

2013 LOUIS-JEANTET SYMPOSIUM

23 October 2013

Centre Medical Universitaire (CMU), Geneva

Auditorium 250



Peter J. Ratcliffe
2009 Louis-Jeantet prize-winner
Nuffield Department of Medicine, University of Oxford (UK)

Wednesday, 23 October 2013, 12:00 – 12:25

Keynote Lecture: Understanding cellular oxygen sensing pathways; what are the implications?

Work on oxygen sensing pathways regulating the erythropoietin gene unexpectedly revealed the existence of a widespread system of gene regulation by oxygen, which is tightly conserved throughout the animal kingdom. Analysis of this system revealed an unprecedented signalling process, based on the post translational hydroxylation of the key transcription factor HIF, by a series of 2-oxoglutarate-dependent dioxygenases. The presentation will review the biochemical, physiological, pathological, and therapeutic challenges arising from this work.

Biography

Professor Peter Ratcliffe trained in medicine at Gonville and Caius College, Cambridge and St. Bartholomew's Hospital, London. He trained as a nephrologist before founding the Hypoxia Biology Laboratory at Oxford, with support from the Wellcome Trust. He is currently the Nuffield Professor of Clinical Medicine and Head of the Nuffield Department of Clinical Medicine at the University of Oxford.

<http://www.ndm.ox.ac.uk>

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Auditorium 250



Roland H. Wenger

Institute of Physiology, University of Zurich (Switzerland)

Wednesday, 23 October 2013, 09:00 – 09:25

Modulating the human hypoxia response

Protein stability and transcriptional activity of hypoxia-inducible factor (HIF) α subunits is regulated by oxygen-sensing protein hydroxylases. When oxygen is abundant, HIF α subunits are hydroxylated and rapidly degraded; but when oxygen is scarce, HIF α subunits remain stable and form active heterodimeric HIF transcription factors which induce a large number of genes involved in the adaptation to hypoxic conditions with pathophysiological implications for erythropoiesis, angiogenesis, cardiovascular function and cellular metabolism in healthy and cancerous tissues. Oxygen-sensing is regulated by the co-substrate-dependent activity and hypoxia-inducible abundance of the HIF α prolyl-4-hydroxylases (PHDs) which trigger HIF α stability even under low oxygen conditions. Based on the subtle balance between PHD and HIF α levels/activities, these two factors form the core of a mutually adjusted, self-adaptive oxygen sensing system. A number of upstream regulators of the PHDs trigger this oxygen sensing system. Moreover, the recent identification of novel downstream targets of PHDs suggests that cellular oxygen sensing by PHDs cross-talks to additional signalling pathways, in addition to the HIF system.

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Biography

Roland H. Wenger is Professor for Physiology at the University of Zurich. Born in Biel/Bienne, he studied chemistry at the University of Berne where he also did his PhD thesis at the Theodor-Kocher-Institute from 1987 to 1990. Following a post-doctoral fellowship at the Max-Planck-Institute for Immunobiology in Freiburg i.Bsg. from 1990 to 1993, he moved to the Institute of Physiology, University of Zürich, where he obtained the Venia legendi in Physiology in 1999. From 2000 to 2001 he was university lecturer at the University of Lübeck and from 2001 to 2003 Associate Professor at the University of Leipzig.

<http://www.physiol.uzh.ch/research/CellularOxygenPhysiology.html>

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Stephen Lee

Department of Cellular and Molecular Medicine, Department of
Medicine, University of Ottawa, Ontario, Canada

Wednesday, 23 October 2013, 09:25 – 09:50

The role of RNA hypoxia response element (rHRE)-driven protein synthesis in the hypoxic cell phenotype

Protein synthesis is typically initiated by the binding of the eukaryotic initiation factor 4E (eIF4E) to the 5' cap found on the vast majority of mRNAs. Hypoxia is a potent inhibitor of eIF4E-directed translation raising an intriguing question as to how hypoxic cells are able to synthesize proteins. We recently reported that hypoxic cells exploit an alternative cap-dependent translation machinery to synthesize the vast majority of their proteins. This system relies on the participation of several new components to the cellular translation apparatus, including the oxygen-regulated HIF2 α , the RNA-binding protein RBM4 and eIF4E2, an homolog of eIF4E that escapes hypoxic inhibition. The HIF2 α /RBM4/eIF4E2 complex is recruited by a small RNA motif present on the 3'UTR of mRNAs, referred to as the RNA Hypoxia Response Element (rHRE). We will show that rHRE-mRNAs undergo translation exclusively during hypoxia to synthesize more than 90% of the hypoxic cell proteome. In contrast, mRNAs that do not encode an rHRE are efficiently translated in normoxic, but not in hypoxic, conditions. As such, preventing rHRE-mediated protein synthesis abolishes the ability of cancer cells to form a hypoxic tumor core, and thus a cellular mass of more than 1/2 mm, as they are unable to synthesize proteins in the absence of oxygen. A model will be presented whereby cells switch to rHRE-directed translation to confer the hypoxic cell phenotype.

Biography

Stephen Lee received his Ph. D from McGill University in 1994 before joining as a postdoctoral fellow the laboratory of Dr. Richard Klausner, the former Director of the (US) National Cancer Institute. He was recruited by the University of Ottawa in 1998, received the Harold E. Johns Award from the National Cancer Institute of Canada in 2004 and was promoted to the rank of Full Professor in 2008. The laboratory of Dr. Lee is funded by grants from Canadian Institutes of Health Research and focuses on the role of non-coding RNA and protein synthesis in the cellular adaptation to hypoxia.

<http://www.med.uottawa.ca/NSC/eng/lee.html>

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M. Celeste Simon

Howard Hughes Medical Institute/Abramson Family Cancer Research Institute, Department of Cell and Developmental Biology, University of Pennsylvania (USA)

Wednesday, 23 October 2013, 10:05 – 10:30

HIF/mTORC1 pathways and their impact on cancer metabolism

Solid tumors exhibit heterogeneous microenvironments, often characterized by limiting concentrations of oxygen (O₂), glucose, and other nutrients. How oncogenic mutations alter stress response pathways, metabolism, and cell survival in the face of these challenges is incompletely understood. Here we report that constitutive mammalian target of rapamycin complex 1 (mTORC1) activity renders hypoxic cells dependent on exogenous desaturated lipids, as levels of de novo synthesized unsaturated fatty acids are reduced under low O₂. Specifically, we demonstrate that hypoxic Tsc2^{-/-} (tuberous sclerosis complex 2^{-/-}) cells deprived of serum lipids exhibit a magnified unfolded protein response (UPR) but fail to appropriately expand their endoplasmic reticulum (ER), leading to inositol-requiring protein-1 (IRE1)-dependent cell death that can be reversed by the addition of unsaturated lipids. UPR activation and apoptosis were also detected in Tsc2-deficient kidney tumors. Importantly we observed this phenotype in multiple human cancer cell lines and suggest that cells committed to unregulated growth within ischemic tumor microenvironments are unable to balance lipid and protein synthesis due to a critical limitation in desaturated lipids.

Biography

M. Celeste Simon, Ph.D. is the Scientific Director of the Abramson Family Cancer Research Institute at the Perelman School of Medicine at the University of Pennsylvania. She is also an Investigator of the Howard Hughes Medical Institute. She received her bachelor's degree from Miami University and completed a Ph.D. in biochemistry at Rockefeller University in 1985. She conducted postdoctoral research with Joseph Nevins at Rockefeller and then with Stuart Orkin at Harvard Medical School. She became an Assistant Professor of Medicine and Molecular Genetics and Cell Biology at the University of Chicago in 1992. In a National Competition, she was named an Assistant Investigator of the Howard Hughes Medical Institute in 1994.

In 1999, she moved to the University of Pennsylvania School of Medicine and was one of the founding laboratories of the newly formed Abramson Family Cancer Research Institute (AFCRI) there. She was promoted to Associate Professor in 1999, and full Professor in 2006.

In 2007, she became the Scientific Director of the AFCRI. Dr. Simon's research is focused on how cells sense and respond to changes in the availability of molecular oxygen. This impacts normal development, physiology, and numerous diseases, such as the growth of solid tumors. The Simon Laboratory is studying how O₂ sensing impacts tumor angiogenesis, metabolism, and metastasis, and overall disease progression. She is studying both animal models and cancer patients with the ultimate goal of developing novel strategies to treat tumors such as pancreatic cancer, soft tissue sarcoma, colorectal cancer, and lung adenocarcinoma. Dr. Simon currently directs a laboratory of 20 individuals, including graduate students, postdoctoral fellows, clinical fellows, and research technicians. The AFCRI employs 400 researchers working in roughly 30 independent laboratories. Dr. Simon has received numerous awards recognizing her research, such as the Stanley N. Cohen Award for Biomedical Research and the Elliot Osserman Award from the Israel Cancer Research Fund

<http://www.med.upenn.edu/apps/faculty/index.php/g20000220/p600>

[1](#)

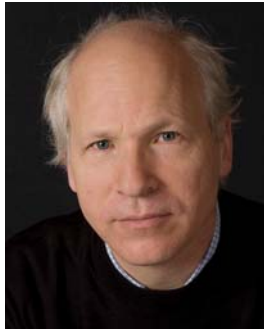
http://www.afcri.upenn.edu/ourfaculty/simon_bio.html

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Randall S. Johnson
Department of Physiology, Development & Neuroscience
University of Cambridge, Cambridge, UK

Wednesday, 23 October 2013, 10:30 – 10:55

Functional diversity in the HIF system; implications for cancer

Biography

Randall S. Johnson, Ph.D.
Professor of Molecular Physiology and Pathology
Wellcome Trust Principal Research Fellow
Department of Physiology, Development & Neuroscience
University of Cambridge
Physiological Laboratory
Downing Street
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<http://www.pdn.cam.ac.uk/staff/rjohnson/index.shtml>

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Wilhelm Krek
Institute of Cell Biology, ETH-Hönggerberg, Zurich (Switzerland)

Wednesday, 23 October 2013, 11:10 – 11:35

HIF-dependent and HIF-independent function of the von Hippel-Lindau tumour suppressor

Biography

Wilhelm Krek has been Full Professor of Cell Biology at ETH Zurich since 2003. He was born in 1962 in Klagenfurt, Austria and studied Chemistry at the Technical University Graz. He obtained his PhD degree in 1991 at the Swiss Cancer Institute in Lausanne, Switzerland. After four years as a postdoctoral fellow at the Dana Farber Cancer Institute/Harvard Medical School in Boston, he worked from 1995-2003 at the Friedrich Miescher Institute (FMI) for Biomedical Research in Basel, Switzerland, first as a Junior Group Leader and START Fellow and after his promotion in 1999, as a Senior Group Leader. He earned international recognition for his research in the field of cell signaling and cancer and received for his work several prizes including the Robert Wenner Prize and the International Steiner Cancer Research Award. He is elected member of EMBO and has served as a member of the editorial board of EMBO Journal. Wilhelm Krek is also co-founder and Chairman of the Competence Center for Systems Physiology and Metabolic Diseases, a joint center of ETH and University-Hospital Zurich in medical systems biology.

<http://www.cell.biol.ethz.ch/people/krek/>

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Massimiliano Mazzone
Vesalius Research Center, VIB, Leuven (Belgium)

Wednesday, 23 October 2013, 11:35 – 12:00

Oxygen vessels, and inflammation: implications for cancer and ischemia

Vessel formation is a multistep process that involves different cell types and fates. When a tissue becomes hypoxic, VEGF is released and the endothelial cell that is exposed to the highest VEGF concentration becomes a 'tip cell'. The tip cell leads the sprout at the forefront while the elongation of the new branch relies on proliferation of endothelial 'stalk cells', which trail behind the pioneering tip cell. Maturation of the nascent plexus into a mature functional network relies on the recruitment of pericytes and smooth muscle cells regulated by the endothelium and inflammatory cells. Deposition of extracellular matrix, tightening of cellular junctions and induction of endothelial quiescence further stabilize the tube. Vessel maturation and the formation of a vascular lumen allow initiation of blood flow and, in turn, tissue oxygenation. Although our understanding on how vessels sprout is increasing, little is known about how vessels regulate their shape and morphogenesis. Nevertheless, these are important processes since a malshaped endothelium accompanies several pathological conditions as cancer and ischemia. Here, I will show direct and indirect (oxygen-dependent and oxygen-independent) regulatory mechanisms of PHD2 in endothelial cells and macrophages, and how this reflects in the formation of a new vascular network and arteriogenic vessel maturation. These findings have strong implications for the treatment of oncological and ischemic diseases

Biography

Massimiliano (Max) Mazzone graduated in Medical Biotechnology at the Medical School of the University of Torino, Italy, and then performed his PhD in Cell Science and Technologies at the Institute for Cancer Research of Torino, under the supervision of Prof. Comoglio. In 2006, he moved to Belgium as an EMBO-awarded postdoctoral fellow in the lab of Prof. Peter Carmeliet, at the University of Leuven. Since February 2009, he is heading the Lab of Molecular Oncology and Angiogenesis at the Vesalius Research Center (VIB) in Leuven and he is Associate Professor at the Katholieke Universiteit Leuven. Max Mazzone has contributed to the field of oncology understanding the mechanisms of cancer metastasis and to vascular biology identifying a new endothelial cell phenotype, the

"phalanx" cell, which takes part in the formation of aligned blood vessels in perfused tissues.

Since he is independent Group leader, his team is focusing in studying the response of inflammatory cells to hypoxic conditions in order to restore blood flow in conditions such as cancer and ischemic pathologies. Max got important national awards (the Belgian Royal Academy Prize, the Italian Lorini Award, and the AIRC Price for excellence in science, etc.) and international recognitions (ERC, EMBO, FEBS, Burgen Award, etc.). He is author in 50 papers, with an average impact factor in first or senior corresponding author research papers of 25, almost 4000 total citations, and an H-index of 25. He is member of the boards of several peer-reviewed journals (such as Cancer Research), he is reviewer for almost 20 journals, and he has been so far invited to speak in more than 40 national and international conferences (including GRC, Keystone, AACR, FEBS meetings, etc.).

<http://www.vrc-lab.be>

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Holger Gerhardt
Vascular Biology Laboratory
London Research Institute - Cancer Research UK, London (UK)

Wednesday, 23 October 2013, 13:40 – 14:05

From cells to networks – Principles of vascular pattern formation

¹Vascular Biology Laboratory, London Research Institute – Cancer Research UK

²Vascular Patterning Laboratory, Vesalius Research Center, VIB, KU Leuven, Belgium

The formation of a hierarchically branched network of large and small blood vessels is critical for the growth and maintenance of healthy tissues. How the endothelial cells that line blood vessels orchestrate their behaviour, morphology and function to achieve functional blood vessel patterning is one of the most exciting questions in vascular biology. Using mosaic models of sprouting and vessel remodelling in vitro, in silico and in vivo, we investigate how endothelial cells stimulated by VEGF-A dynamically specify their behaviour and neighbourhood relationships to branch or expand new vessels. I will present new insights into the principles of vascular pattern formation, focussing on cell specification, coordination, endothelial cell competition and dynamic rearrangements during sprouting and remodelling.

Biography

Holger Gerhardt studied Biology in Darmstadt and Neurobiology in Tuebingen, Germany, where he also completed his PhD in Cell Biology in 2000. During his post-doctoral research with Christer Betsholtz at Gothenburg University, Sweden, Dr. Gerhardt conceptualized the endothelial tip and stalk cells; a discovery that kick-started his work on endothelial guidance and vascular patterning. Since 2004, he is a group leader at the London Research Institute-Cancer Research UK. Dr. Gerhardt is EMBO Young Investigator (2007) and recipient of the prestigious Lister Prize (2008). In 2009, he received the Walter Fleming Medal of the German Society for Cell Biology, in 2011 the Judah Folkman Award of the North American Vascular Biology organization and in 2012, the Hooke Medal of the British Society of Cell Biology. Since 2010, Dr. Gerhardt also heads the Vascular Patterning Laboratory at the VIB, KU Leuven, Belgium, building an integrated research team across the two institutions to combine expertise in vascular disease models with his cell biology approach to unravel principles of vascular network formation in development and disease. Dr. Gerhardt's research activity will become part of the new Francis Crick Institute opening in central London in 2015.

<http://www.london-research-institute.org.uk/research/holger-gerhardt>

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Anne Eichmann

Yale School of Medicine, Yale Cardiovascular Research Center,
New Haven (USA)

Wednesday, 23 October 2013, 14:05 – 14:30

Factors guiding of vascular patterning

Biography

Ensign Professor of Medicine (Cardiology) and Professor of Cellular and Molecular Physiology

Research Interests: Vascular development and angiogenesis; guidance of vascular patterning; tip cells; axonal growth cones; vascular growth factors in the nervous system more ...

Education:

M.Sc., Weizmann Institute of Science, Isarel, 1989

Ph.D., Universite Paris XI, Orsay, 1994

Her laboratory studies vascular and lymphatic development, with particular emphasis on mechanisms that direct patterning and guidance. Specialized endothelial cells (EC) called tip cells located at the extremities of growing capillary sprouts mediate guided vascular patterning. Tip cells exhibit characteristic features, including extension of filopodia that explore the tip cell environment, lack of a lumen and a slow proliferation rate. EC behind tip cells, termed stalk cells form the capillary lumen and proliferate.

<http://medicine.yale.edu/intmed/cardio/ycvrc/facultylabs/eichmann.aspx>

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Christer Betsholtz

Department of Immunology, Genetics and Pathology,
Rudbeck Laboratory Uppsala University (Sweden)

Wednesday, 23 October 2013, 14:45 – 15:10

Pericytes, the blood-brain barrier, and brain diseases

Our previous work identified platelet-derived growth factor B-chain (PDGF-B) signaling through PDGF receptor beta (PDGF-Rb) as a major mechanism in pericyte recruitment during normal and pathological blood vessel formation. Mice with null or hypomorphic mutations in *Pdgfb* show pericyte hypoplasia and display an impaired maturation of blood-brain barrier (BBB) through a combination of activated endothelial transcytosis and abnormal astrocyte end-foot polarization. Until recently, this phenotype was not connected to any specific CNS pathology. However, we have now found that loss-of-function mutations in PDGF-B in humans and mice cause idiopathic basal ganglia calcification (IBGC). Calcifications in the basal ganglia are a common incidental finding but sometimes inherited as an autosomal dominant trait (IBGC). In collaboration with a consortium of clinical geneticists, we identified six families of different ancestry with nonsense and missense mutations in the *PDGFB* gene. We also found that mice carrying hypomorphic *Pdgfb* alleles developed brain calcifications with similar composition, regional distribution and age-related expansion as human IBGC. These calcium depositions depend on the loss of endothelial PDGF-B, and correlate with the degree of pericyte and blood-brain barrier deficiency. Our data show that loss-of-function mutations in the gene for PDGF-B cause IBGC and IBGC-like disease in humans and mice, respectively. Somatic gain-of-function mutations in PDGF and PDGF-receptor genes have previously been connected to various types of cancers, but this is the first case where a human disease has been connected to an inherited loss of PDGF or PDGF-receptor function.

Biography

Christer Betsholtz is professor of Vascular and Tumor Biology at Uppsala University and professor of Vascular Biology at Karolinska Institutet. His research deals with the role of growth factors in blood vessel formation and function. His research has elucidated mechanisms of angiogenic sprouting, recruitment of pericytes and the role of these cells in vascular morphogenesis and function. A current interest concerns how pericytes regulate the blood-brain barrier, and how this regulation may impinge on diseases in, and the delivery of drugs to, the brain.

[http:// www.igp.uu.se](http://www.igp.uu.se)

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Ralf H. Adams

Department of Tissue Morphogenesis

Max Planck Institute for Molecular Biomedicine and

University of Münster (Germany)

Wednesday, 23 October 2013, 15:10 – 15:35

Molecular regulation of angiogenic blood vessel growth

Angiogenesis is the main process mediating the expansion of the blood vessel network during development, tissue regeneration or in pathological conditions such as cancer. The formation of new endothelial sprouts, a key step in the angiogenic growth program, involves the selection of endothelial tip cells, which are highly motile, extend numerous filopodia, and lead new sprouts. Key aspects of angiogenesis, such as endothelial proliferation and tip cell formation, are positively modulated by vascular endothelial growth factor (VEGF), whereas Notch and the ligand Dll4 are important negative regulators. Our work has identified the Notch ligand Jagged1 as a potent pro-angiogenic regulator with the opposite role as Dll4. We also found that blocking of Notch activity enables strong angiogenic growth even in mutant animals lacking endothelial VEGF receptor-2 expression, which could be relevant for resistance to anti-VEGF therapies. Ephrin-B2, a ligand for Eph family receptor tyrosine kinases, controls endothelial cell motility by modulating VEGF receptor endocytosis and the activation of downstream signal transduction cascades. Moreover, we found that the spatial pattern of VEGF endocytosis in growing vessels is controlled by the clathrin-associated sorting protein Dab2, the cell polarity protein PAR-3 and ephrin-B2, which cooperate to promote efficient expansion of the vascular network. Our recent work focuses on organ-dependent differences in vessel growth, the regulation of tissue patterning by blood vessel-derived signals, and the formation of endothelial cell-associated microenvironments.

Biography

Ralf H. Adams did his Ph. D training at the Max Planck Institute for Brain Research before he joined the laboratory of Rüdiger Klein at EMBL in 1996. In 2000, he started his own research group at the Cancer Research UK London Research Institute. Since he has moved as Director to the Max Planck Institute for Molecular Biomedicine and Professor the University of Münster in 2008, Ralf Adams and his group have continued to provide insight into key processes controlling developmental blood vessel growth and, in particular, its regulation by Notch, VEGF and Eph/ephrin signaling.

<http://www.mpi-muenster.mpg.de>

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Tajia Makinen

Uppsala University, Sweden and Cancer Research UK London
Research Institute, Uppsala (Sweden)

Wednesday, 23 October 2013, 15:50 – 16:15

Organ-specific mechanisms of lymphatic development

The lymphatic system is composed of a hierarchy of vessels with specific features serving their unique functions: the blind-ended lymphatic capillaries that absorb the interstitial fluid and the collecting lymphatic vessels that transport the lymph to the cardiovascular system. Failure of the lymphatic vessels, caused by a genetic defect (primary) or damage following surgery or radiation therapy (secondary) can lead to lymphoedema and contribute to pathogenesis of obesity, atherosclerosis and cardiovascular disease. Lymphoedema is a progressive and lifelong condition characterised by gross swelling of the affected tissue. Notably, several primary lymphoedemas are characterised by defects that affect specifically either the collecting vessels or the capillaries. In addition, specific area(s) of the body are affected in different types of lymphoedemas. Molecular mechanisms underlying organ- and vessel-type specific manifestation of lymphatic dysfunction are poorly understood yet this knowledge is instrumental in designing therapeutic strategies for lymphoedema and other lymphatic disorders that are currently lacking. In this lecture I will discuss our new findings that reveal organ-specific mechanisms required for the formation of a functional lymphatic vascular network and provide insight into pathophysiological mechanisms involved in lymphoedema.

Biography

Tajia Makinen obtained her PhD in Prof. Kari Alitalo's laboratory at the University of Helsinki. After post-doctoral training in Prof. Rudiger Klein's laboratory at the Max-Planck-Institute of Neurobiology in Martinsried, she moved to London to establish her research group at the Cancer Research UK London Research Institute. In 2013 she moved to Rudbeck Laboratory at the Uppsala University, where her laboratory continues to study the mechanisms of lymphatic vascular development.

http://www.igp.uu.se/research/cancer_and_vascular_biology/tajia-makinen/?languageld=1

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Tatiana Petrova

Department of Oncology, CHUV and University of Lausanne
(Switzerland)

Wednesday, 23 October 2013, 16:15 – 16:40

Biomechanical and transcriptional regulation of lymphatic vascular development

Vertebrates have two vascular systems, both of which are indispensable for life: blood vessels, which bring oxygen and nutrients to the tissues, and lymphatic vessels, which remove proteins and excess of fluid from the interstitial space and return them back to the blood circulation. Lymphatic vessels are also important regulators of the immune response, as they transport peripheral antigens to lymph nodes.

The directional flow of lymph is maintained by intraluminal lymphatic valves. Lymphatic valves are therefore crucial to prevent lymphedema, accumulation of fluid in the tissues; yet, the mechanisms of valve formation are not fully understood. In addition, the role of flow in lymphatic vascular development is only beginning to be appreciated. We use a combination of the in vivo genetic approaches and in vitro studies of mechanotransduction to establish the hierarchy of molecular events in lymphatic valve morphogenesis and vascular patterning. We aim to uncover novel pathways implicated in the regulation of endothelial mechanotransduction and to study their role in developmental and pathological remodeling of lymphatic vessels.

Biography

Tatiana Petrova received her M.Sc in chemistry from Moscow State University and a Ph.D. in biochemistry from the University of Geneva. She did a post-doctoral work at Northwestern University in Chicago, and then moved to a second postdoctoral position at the University of Helsinki, Finland. In 2004 she became a group leader at Molecular Cancer Biology Program at the University of Helsinki, and in 2008 joined CHUV and University of Lausanne as an SNF professor. Her main research interests are the molecular mechanisms of vascular growth and remodeling.

<http://www.unil.ch/deo/page57972.html>

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Kari Alitalo

2006 Louis-Jeantet prize-winner

Wihuri Research Institute and Translational Cancer Biology Program
Biomedicum Helsinki, University of Helsinki (Finland)

Wednesday, 23 October 2013, 16:40 – 17:05

Keynote lecture: Biological functions and therapeutic potential of vascular endothelial growth factors

Because the growth of new blood vessels, or angiogenesis, is involved in tumour progression, anti-angiogenic agents are currently employed in tumour therapy. Although these treatments have been successful in the treatment of many types of solid tumours, most patients are either refractory or eventually acquire resistance to anti-angiogenic therapeutics. A combination of angiogenesis inhibitors based on solid knowledge of the major interacting angiogenesis signalling pathways could be used to significantly advance the efficacy of tumour therapy. – The idea of pro-angiogenic therapy is to grow new functional blood vessels and thus restore blood flow to ischemic tissue. In addition to angiogenesis of blood capillaries, growth of larger arterioles/arteries (arteriogenesis, or collateral formation) is especially beneficial for this goal. Several attempts have been made to stimulate angiogenesis and arteriogenesis in tissue ischemia, with limited success. One of the obstacles has been the property of angiogenic growth factors to promote vascular leakage, leading to tissue oedema and fibrin deposition. Despite intensive efforts, growth factors suitable for angiogenic therapy have not yet provided significant help in the treatment of cardiovascular disease. – A better understanding of the biology of the vascular growth factors can facilitate therapeutics development for cardiovascular diseases. – The growth of lymphatic vessels, lymph angiogenesis, is actively involved in a number of pathological processes including tissue inflammation and tumour dissemination but is insufficient in patients suffering from lymphedema; a debilitating condition characterized by chronic tissue oedema and impaired immunity. Lymph angiogenic growth factors provide possibilities to treat these diseases.

Biography

Dr. Kari Alitalo discovered lymph angiogenesis and its regulators. He isolated several novel endothelial receptor tyrosine kinases and showed that some of these are important in tumor angiogenesis. A significant achievement by Dr. Alitalo was the isolation and characterization of the first lymphangiogenic growth factor VEGF-C, its receptor VEGFR-3, and lymphatic endothelial cells, opening up the lymphatic vascular system to molecular analysis. He discovered mechanisms of lymphedema and devised molecular therapies for its treatment. He demonstrated that VEGF-C induced tumor angiogenesis and lymphangiogenesis, intralymphatic tumor growth, and VEGF-C association with tumor metastasis and its inhibition by blocking the VEGFR-3 signal transduction pathway.

[http:// research.med.helsinki.fi/cancerbio/alitalo/default.htm](http://research.med.helsinki.fi/cancerbio/alitalo/default.htm)
