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The 461th International Symposium on Therapy

The 461th International Symposium on Therapy was held at the Kioi forum in Tokyo on September 21, 2023. Dr. Ryozo Nagai, Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

Inflammation and disease

Introductory Message from the Chair

Ryozo Nagai, MD, PhD
Director, IMSJ

【Discourse】

Diversification of pharmaceuticals and future prospects

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Lecture I

Chronic inflammation in multimorbidity

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With the aging of the population, the number of patients with multimorbidity, who suffer from a variety of chronic noncommunicable diseases, especially cardiovascular diseases, is rapidly increasing. There are interplays between comorbidities; for example, heart failure and chronic kidney disease interact with one another (cardiorenal syndrome). It is therefore important to understand how multimorbidity develops through the interactions between diseases. In my talk I will focus on macrophages and show how macrophages contribute to organ crosstalk and chronic inflammation.

Lecture Ⅱ

Sterile inflammation and inflammasomes

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Inflammation plays a pivotal role in the pathogenesis of cardiovascular and lifestyle-related diseases, including atherosclerosis and myocardial infarction. Inflammation is a biological process in which inflammatory and immune cells, such as macrophages and neutrophils, respond to infection or harmful substances to defend the body and eliminate pathogens and harmful substances. However, pathogens and harmful substances are not directly involved in cardiovascular and lifestyle-related diseases, and it has been unclear how such inflammation is triggered. Such inflammation in the absence of infection is referred to as sterile inflammation. Recent evidence indicates that intracellular molecular complexes called inflammasomes play an important role as one of the triggering mechanisms of sterile inflammation.

The inflammasomes generally consist of three components: a pattern-recognition receptor (PRR) as a sensor, ASC as an adaptor, and inflammatory caspases as an effector. To date, there have been reported several types of inflammasomes. Of these, the NLRP3 inflammasome, formed by the sensor NLRP3, is primarily implicated in the pathogenesis of sterile inflammatory diseases. When stimulated by danger signals, such as ATP released from dead cells or uric acid crystals that cause gout attacks, NLRP3 is activated and forms NLRP3 inflammasome complex, resulting in the activation of caspase-1 (Casp1). Since Casp1 is originally identified as an IL-1β-converting enzyme (ICE), activated Casp1 processes the pro-IL-1β to the active (mature) IL-1β, a potent inflammatory cytokine. Activated Casp1 also processes a pore-forming molecule GSDMD to form pores on the plasma membrane, releasing active IL-1β to the outside of the cells and triggering inflammation. On the other hand, the influx of water into the cells through these pores causes lytic cell death due to cell swelling and rupture. This type of inflammatory cell death is known as pyroptosis. The concept of inflammasome was discovered and proposed in 2002,

and in 2006, it was revealed that NLRP3 inflammasome mediates inflammation in gout attacks; therefore, NLRP3 inflammasome has attracted much attention as a new molecular mechanism that induces sterile inflammation.

Dysregulation of the NLRP3 inflammasome has been implicated in various diseases including cryopyrin periodic fever syndrome (CAPS), cardiovascular disease, kidney disease, metabolic diseases, and cancer. Among them, CAPS is a rare autoinflammatory syndrome caused by a gain-of-function mutation of NLRP3, which is characterized by cold-induced fever and inflammation. We recently found that CAPS-associated NLRP3 mutants form cryo-sensitive aggregates that function as a scaffold for inflammasome assembly and reported a novel mechanism of NLRP3 inflammasome activation. We have also reported that excessive IL-1β production via NLRP3 inflammasome activation occurs in cardiovascular diseases such as atherosclerosis, aortic aneurysm, myocardial infarction, Kawasaki disease, and septic cardiomyopathy, and that inhibition of NLRP3 inflammasome lead to improvement of these diseases. Furthermore, we have reported novel danger signals to activate NLRP3 inflammasome and regulatory mechanisms of NLRP3 inflammasome activation.

At present, there are no direct inhibitors targeting the NLRP3 inflammasome available for clinical application. Instead, IL-1β-targeting agents have been used. Among these, canakinumab, a fully humanized monoclonal IL-1β antibody, has been approved for CAPS in Japan since 2011 and has shown significant efficacy. In addition, in 2017, a large clinical trial (CANTOS) demonstrated that canakinumab significantly improved inflammatory status and reduced recurrent cardiovascular events in patients with previous myocardial infarction who had residual inflammatory risk. Furthermore, the use of colchicine, which can inhibit the NLRP3 inflammasome formation, reduced the occurrence of cardiovascular events in patients with recent myocardial infarction or chronic coronary artery disease (COLCOT [2019] and LoDoCo2 [2020] trials). These findings suggest that the NLRP3 inflammasome is a novel therapeutic target for sterile inflammatory diseases.