The 608th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H25.2.6)

Branch or expand? Endothelial cell dynamics regulating vascular patterning

Holger Gerhardt
(Vascular Biology Laboratory,
London Research Institute－Cancer Research UK
Vascular Patterning Laboratory, Vesalius Research
Center, VIB3, Department of Oncology, KU Leuven)

Blood vessel patterning involves the iterations of sprout initiation, elongation, anastomosis, lumen formation, and stabilization. Endothelial cells concurrently migrate, divide, select dynamic phenotypes, and rearrange positions to allow organized branching morphogenesis. How exactly the cells orchestrate their behaviour remains poorly understood. Our recent work identified a regulatory network of VEGF-VEGFR and Dll4/Notch signalling as a key mechanism of pattern generation. Mosaic analysis in zebrafish and embryoid body sprouting assays illustrated a constant competition between cells for the leading tip cell position utilizing differential VEGFR levels. Computer simulations suggest that the coordination and timing of the competitive cell behaviour and Dll4/Notch signalling drives the angiogenic branching "pattern generator". Observations of emergent behaviour in computer simulations of pathological blood vessel growth driven by high VEGF levels, as in ischemia or tumour angiogenesis, now provide the first predictions for a mechanism of pathological vascular patterning, and possibly for organ specific branching adaptations. Studies into the dynamic regulation of Dll4 in vitro and in vivo indicate that high VEGF levels disrupt the "salt-and-pepper" pattern of Dll4 underlying branching morphogenesis. Instead, high VEGF levels promote contiguous Dll4 expression in clusters of adjacent cells that synchronize their behaviour, fail to rearrange and thus form vessel dilation domains leading to tortuosity. We propose that changes in the behaviour of the VEGF-Dll4-Notch feedback loop determine whether to branch or to expand a vessel during angiogenesis.

Further iterations of simulation and experimentation identified differential adhesion between endothelial cells as key determinant of dynamic cell rearrangements within the sprout. The pattern and endocytosis of VE-cadherin at individual endothelial cell junctions is highly differential between cells, under the control of VEGFR2 and Notch activity. We find that synchronization of Dll4/Notch signalling under pathologically high VEGF conditions halt cell rearrangements due to the loss of differential adhesion. Together, the identification of a phase transition in Dll4/Notch dynamics and the control of rearrangements by differential adhesion establish a novel mechanistic understanding of how endothelial cell signalling and behaviour is coordinated, determining whether to branch or expand new vessels during angiogenesis.

The 611th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H25.2.20)

Sensing changes in oxygen content: the role in health and disease

Mieczyslaw Pokorski
(Head of the Department of Respiratory Research, Polish Academy of Sciences Medical Research Center)

Oxygen is indispensible for life, as its molecule participates in energy metabolism in the mitochondrial electron transport chain. Sensing changes in oxygen is thus a vital homeostatic function of the organism. Oxygen is basically sensed by the sensory organ of the carotid body located at the bifurcation of the common carotid artery. The organ produces a powerful defensive chemoreflex consisting of lung hyperventilation in response to reductions in O_2. The innate mechanisms of carotid body function are still unknown and are subject of intensive research; in particular, the role of a spate of neurotransmitters and/or ionic channels in the organ's receptor neurons, called chemoreceptor cells or Type I cells, is unsettled.

The assessment of carotid body function consists of taking the ventilatory responses to hypoxia (HVR) and hyperoxia. Clinical usefulness of these tests is subject to debate. In health, the HVR may be used to predict the ability to adaptively respond to hypoxia, e.g., during strenuous exercise, which comes down to the prediction of safety of hypoxic episodes which someone may encounter. In disease, the HVR may be used to predict, e.g., if supplemental oxygen given to patients in case of emergency or in chronic respiratory disease would diminish ventilation.

Hypoxic ventilatory response, and thus the ability to deliver oxygen through the aged lung, also is crucially important during the aging process. Interestingly, despite severe structural and utrastructural changes in the aged lungs, the response to hypoxia is well preserved. Therefore, in advanced, but healthy, old age, the central and peripheral neural respiratory drive is able to compensate for the morphological lung tissue decline.
The lecture will end up with the hints on the newest theories concerning the detection of oxygen changes along the hyperoxia-hypoxia continuum, having to do with the transient receptor potential channels.

The 612th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H25.2.25)

Clinical-anatomical aspects of the lateral scull base

Bernhard Hirt
(Professor, Department of Clinical Anatomy, Eberhard-Karls-University of Tübingen)

The topographically complex structure of the lateral scull base is used to show the bandwidth of clinical anatomical activity, such as Translational molecular research, Medical engineering, and Teaching. Anatomical moderation during scull base surgery was performed and transmitted via the Internet. More than 13,000 medical students all over Germany, Swizerland, and Austria applied for this event which is called "The Sectio Chirurgica."

The 613th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H25.3.9)

Beyond mineral metabolism: regulation and function of 1,25(OH)2D3

Florian Lang
(Professor, Department of Physiology, Eberhard-Karls-University of Tübingen)

Adequate regulation of Ca^{2+} Phosphate metabolism requires the maintenance of constant plasma Ca^{2+} and phosphate concentrations, adequate mineralization of bone and avoidance of vascular and tissue calcification. Regulating hormones include 1,25(OH)2D3, thus, controls plasma Ca^{2+} and phosphate concentrations and mineralization of bone. Deficiency of either, FGF23 or klotho leads to excessive 1,25(OH)2D3 formation, profuse vascular calcification, premature appearance of age related disorders, and early death. Thus, functions of 1,25(OH)2D3 are not only relevant for mineral metabolism but affect a wide variety of functions not related to kidney and bone.

The 614th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H25.3.19)

Tumor-associated lymphatic vessels: more than an escape route

Melody A. Swartz
(Professor of Bioengineering and Cancer Research, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland)

Lymphatic vessels drain fluid, antigens, and immune cells from the periphery to the lymph nodes (LNs). In addition to transporting activated dendritic cells to mount adaptive immune responses in the LNs, lymphatic drainage brings soluble antigens from the periphery to LN-resident immature dendritic cells and B cells. It is also the most common site for cancer metastasis. Despite its importance, the role of tumor-associated lymphatic vessels and their drainage to the LN in regulating host immune responses to the tumor is poorly understood. We show that tumor expression of VEGF-C, the most potent lymphatic growth factor, promotes pro-tumor immune tolerance by several mechanisms. For one, it enhances drainage to the draining LN, where tumor antigens along with suppressive cytokines bathe the LN and could affect B and T cell education there. Second, tumor VEGF-C upregulates CCL21 in the tumor stroma and surrounding lymphatic vessels, which itself promotes the infiltration of naïve T cells into the suppressive tumor microenvironment. Third, VEGF-C drives expansion of peritumoral and LN lymphatic vessels, and we show that lymphatic endothelial cells can not only inhibit dendritic cell maturation and ability to activate anti-tumor cytotoxic T cells, but also scavenge tumor antigen for direct cross-presentation and cross-tolerance of tumor-reactive T cells. The combined effects of lymphatic expansion in the tumor microenvironment led to overall suppression of the effects of anti-tumor immunotherapy. Together, these findings suggest that lymphatic drainage and inflammation-induced lymphangiogenesis may serve to maintain peripheral tolerance to self-antigens, and that tumors may hijack such mechanisms to escape host immunity.