The 568th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H23.7.22)

A systems approach reveals that the locomotive systems development and homeostasis network

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We created a whole-mount in situ hybridization (WISH) database, termed EMBRYS (http://embrys.jp), containing expression data of 1520 transcription factors and cofactors expressed in E9.5, E10.5, and E11.5 mouse embryos--a highly dynamic stage of skeletal myogenesis. This approach implicated 43 genes in regulation of embryonic myogenesis, including a transcriptional repressor, the zinc-finger protein RP58 (also known as Zfp238). Knockout and knockdown approaches confirmed an essential role for RP58 in skeletal myogenesis. Cell-based high-throughput transfection screening revealed that RP58 is a direct MyoD target. Microarray analysis identified two inhibitors of skeletal myogenesis, Id2 and Id3, as targets for RP58-mediated repression. Consistently, MyoD-dependent activation of the myogenic program is impaired in RP58 null fibroblasts and downregulation of Id2 and Id3 rescues MyoD's ability to promote myogenesis in these cells. Our combined, multi-system approach reveals a MyoD-activated regulatory loop relying on RP58-mediated repression of muscle regulatory factor (MRF) inhibitors. We applied our systems approaches to other locomotive tissues research including cartilage and tendon, and revealed novel molecular network regulating joint cartilage development and homeostasis via miRNA-140 (Genes and Development, 2010; Arthritis and Rheum, 2009) and tendon development by Mkx (PNAS, 2010).

The 570th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H23.9.26)

Biochemical analyses of postsynaptic density (PSD) and postsynaptic membrane rafts

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Postsynaptic density (PSD) is a major machinery localizing at the postsynaptic side of the synapses, which highly efficiently processes cellar signals and involved in synaptic transmission and its regulation, synaptic plasticity. About a thousand kinds of proteins are working at the PSD of excitatory synapses in the CNS. Postsynaptic membrane rafts are also believed to play important roles in synaptic signaling, plasticity, and maintenance. Postsynaptic membrane rafts, along with PSDs, are considered major sites of synaptic signaling, function, and maintenance. However, protein composition and physiological function of the postsynaptic membrane rafts and relationship between PSD and postsynaptic rafts have not yet been investigated in detail. It is essential to know the structures and functions of these subcellular structures for full understanding of mechanisms of synaptic and brain plasticity, bases for higher brain functions. The speaker presents a brief overview of PSD research and talks about recent topics regarding the PSD and the postsynaptic membrane rafts.

The 580th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H23.12.26)

Monocyte and macrophage diversity promotes tumor progression and metastasis

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There is persuasive clinical and experimental evidence that macrophages promote cancer initiation and malignant progression. Macrophages enhance malignancy at the primary site by stimulating angiogenesis, inducing tumor cell migration, invasion and intravasation and by suppressing anti-tumor immunity.[1,2] At metastatic sites macrophages promote tumor cell extravasation, survival and subsequent growth. Each of these activities is stimulated by a different population of macrophages whose unique signaling pathways might represent new therapeutic targets.[1] We have argued that these pro-tumoral functions are a recapitulation of roles that macrophages play during development and in tissue repair.[3,4] Consistent with this hypothesis are expression profiles of various populations of tumor associated macrophages that indicate similarity to embryonic macrophages and which also show enriched expression of "developmentally relevant" molecules such as Wnt proteins.[5,6]

Our recent studies have focused on the origin of different populations of macrophages.[7] Recent lineage tracing studies indicate that the primary and metastatic tumors recruit different populations of monocytes partially explaining the macrophage diversity. At the metastatic site the recruitment of CCR2 expressing monocytes requires tumor synthesized CCL2, the ligand for CCR2. Inhibition of CCL2 reduces this monocyte recruitment and subsequent differentiation into macrophages and this in turn reduces tumor cell extravasation and metastatic growth. This generation of macrophage diversity will be discussed in this presentation as well as their trophic roles in tumor growth.

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3. Lin EY, Gouon-Evans V, Nguyen AV, Pollard JW. The macrophage growth factor, CSF-1, in mammary gland development and tumor progression. *J Mammary Gland Biol Neoplasia* 2002; 7: 147-62.
4. Pollard JW. Trophic macrophages in development and disease. *Nat Rev Immunol* 2009; 9: 259-70.
5. Ojalvo LS, King W, Cox D, Pollard JW. High-density gene expression analysis of tumor-associated macrophages from mouse mammary tumors. *Am J Pathol* 2009; 174: 1048-64.
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7. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* 2011; 475: 222-5.

The 584th Kitasato Medical Society

Invitational Academic Lecture Series Abstract

(H24.2.2)

Stereotactic Body Radiation Therapy (SBRT)/ Stereotactic Ablative Body Radiotherapy (SABR) for "Radio-Resistant" Renal Cell Carcinoma

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Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative body radiotherapy (SABR) is an emerging modality in radiation oncology that delivers very high dose radiation to the tumor target with high precision using single or a small number of fractions. SBRT/SABR is the result of technological advances in radiation oncology especially patient/tumor immobilization, image guidance, treatment planning and delivery. Radiobiologically, more potent biological equivalent dose (BED) is delivered to the tumor as higher dose per fraction is used. This promising modality has been found to be safe and effective in both early stage primary cancer and oligometastases.

Renal cell carcinoma (RCC) is traditionally believed to be more radioresistant. In recent years, the molecular mechanisms explaining radioresistance of RCC have been linked to hypoxia-inducible factor-2 α and STAT-1. For many years, conventional radiotherapy has been used for palliative purposes, e.g., pain control. This is probably because high-dose radiation cannot be delivered safely to overcome radio resistance. SBRT/SABR, with the rapid-dose falloff and image guidance, allows the delivery of high-doses of radiation to the tumor target while limiting the volume of critical surrounding normal tissues receiving high-dose radiation. This is ideal to overcome RCC radioresistance and not causing treatment toxicity. Recent studies reported the cell killing mechanisms of SBRT/SABR are distinctive from those of conventional fractionated radiotherapy. SBRT/SABR may also target cancer stem cells, hypoxic cells and cancer neovasculature in addition to classical cell killing by radiation.

Radical or partial nephrectomy is still the standard of care for the management of primary RCC. Metastatectomy is also used for metastatic RCC in selected group of patients. Other options include radiofrequency ablation (RFA) and cryoablation. All these options are invasive. In the era of targeted therapy such as antiangiogenic tyrosine kinase inhibitors (sorafenib and sunitinib) and mTOR inhibitors (temsirolimus and everolimus), patients with RCC are living longer. There is now more rationale to provide best local control. There is now more evidence to use SBRT/SABR to treat primary RCC as well as metastatic RCC. The best outcome results have been reported in using stereotactic radiosurgery (SRS) to treat RCC brain metastases. The advantages of SBRT/SABR include outpatient procedure, noninvasiveness, patient convenience, radiobiologically more potent and can be integrated with systemic therapy. SBRT/SABR has been used safely and effectively in patients with primary RCC, recurrent RCC in contralateral kidney or initial nephretomy bed as well as metastatic RCC. SBRT/SABR is promising for the treatment of radioresistant RCC but more prospective clinical studies with long term outcome are warranted.

The 587th Kitasato Medical Society

Invitational Academic Lecture Series Abstract

(HH24.3.12)

Lymphangiogenesis: the plasticity of lymphatics in disease

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Many advances in understanding of the lymphatic system have been made over the past decade, but the mechanism of entry of fluid and cells into the initial part of lymphatics was a controversial topic until recently. This mechanism is important to lymphatic function because it influences the clearance of edema fluid from tissues, transport of antigen-presenting cells, and entry of tumor cells for spread to distant sites. With the discovery of button-like junctions ("buttons") between endothelial cells of initial lymphatics, the cellular basis of the primary valves for fluid and cell entry ceased to be a mystery. These discontinuous junctions are unique to initial lymphatics and distinctly different from the continuous zipper-like junctions ("zippers") between endothelial cells of collecting lymphatics and blood vessels. Junctions of initial lymphatics undergo changes during development and in disease. Buttons are not present when initial lymphatics first appear in the embryo but transform to zippers around the time of birth. Importantly, buttons revert back to zippers at sites of inflammation or high VEGF-C expression. These conditions are also accompanied by growth of new lymphatics. Lymphangiogenesis would be expected to improve lymphatic function, but this would not occur if conversion of buttons to zippers resulted in functional impairment. Changes in junctional phenotype in disease indicate that the abundance of lymphatics does not reflect lymphatic function. Recognition that lymphatics can undergo functional changes expands the significance of lymphatic plasticity in disease.