

## **The role of the innate immune system regulated by DNA sensors in the development of vascular and metabolic diseases**

Daiju Fukuda, MD, PhD.

Department of Cardiovascular Medicine, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Sterile chronic inflammation causes cardiometabolic disorders, however, the mechanisms still remain obscure. Exogenous DNA fragments, such as from pathogens, strongly induce inflammation by the activation of DNA sensors which function as self-defense systems in the innate immune system. Meanwhile, growing evidence suggests that DNA sensors also recognize self-derived DNA fragments, contributing to the progression of inflammatory diseases. Recent studies have demonstrated DNA damage and the release of endogenous DNA fragments under excessive nutrient levels, such as those in hyperglycemia and hyperlipidemia. There are several types of DNA sensors in our bodies. Toll-like receptor 9 (TLR9), one of the most studied, recognizes DNA fragments in endosome. Also, stimulator of interferon genes (STING), which has recently been investigated extensively, recognizes cyclic GMP-AMP (cGAMP) generated from DNA fragments in the cytosol. Both TLR9 and STING are known to play pivotal roles in host defense, as the innate immune system. However, recent studies have indicated that activation of these DNA sensors in immune cells, such as macrophages, promotes inflammation leading to the development of vascular and metabolic diseases associated with lifestyle. Here, we discuss recent advances in determining the roles of DNA sensors in these diseases. Revealing a novel mechanism of sterile chronic inflammation regulated by DNA sensors might provide new insights to develop therapeutic strategies for these disease conditions.