S7-2
Maturation of Blood Vessels in The Tumor Environment
N. Takakura*
Department of Signal Transduction, Research Institute for Microbial Diseases, Osaka University.
*Contact author: ntakaku@biken.osaka-u.ac.jp
Recent evidence suggests that cancers arise from cancer stem cells/initiating cells (CSCs/CICs). The niche for the maintenance of stemness has been identified in normal organs. Understanding the molecular mechanisms of how niche cells regulate stemness is very important for understanding the biology of stem cells. Although the niche in each organ is composed of different non-stem cell as well as stem cell types, it is likely that there is some commonality required for maintaining the slow-cycling, self-renewing, undifferentiated state of stem cells, as well as enhancing their resistance to stress; however, the molecular mechanisms supporting these behaviors are not clearly understood. As in normal tissue, it has been suggested that CSCs are maintained within peri-vascular niches. To study the localization of CSCs/CICs, we attempted to visualize them in tumor tissue by using a certain gene promoter tagged with LacZ or the EGFP gene. We found that CSCs/CICs are located near the blood vessels and form a cluster-like structure. Interestingly, the vascular niche for CSCs/CICs was mainly observed at the edge of the tumor mass, where the blood vessels are well matured, reflected by the adherence of mural cells to endothelial cells as frequently as observed in normal tissues. This implies that such mature blood vessels would be resistant against agents that disrupt angiogenesis. To destroy such vascular niches for CSCs/CICs, precise molecular mechanisms controlling the maturation of blood vessels at the edge of the tumor compared to the central region of tumor, where there are fewer mural cells adhering to endothelial cells, needs to be properly understood. In this session, we would like to present the association of Tie2/angiopoietin-1 [1-3] and APJ/apelin [4], receptor/ligand systems involved in the maturation process of blood vessel formation.


S7-3
"Mouse Models for Colon Cancer Invasion and Metastasis"
Makoto Mark Taketo, M.D., Ph.D.*
Department of Pharmacology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo, Kyoto 606-8501, Japan
*Contact author: taketo@mfour.med.kyoto-u.ac.jp
Most colorectal adenomas are initiated by the APC gene inactivation, and progress to malignant adenocarcinomas through additional mutations in the genes encoding RAS, TGF-β type II receptor, p53, etc.
To investigate the role of impaired TGF-β family signaling in colon cancer progression, we earlier constructed compound mutant mouse strain "cis-Apc
−/−Smad4+/− (cis-Apc/Smad4)" that carried a knockout allele of the Smad4 gene on the same chromatin as that of Apc (Apc
−/−) [1]. In the compound mutant, loss of the SMAD4-dependent TGF-β family signaling turns the intestinal adenomas into invasive adenocarcinomas, although SMAD4-independent signaling remains unaffected. Because polyp adenomas are initiated by loss of heterozygosity (LOH) of Apc that is caused by recombination at the centromeric rDNA cluster on chromosome 18, the tumor epithelial cells in the cis-Apc/Smad4 mice carry homozygous mutations in both Apc and Smad4 genes.
Focusing on the tumor-stromal interactions, we have investigated here the mechanism of intestinal tumor invasion in the cis-Apc/Smad4 mice. We demonstrate here that a novel type of immature myeloid cells (iMCs) is recruited from the bone marrow to the tumor invasion front. These CD34+ iMCs express MMP9/2 and CC-chemokine receptor 1 (CCR1), and migrate toward its ligand CCL9. In the adenocarcinomas, expression of CCL9 is increased in the tumor epithelium. By knocking out Ccr1 gene in the cis-Apc/Smad4 mutant mice, we further demonstrate that lack of CCR1 prevents the accumulation of CD34+ iMCs at the invasion front and suppresses tumor invasion. Analysis of human colon cancer specimens that carried mutant TGF-β type II receptor showed similar iMCs expressing CCR1 and MMP9/2. These results indicate that loss of the TGF-β family signaling in tumor epithelium causes accumulation of iMCs that help tumor invasion [2], and show therapeutic implications in treating invasive colon cancer.