Institute of Medical Biology
A*STAR

Seminar Announcement

- All Are Welcome -

Speaker: **Dr Toshiro Sato**
Keio University School of Medicine, Tokyo

Title: **Intestinal stem cells in homeostatic and regenerative state.**

Date : **23 Nov 2012 (Friday)**

Time : **11.00am – 12.00pm**

Venue: **Breakthrough Theatrette, Matrix Level 4, Biopolis**

Host : **Dr Nick Barker**
(Tel: 64070695, email: nicholas.barker@imb.a-star.edu.sg)

Abstract of the Seminar:

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. Lgr5+ intestinal stem cells (ISC) are located at crypt bottom and identified as intestinal stem cells. We developed a new culture system in which single ISC form organoid structure showing stem cell self-renewal and multiple lineages differentiation in the absence of non-intestinal epithelial cells. We successfully adapted the culture system to human and mouse stomach, colon, liver and pancreas duct cells. These culture systems can be used for regenerative medicine.

During the development of culture system we observed that Paneth cells, one of the daughter cells from Lgr5 ISC, supported organoid formation. We purified Paneth cells using CD24 and found that they express EGF, Wnt3 and the Notch ligand Dll4, all essential signals for stem cell maintenance in culture. Co-cultureing of sorted ISC with Paneth cells dramatically improves organoid formation. This Paneth cell requirement can be substituted by a pulse of exogeneous Wnt. Genetic removal of Paneth cells in vivo results in the concominant loss of Lgr5 stem cell, indicating Paneth cells function as intestinal stem cell niche. In homeostatic condition, most of lateral cell surface of Paneth cells are occupied by ISC. After irradiation injury, ISC are massively depleted and non-ISC can attach to Paneth cells. Genetic lineage tracing experiments demonstrated that Dll1+ intestinal progenitors generate small, short-lived clones of all four secretory cell types in homeostatic condition. When Dll1 cells are genetically marked prior to tissue damage, significant numbers of stem cells tracing events occur. In culture, sorted Dll1+ cells can form long-lived organoids when briefly exposed to Wnt3A. Secretory progenitors could attach to stem cell niche upon stem cell depletion by tissue damage and revert to ISC with dedifferentiation. We suggested that ISC is a cellular ‘state’ determined by location rather than a cellular ‘fate’ determined by history.

About the Speaker:

Dr. Toshiro Sato is Assistant Professor of Gastroenterology in Keio University School of Medicine, Tokyo. He obtained his MD from Keio University and completed his internship at Keio University Hospital in 1999. He then completed his residency program in Department of Gastroenterology, Keio University Hospital. He started basic research on inflammatory bowel disease and received PhD from Keio University in 2004. He took post-doctoral fellowship in Stowers Institute for Medical Research, Kansas City in 2006 and investigated the dynamic role of intestinal stem cells during intestinal damage. In 2007, he joined the Hans Clevers lab, Hubrecht Institute, Utrecht to investigate intestinal stem cells. In 2009 he established a novel intestinal stem cell culture system, by which single intestinal stem cells form stereotypic organoid mimicking in vivo intestinal crypt structures. This culture system is the first system to visualize intestinal stem cell self-renewal and differentiation in vitro. This work led to the identification of the intestinal stem cell niche, which is the first proof of mammalian stem cell niche system at cellular level. He subsequently adapted the culture system to other human and mouse tissues, including stomach, pancreas and liver. This has resulted in a widely applicable organoid culture system that is invaluable for basic research, translational regenerative medicine and drug screening. In 2011, Dr. Sato joined the Keio University as Assistant Professor, where he focuses on the role of intestinal stem cells in tissue homeostasis and regeneration. He exploits his combination of clinical experience and basic science background to develop methods for transplanting intestinal organoids via endoscopy as an effective treatment of inflammatory bowel disease. He also attempts to generate ex vivo human colorectal cancer cells via genetic manipulation of normal intestinal organoids. This work may reveal molecular mechanisms of colon cancer carcinogenesis.