General Summay of Division of Stem Cell Medicine

In 2006, Dr. Nishimura was appointed to the professor of Division of Stem Cell Medicine. Our goal is to understand the mechanisms of tissue homeostasis driven by stem cell systems and to understand physiological or pathological conditions resulting from stem-cell system defects. Our studies started from our previous discovery of "melanocyte stem cells" (MSC), which supply melanocytes (pigment cells) required for hair pigmentation. The system has a number of advantages for stem cell research. Localization of MSCs and their niche can be visualized and the functional levels of the system cell system can be easily monitored. By taking those advantages, we have demonstrated that the stem cell niche plays a dominant role in stem cell fate determination. We searched for molecular mechanisms responsible for the phenomenon using a candidate approach with mouse coat color genetics. We have identified MITF, a master regulator for melanocyte development and its downstream effector, BCL2 as essential for MSC maintenance. In the past three years, we have identified the niche cells for MSCs and niche-derived extrinsic factors key for MSC maintenance. Through those approaches, we are trying to understand the underlying mechanisms for tissue homeostasis, ageing and cancer development.

A) Identification of niche cells and niche-derived factors for MSC maintenance.

Organization of the stem cell niche is fundamental for stem cell maintenance. However, it is largely unknown in majority of stem cell systems. We have identified hair follicle stem cells as functional niche-cells for MSCs and the niche-derived TGF-b as a key extrinsic factor for MSC renewal/maintenance. Furthermore, we demonstrated the Endothelin signaling regulates the expression and transcriptional activity of MITF, a master transcription factor for melanocyte development and also for MSC maintenance.

B) Mechanisms for MSC ageing and quality control of stem cell pools.

Physiological hair graying is the most obvious outward sign of aging even in normal mammals. We previously demonstrated that physiological hair graying is caused by incomplete self-renewal/maintenance of MSCs. However, it is still not known why self-renewal of MSCs becomes defective during the course of ageing. Accumulation of DNA damage is currently implicated in somatic stem cell ageing and appearance of age-related phenotypes, while little is known about the fate of stem cells under the genotoxic stress and its overall outcome. Our recent data indicated that stem cell differentiation but not stem cell apoptosis nor senescence is the major fate of MSCs under irrepairable/excessive genotoxic stress.