

Special Issue: Cutting-edge research exploring mechanisms of tissue homeostasis in health and disease

Brief Review

Cutting-edge research exploring mechanisms of tissue homeostasis in health and disease

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Since the human race began, we have struggled to overcome infection, injury, and starvation in order to conserve the species. In this effort, our bodies mobilize critical defense systems including immunity, inflammation, and energy metabolism¹⁾. However, in the past decades, rapid changes in the environment inhabited by many humans have created numerous lifestyle habits plus a rapidly aging society that now lead to an a different problem: a pandemic of aging- or lifestyle-related diseases, such as cancer, cardiovascular disease, diabetes, chronic respiratory disease, and neurodegeneration. Cellular senescence, which occurs in vivo with aging, and chronic tissue inflammation, which is accelerated by obesity brought on by insufficient exercise or overnutrition, underlie development of many of these diseases^{2, 3)}. These conditions are not infectious, but these so-called "noncommunicable" diseases are marked by alterations in

immunity and inflammation that affect their development and progression. Furthermore, recent studies demonstrate that maintenance of homeostasis via cell-to-cell or organ-toorgan communication or through clearance of pathologically altered cells, such as malignant or dying cells, protects us against development of non-communicable diseases, whereas breakdown of homeostasis predisposes us their development. In this special issue of Inflammation and Regeneration, several groups engaged in research relevant to mechanisms of homeostasis in health and disease summarize their recent findings and present new concepts as review articles.

Recent reports indicate that expression of genes critical for development or prevention of lifestyle-related diseases might be regulated by core clock genes. Our group (the Oike group) at Kumamoto University has reported that periodic angiopoietin-like protein 2 (ANGPTL2) signaling regulated by a molecular clock maintains tissue homeostasis by tissue remodeling and repair through cell-to-cell communication as an adaptive inflammatory response. However, overnutrition and/or inactivity disrupt periodicity of ANGPTL2 expression, and subsequent prolonged, excessive ANGPTL2 function promotes chronic inflammation and subsequent pathologic irreversible tissue remodeling, resulting in development of lifestyle-related diseases, including cancer. Moreover, we recently found that ANGPTL2 is relevant to Senescence-Associated Secretory Phenotypes (SASPs) and that excess ANGPTL2 is secreted from senescent cells in various aging-related diseases. In this issue, we describe ANGPTL2 function in these activities and discuss whether excess ANGPTL2 activity is a common molecular mechanism underlying lifestyle diseases and cancer.

It is well known that the prevalence of obesity, diabetes and heart failure increases with aging, and that age-related disorders share common pathologic features such as chronic low-grade inflammation and systemic metabolic dysfunction. The group of Drs. Yoshida, Shimizu, and Minamino at Niigata University has demonstrated that p53-induced cellular senescence plays a critical role in this pathological process. They found that heart failure and obesity induced adipose tissue aging and systemic insulin resistance, while systemic insulin resistance had a causal role in progression of age-related disorders like diabetes and heart failure. In this issue, Dr. Minamino's group proposes a model describing how a vicious metabolic cycle in organ-to-organ communication accelerates development of age-related disorders. They also address a pathological role played by p53-induced cellular senescence in obese or aging white adipose tissue in promoting development of heart failure and diabetes.

Parenchymal/stromal cell communication is receiving much attention as playing an important role in development of several metabolic diseases. The group of Drs. Ogawa, Suganami, Tanaka and Itoh at Tokyo Medical and Dental University has demonstrated that saturated fatty acids, which are released from obese hypertrophied adipocytes as a "danger-associated molecular pattern (DAMP)" factor, stimulate the pathogen sensor TLR4 in infiltrating macrophages, thereby establishing a different vicious cycle that augments adipose tissue inflammation. Histologically, macrophages aggregate to form recognizable crownlike structures (CLS) to scavenge residual lipid droplets of dead adipocytes. In this pathology, macrophageinducible C-type lectin (known as Mincle), which is derived from macrophages in CLS, contributes to adipose tissue inflammation and fibrosis. More recently, the group found that free fatty acids released from obese visceral fat deposits accumulate as ectopic fat in liver via the portal vein, leading to development of nonalcoholic steatohepatitis (NASH). Interestingly they also found that macrophages aggregate to surround dead hepatocytes with large lipid droplets, a histological feature termed "hepatic CLS" (hCLS), which marks the NASH liver. In this issue, Dr. Ogawa' s group proposes that CLS/hCLS represents a unique microenvironment for parenchymal/stromal cell interactions favoring tissue inflammation and fibrosis in metabolic diseases.

Chronic inflammation underlies an array of chronic, noncommunicable diseases, including cardiovascular and metabolic diseases as well as cancer. Recent studies show that mechanisms underlying immunity and metabolism are intricately linked and that cell-to-cell communication between infiltrated and/or resident immune cells and resident metabolic tissue cells plays an important role in this linkage, an activity described as "immunometabolism". Dr. Oishi at Tokyo Medical and Dental University and Dr. Manabe at the University of Tokyo have demonstrated a crucial role for macrophages in chronic inflammatory processes promoting development of non-communicable diseases. In this issue, Dr. Manabe's group provides an overview of how both physiological and pathological activities of macrophages located within major metabolic tissues control liver function, skeletal muscle development and function, and development of type 2 diabetes. They also discuss the role of macrophages located within the hypothalamus in controlling appetite. Their review presents the concept of immune cell-mediated regulation of homeostasis in major metabolic tissues and its pathology.

Adenosine 5'-triphosphate (ATP) functions in most cellular activities by providing energy through its hydrolysis. Recent studies demonstrate that extracellular ATP acting via several purinergic receptors mediates cell-to-cell communication in the immune system. ATP, which is released from damaged cells as a "danger-associated molecular pattern (DAMP)" factor and secreted by activated immune cells such as T lymphocytes and neutrophils and/or symbiotic/pathogenic bacteria in the intestine, mediates immune responses through purinergic P2X and P2Y receptors expressed on a variety of immune cells. The group of Drs. Takeda, Tsai,



and Kayama at Osaka University has demonstrated that ecto-enzymes modulate the immune response through catalyzing ATP hydrolysis. For example, the ecto-nucleoside triphosphate diphosphohydrolase 7 (E-NTPDase7) regulates ATP-dependent Th17 responses in the small intestine, while the ecto-nucleoside pyrophosphate/phosphodiesterase 3 (E-NPP3) regulates ATP-dependent chronic allergic responses by basophils and mast cells. In this issue, Dr. Takeda's group describes ecto-enzyme function in maintaining tissue homeostasis.

The group of Drs. Miyazaki and Arai at the University of Tokyo recently revealed a new concept regarding a new cellular "garbage" clearance system mediated by circulating factors. Specifically, Dr. Miyazaki's group previously identified the circulating protein known as Apoptosis Inhibitor of Macrophage (AIM). They found that AIM is incorporated into normal hepatocytes and inhibits lipid storage within those cells, thereby decreasing liver steatosis. By contrast, AIM accumulates on the surface of hepatocellular carcinoma (HCC) cells and induces their elimination, preventing HCC tumor development. Based on these findings, they hypothesize that the presence of a set of circulating proteins that specially mark biological "garbage" (such as cancer cells, dead cell debris, or degraded proteins or damaged cells) promotes efficient elimination of undesired substances and can prevent disease progression. Based on these findings, they propose designating these marker proteins as "soluble scavenger proteins (SSPs)". In this issue, Dr. Miyazaki's group proposes a new defense system against multiple diseases via biological garbage clearance mediated by SSPs.

Finally, I express my sincere appreciation toward all the authors who contributed to this special issue. All are experts in research fields related to mechanisms of homeostasis in health and disease, and they have provided us with informative and useful reviews. I hope that this special issue will provide an opportunity for readers to gain novel insight that will contribute to their own research relevant to inflammation and regeneration.

References

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