The 656th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H27.8.20)

Endothelial mutagenesis reveals key regulatory pathways that maintain vascular homeostasis

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Vascular tumors are characterized by highly proliferative and invasive endothelial cells. These lesions can range from cosmetically disfiguring to lethal, depending on location. Currently, no targeted therapies exist because the underlying genetic mechanisms remain largely unknown. In order to investigate the genes underlying vascular tumors, we have employed the endothelial cell specific VE-Cadherin-Cre to drive Sleeping Beauty (SB) transposon mutagenesis in mice. The transposons are engineered to contain viral promoters/enhancers to drive oncogene expression. They also contain a polyA sequence on opposing strands to truncate tumor suppressor genes despite transposon insertion orientation. To maximize tumor induction, we have developed two separate mouse lines that contain two distinct promoters driving transposons. The first uses the MSCV viral promoter/enhancer to drive oncogene expression (onc 2). The onc3 transposon transgene relies on the CAG promoter. The talk will present a summary of the tumor distribution, onset, and characteristics induced by the onc 2 and onc 3 transposon transgenic system. From the 125 animals evaluated 58% developed vascular tumors. They most often occurred in the uterus and skeletal muscle. Further assessment, using immunohistochemical staining and VE-Cadherin Lac-Z reporter lineage tracing, shows that the tumors resemble solid masses of endothelial cells reminiscent of angiosarcoma. Coupled with linker-mediated PCR, the DNA from lesions can be sequenced to determine the specific genes that were disrupted by the transposon. Understanding the genetic mutations associated with these vascular tumors is likely to carry significant clinical impact by laying the foundation for targeted therapies.

The 657th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H27.9.28)

MicroRNA regulation of adult lymphangiogenesis

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The process of lymphangiogenesis is elegantly controlled during development by the coordinated action of ligands (VEGFC, VEGFD), kinases (VEGFR3, SLP-76 and Syk) and transcription factors (Prox1). Adult lymphangiogenesis often involves similar processes but is less well investigated. While microRNAs regulate a diversity of biological pathways, their involvement in lymphangiogenesis is poorly documented. We and others have previously described the microRNA miR-126 as an essential regulator of developmental blood angiogenesis and vascular integrity through embryonic lethal null phenotypes. Here, we describe initial studies towards studying the roles of miR-126 during adult lymphangiogenesis using genetic and cell biology approaches.

The 658th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H27.9.28)

Endothelial cell metabolism in normal and diseased vasculature

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Higher organisms rely on a closed cardiovascular circulatory system with blood vessels supplying vital nutrients and oxygen to distant tissues. Not surprisingly, vascular pathologies rank among the most life-threatening diseases. At the crux of most of these vascular pathologies are (dysfunctional) endothelial cells (ECs), the cells lining the blood vessel lumen. ECs display the remarkable capability to switch rapidly from a quiescent state to a highly migratory and proliferative state during vessel sprouting. This angiogenic switch has long been considered to be dictated by angiogenic growth factors (e.g., vascular endothelial growth factor) and other signals (e.g., Notch) alone, but recent findings show that it is also driven by a metabolic switch in ECs. Furthermore, these changes in metabolism may even override signals inducing vessel sprouting. Here, we review how EC metabolism differs between the normal and dysfunctional/diseased vasculature and how it relates to or affects the metabolism of other cell types contributing to the pathology. We focus on the biology of ECs in tumor blood vessel and diabetic ECs in atherosclerosis as examples of the role of endothelial metabolism in key pathological processes. Finally, current as well as unexplored EC metabolism-centric therapeutic avenues are discussed.

The 659th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H27.9.28)

Biomedical significances of Tie2 activation for pathologic vasculatures

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It has been long sought to find a superior Tie2 agonist, because it can be a potential therapeutic agent mediated though promotion of vascular protection and stabilization.

Although Ang1 is a specific, agonistic ligand to Tie2, it has numerous hurdles in production, purification, storage, half-life, and efficacy. We invented COMP-Ang1 to overcome the drawbacks of native Ang1 protein, but it can be useful as a local therapy due to the drawbacks in half-life and efficacy for systemic use. Although Vasculotide was first developed as a synthetic Tie2 agonistic peptide, a recent study convincingly demonstrated that "Vasculotide" actually is not a Tie2 agonistic peptide, has no actions for Tie2 activation, and even does not bind to Tie2. Here, we develop a novel Tie2-agonistic antibody, ABTAA, which robustly induces Tie2 activation and its downstream signaling by inducing Ang2 oligomerization. By applying ABTAA to several sepsis models for therapeutic purposes, we not only unveiled the roles of Tie2 activation in vascular protection during sepsis progression but also provided a rationale for the use of ABTAA as an antiseptic antibody in clinics. Moreover, by pretreating of advanced orthotopic glioma, implanted LLC tumor and spontaneous breast cancer models with ABTAA, we found that much less hypoxic tumor microenvironment and enhanced drug delivery into the core region of growing tumors can be achieved by the promoted blood flow mediated through suppression of vascular destabilization and induction of normalization in tumor vasculatures. Thus, ABTAA is the first convincing and potent Tie2 agonist and provides beneficial functions against pathologic vasculatures.

The 660th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H27.9.28)

Vascular normalization as an emerging strategy to enhance cancer immunotherapy

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The recent approval of Provenge has brought new hope for anticancer vaccine therapies. However, the immunosuppressive tumor microenvironment seems to impair the efficacy of vaccine therapies. The abnormal tumor vasculature creates a hypoxic microenvironment that polarizes inflammatory cells toward immune suppression. Moreover, tumors systemically alter immune cells' proliferation, differentiation, and function via secretion of growth factors and cytokines. For example, VEGF, a major proangiogenic cytokine induced by hypoxia, plays a critical role in immunosuppression via these mechanisms. Hence, antiangiogenic treatment may be an effective modality to potentiate immunotherapy. Here, we discuss the local and systemic effects of VEGF on tumor immunity and propose a potentially translatable strategy to re-engineer the tumor-immune microenvironment and improve cancer immunotherapy by using lower "vascular normalizing" doses of antiangiogenic agents.

The 661st Kitasato Medical Society Invitational Academic Lecture Series Abstract

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Angiogenesis in cancer-general pathways and their therapeutic implications

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A vast amount of data shows that angiogenesis has a pivotal role in tumor growth, progression, invasiveness and metastasis. This is a complex process involving essential signaling pathways such as vascular endothelial growth factor (VEGF) and Notch in vasculature, as well as additional players such as bone marrow-derived endothelial progenitor cells. Primary tumor cells, stromal cells and cancer stem cells strongly influence vessel growth in tumors. Better understanding of the role of the different pathways and the crosstalk between different cells during tumor angiogenesis are crucial factors for developing more effective anticancer therapies. Targeting angiogenic factors from the VEGF family has become an effective strategy to inhibit tumor growth, and so far the most successful results are seen in metastatic colorectal cancer, renal cell carcinoma and non-small cell lung cancer. Despite the initial enthusiasm, the angiogenesis inhibitors showed only moderate survival benefit as monotherapy, along with a high cost and many side effects. Obviously, other important pathways may affect the angiogenic switch, among them the Notch signaling pathway attracted interest because of its ubiquitous role in carcinogenesis and angiogenesis. Herein we present the basics for VEGF and Notch signaling pathways and current advances in targeting them in antiangiogenic and antitumor therapy.