1. Background of research

Lifestyle diseases, including cardiovascular disease and type 2 diabetes, and cancer cause disturbance of healthy daily living. Because lifestyle changes, such as inactivity and overnutrition increase the development of lifestyle diseases and cancer, it is increasingly prevalent medical and social problem. Therefore, it is important to understand the molecular basis of lifestyle diseases and cancer in order to develop effective preventive and therapeutic approaches against these diseases. Recently, it is noted that dysregulation or dysfunction of homeostatic response lead to the induction of persistent low-grade inflammation, which is a common pathogenesis of lifestyle diseases and cancer. However, the detailed molecular mechanisms underlying persistent low-grade inflammation are poorly understood.

2. Research objectives

We originally identified angiopoietin-like protein (Angptl) and showed that it plays roles in the homeostatic response. We focus our investigation on roles of Angptl2 and AGF/Angptl6, which are Angptl family members, in the homeostatic response and the common molecular mechanisms underlying lifestyle diseases and cancer.

3. Research characteristics (incl. originality and creativity)

Elucidation of Angptl2 and AGF/Angptl6 functions contributes to understanding of molecular mechanisms underlying lifestyle diseases and cancer.

4. Anticipated effects and future applications of research

We believe that elucidation of common molecular mechanisms underlying lifestyle diseases and cancer leads to development of novel and effective diagnostic and therapeutic approaches against these diseases.
Healthy aging and Longevity

The study for realization of healthy aging and longevity by elucidating the common molecular mechanisms of lifestyle diseases and cancer (Research plan)

- **Functional studies of Angptl2**
  - Analysis of transcriptional regulatory mechanisms underlying cardiovascular and metabolic diseases and cancer
  - Identification of Angptl2 receptor and signaling pathway
  - Development of diagnoses by elucidating the relationships between serum Angptl2 levels and tumor invasion and metastasis
  - Development of therapy using neutralizing antibody
  - Elucidation of the relationships between Angptl2 functions and healthy aging and longevity

- **Functional studies of AGF/Angptl6**
  - Identification of AGF/Angptl6 receptor and signaling pathway
  - Analysis of transcriptional regulatory mechanisms underlying metabolic diseases
  - Elucidation of molecular mechanisms underlying AGF/Angptl6 resistance in obesity
  - Analysis of regulatory mechanisms of AGF/Angptl6 signaling

Overnutrition, Inactivity, Lifestyle, Heredity

Stress

Homeostatic response

- Suppression
  - Dysregulation of Angptl2 expression / Appearance of excess Angptl2 signaling
  - Appearance of AGF/Angptl6 resistance

- Suppression
  - Persistent low-grade inflammation

- Therapy
  - Metabolic disease
    - Diabetes, Obesity, Hyperlipidemia
    - Metabolic syndrome
  - Atherosclerotic disease
    - Ischemic heart disease, Peripheral arteriosclerotic disease
    - Hypertension, Aortic aneurysm, Cerebral apoplexy, Retinopathy, Renal disease
  - Malignant neoplasm
    - Carcinogenesis, Invasion, Metastasis
  - Chronic inflammation

- Improvement
  - Disturbance of healthy life
    - Visual loss, Heart failure, Dementia, Dialysis, Abrasion of extremity, etc

- Increment of health care cost