interesting article by Dr. Zhang and colleagues [7] discusses the role of TLRs in macrophages and natural killer (NK) cells in female reproductive health. Macrophages and NK cells participate in a wide range of patho-physiological processes in the female reproductive organs and adapt their phenotype to the local micro-environment. Emerging evidence demonstrates that TLRs in macrophages and NK cells are involved in many diseases of female reproductive systems including polycystic ovary syndrome. The article points out that in the female reproductive organs, TLRs, macrophages and NK cells not only provide protection against infections by exogenous pathogens, but also regulate essential functions of the uterus and ovary.

Dysfunction of TLRs is implicated in a wide range of human diseases, especially in infection, immunodeficiency, sepsis, autoimmune disorders and allergy. Agonists or antagonists of the TLRs from plant sources may be utilized to interfere with abnormal immune responses. In the article by Dr. Zhou and colleagues [8], the biological function of a group of compounds identified and isolated from medicinal plant extracts is discussed. These compounds act as agonists or antagonists for TLRs. They include poly galatans, fructan, polyphenols, alkaloids, flavonoids, coumarin and terpenoids. Animal tests have revealed promising prospects of some of the compounds as drug leads for therapies of infectious and inflammatory diseases.

The surface of pathogens typically bears PAMPs recognized by PRRs of the innate immune system. Several families of PRRs have been characterized, including TLRs, intracellular Nod proteins, Nod-like receptors, RIG-like receptors, and dectin proteins. Dr. Rabinovich and colleagues [9] discuss the role of glycans and lectins (particularly galectins) in mediating microbial recognition and initiation of innate immune responses. Galectins are widely expressed in host cells and participate in different steps of infection such as pathogen recognition, invasion and resolution. In addition, recent studies report the presence of

conserved ‘galectin-like’ domains in certain pathogens including helminths and protozoan parasites potentially serving as virulence factors. Dissecting the role of cell surface glycosylation during host-pathogen interactions is therefore critical for better understanding of the mechanisms involved in pathogen recognition by the host and for designing novel therapeutic strategies based on galectin–glycan interactions.

Despite the progress achieved in recently years, studies of TLRs in diseases still face challenges. Many fundamental questions concerning the precise role of each TLR in a particular disease remain to be elucidated. This calls for more rigorous testing with in vivo models using animal deficient in one or more TLRs, and in some more mature circumstances, agonists or antagonists of TLRs with clear molecular mechanisms and under strict ethical regulation need to be tested directly on human diseases. It is conceivable that with time new questions may arise but we have every reason to be optimistic that rapid growth in our knowledge of TLRs should result in major breakthrough in the development of therapeutic agents for human diseases.

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