The purpose of this R&D area is to elucidate the mechanisms through which inflammation becomes chronic, and to create basic technologies for the early detection, control, resolution, and reparation of chronic inflammation.

More specifically, this involves research aimed at: (1) identifying factors that induce and maintain the chronicity of inflammation by determining failure mechanisms of inflammation control; (2) clarifying the mechanisms through which specific diseases (including cancer, degenerative neurological disorders, and arteriosclerotic diseases) develop as a result of chronic inflammation, and to create basic technologies to control them; and (3) creating basic technologies that allow for the early detection and quantitative assessment of chronic inflammation. This not only involves established basic and clinical research, but also emphasizes research that sufficiently sublimes evidence-based findings for understanding higher order inflammation control mechanisms, and leads to the development of new preemptive basic medical technologies.
Chronic inflammation causes many diseases, including arthritis and autoimmune diseases, however, precise molecular mechanisms how termination of inflammatory response is disturbed remains unclear. Here we will address this question by examining the role of microRNA in inflammation and arthritis pathogenesis. Utilizing high throughput sequencer and cell-based functional screening systems, we will uncover novel molecular cascade regulating inflammatory time signal at RNA level. This may provide a novel targets or strategy for inflammatory diseases, such as rheumatoid arthritis.

Chronic inflammation has been shown to cause various adult diseases such as metabolic syndrome and cancer. By exploiting biological imaging technologies, this study will analyze the crucial roles of tissue-resident macrophages in chronic inflammation. Several novel methodologies, such as those for detecting phenotypical changes in situ and for manipulating cell function using light at single-cell levels, would be developed. This will help to ascertain the in vivo mode of action of macrophages under pathophysiological conditions. This study will lead to the discovery of new concepts for controlling chronic inflammation, which is conducive for the development of revolutionary therapeutics against diverse common diseases.

A type of intractable pain including neuropathic pain typically develops when peripheral nerves are damaged by surgery, bone compression in cancer, diabetes or infection, and does not go away even though tissue damage or inflammation has already healed. The pain is frequently resistant to NSAIDs and opioids, and many patients more than 20 millions in the world are in distress. We have discovered that brain immunocompetent cell microglia have very important role in evoking the intractable pain. In this project, we clarify the mechanism of the pain based on the functions of microglia and contribute to develop great medicines against the pain.

The healthy intestinal tract is maintained by the highly sophisticated homeostatic mechanism operating between symbiotic bacteria and mucosal immune cells, and collapse of this mutually beneficial mucosal bidirectional interaction system leads to the development of refractory chronic inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis. In this project, through investigating the cellular and molecular mechanisms of intestinal homeostatic and pathological inflammations by meaning of the contribution made by the symbiotic cohabiting microflora, the carbohydrate-chains on epithelial cells, and the innate immune cells at the intestinal mucosa, we aim to develop new treatments, preventions and diagnostic methods for intestinal inflammatory diseases.

For the study of chronic inflammation, in which innate and adaptive immune cells play crucial roles, it is important to understand the functions of the special microenvironments known as niches, which control hematopoietic stem and progenitor cells to provide appropriate numbers of blood cells, including immune cells in the bone marrow. Although the nature of the niches have been the long-lasting unresolved issue, we found that a small population of bone marrow non-hematopoietic cells with long processes, expressing high amounts of the chemokine CXCL12, termed CXCL12-abundant reticular (CAR) cells function as niches for hematopoiesis. Our aim is to clarify the role and molecular regulatory mechanism of CAR cells in controlling hematopoiesis in chronic inflammation, providing new insight and basis for developing novel niche-based therapies.
Prostaglandins (PGs) are bioactive substances mediating fever, swelling and pain of acute inflammation. Our studies have not only elucidated the mechanism how PGs elicit these acute inflammatory symptoms but also suggested a possibility that PGs also mediate some of chronic inflammatory processes such as allergy, fibrosis and cerebral aneurysm through regulation of gene expression. In this study, we aim to clarify molecular mechanisms how PGs in collaboration with cytokines and innate immunity substances initiate and maintain chronic inflammatory processes, and how much they contribute to diseases such as cancer, metabolic diseases and depression. We also aim to determine three dimensional structures of PG receptors to facilitate drug development targeted to these actions.

Chronic inflammation associated-organ fibrosis causes serious functional impairment. In this project, we will examine the source of the myofibroblasts that play a key role in organ fibrosis. The regulation of the trafficking and differentiation of these cells by chemokines and other inflammatory mediators will be analyzed. In addition, we will clarify the changes in the epigenome and transcriptome that accompany fibrosis. Based on the information obtained from these studies, by conducting experiments in murine fibrotic disease models, and by testing human clinical samples, we aim to develop novel approaches for the prevention and treatment of human fibrotic diseases.

Chronic inflammation is linked to aging-associated diseases such as heart failure, diabetes, and atherosclerosis. However, the pathophysiological role of chronic inflammation in aging-associated diseases is currently unknown. We have recently found that the C1q component of the complement system is increased in multiple tissues of aged animals and contributes to the onset of heart failure, diabetes, and atherosclerosis. The ultimate goal of this study is to identify the mechanisms by which C1q promotes the onset of aging-associated diseases and to develop novel therapeutic strategies for the diseases linked to chronic inflammation.

Many Japanese people suffer from chronic inflammatory diseases of the upper and lower respiratory tracts, such as chronic rhinosinusitis and chronic bronchial asthma. These diseases are generally resistant to steroids, and no effective treatment has yet been developed. Chronic allergic airway inflammation is thought to be induced and maintained by allergen-specific memory CD4$^+$ helper T (Th) cells (Th1, Th2, and Th17 cells), although the precise roles of these Th subsets in chronic inflammatory diseases remain unknown. In this project, we clarify the cellular and molecular bases for induction and maintenance of chronic airway inflammation, and propose therapeutic strategies that may be used for chronic airway inflammatory diseases.

Chronic inflammation results from excessive physiological responses, which are intrinsically essential for maintaining normal life, or by disturbances of physiological responses triggered by viral and bacterial infections. Chronic inflammation can cause adult-onset diseases, such as cancers, diabetes, arterial sclerosis, and others. We primarily focus on the following three areas: 1. Lipid mediators and the enzymes that produce them, which cause chronic inflammation via GPCR; 2. Toll-like receptors (TLRs) and signal transducers involved in natural inflammation downstream of TLR activation; 3. Transcriptional regulators that control cellular signaling in the nucleus, particularly NF-κB. We determine the three-dimensional structures of the target proteins and their complexes by X-ray crystallography, and provide evidence for the working hypothesis by mutant analyses, that identifies the mechanisms of chronic inflammation causing various diseases, from atomic to individual levels.
Control of chronic inflammation through elucidation of organ-specific autoimmune disease mechanisms

Mitsuru Matsumoto
Professor, Tokushima University

The human immune system normally distinguishes between microorganisms (non-self) and components of the body (self), thereby providing protection against invasion by numerous pathogens. However, an intractable autoimmune disease in which the immune system tends to attack the body itself can develop due to unknown mechanisms. With the aim of developing novel therapeutic approaches for chronic inflammation caused by autoimmunity, we study the mechanisms underlying the development of organ-specific autoimmune disease caused by the abnormal function of AIRE, a gene that plays an essential role in establishing self-tolerance in the thymus.

Identification of critical genes involved in the pathogenesis of human chronic inflammatory diseases

Koji Yasutomo
Professor, Tokushima University

The aim of this study is to identify critical genes, which are involved in the onset or progression of chronic inflammation, using genetic analysis of familial inflammatory diseases. If successful, these studies would aid in revealing previously unappreciated molecular mechanisms of chronic inflammation, and thereby, contribute to establish innovative therapeutic strategies for human inflammatory diseases.

Protective mechanisms against environmental stresses leading to therapeutic strategies for chronic inflammation

Masayuki Yamamoto
Professor, Tohoku University

We are constantly exposed to various environmental stresses in our daily life, including chemicals, ultra-violet light, pathogenic microorganisms, and dietary toxicants. Cellular detoxification is crucial for the maintenance of health by providing protection against these environmental stresses. The aim of this study is to clarify how dysregulation of stress responses exacerbates chronic inflammatory diseases and also, to evaluate the effectiveness of intervention into the cytoprotection mechanisms to prevent and alleviate these pathologic conditions. Our research aims to identify novel relationships between environmental stresses and chronic inflammation and provide advances in therapeutic strategies for chronic inflammatory diseases.

The role of chronic inflammation in promotion and malignant progression of cancers

Masanobu Oshima
Professor, Kanazawa University

Most cancers are associated with chronic inflammation. However, the mechanisms for induction of inflammation and its role in tumorigenesis have not been elucidated yet. In this project, we will investigate how inflammation is induced in cancer tissues, and how chronic inflammation accelerates promotion and malignant progression of gastrointestinal cancers using unique mouse models. We believe that the results will contribute to “regulation of cancer by regulation of chronic inflammation” in future.

Investigation of pathological implications of guidance molecules in chronic inflammation

Atsushi Kumanogoh
Professor, Osaka University

Semaphorins exerts multiple functions in neuronal development, neurodegeneration, vasculogenesis, tumorigenesis, bone homeostasis, and immune-regulation. In particular, we have determined critical roles of semaphorins in the last couple of years. In this study, we try to determine the pathological implications of semaphorins and their related molecules in chronic inflammation, thereby providing useful insights into manipulation of human disorders.
Devising novel methods to control chronic inflammation via regulatory T cells

Shimon Sakaguchi
Professor, Osaka University

Regulatory T cells are a lymphocyte population that is specialized for suppressing abnormal or excessive immune responses. They can be exploited to suppress chronic inflammation in autoimmune disease and chronic rejection in organ transplantation or to enhance immune responses in tumor immunity and chronic infection. We plan to devise novel methods to control immune responses via targeting regulatory T cells either by attenuating or strengthening their suppressive activity.

Analysis of mechanisms suppressing chronic inflammation via posttranscriptional regulation in innate immunity

Osamu Takeuchi
Professor, Kyoto University

Macrophages and dendritic cells play an important role in innate immunity, which are critical for initial responses against infection. Although the activation and suppression of innate immunity is well balanced, prolonged activation of innate immunity leads to the development of chronic inflammatory diseases. This study is aiming to re-define the regulatory mechanisms of innate immunity from posttranscriptional control point of view based on the roles of RNase we identified, in addition to transcriptional control. Ultimate goal of this study is to develop a novel method for the regulation of inflammation.