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POSTERS

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P.2.1-002
Regulation of VEGF-induced vascular hyperpermeability by the neuropilin 1 cytoplasmic domain

J. Brash, A. Fantin, A. Lampropoulou, C. Ruhrberg
Institute of Ophthalmology, UCL, London, United Kingdom

The vascular endothelial growth factor (VEGF) is a secreted glycoprotein that can induce the growth of new blood vessels, known as angiogenesis, and stimulate vascular hyperpermeability. Upregulation of VEGF has been observed in ischemic disease, where angiogenesis is beneficial for recovery from hypoxia, whilst hyperpermeability causes damaging oedema. VEGF is expressed as three main isoforms, termed VEGF121, VEGF165 and VEGF189, of which VEGF165 is the most commonly studied. VEGF165 acts through two receptors to promote VEGF-signalling, the tyrosine kinase VEGF receptor 2 (VEGFR2) and the non-catalytic neuropilin 1 (NRP1). Although the short cytoplasmic domain (NCD) of NRP1 lacks kinase activity, *in vivo* studies from our group have recently demonstrated that this domain is required for VEGF165-induced hyperpermeability, even though it is dispensable for angiogenesis. Here, we investigate the role of the NCD in VEGF165-induced vascular hyperpermeability. Specifically, we have used *in vitro* models to study VEGF signalling pathways that depend on the NCD and to identify NCD binding partners that may be required for NRP1's role in promoting vascular hyperpermeability. We have further determined which of the VEGF isoforms require the NCD to induce permeability, and whether NCD use influences the potency of each isoform in evoking hyperpermeability. These findings will help develop our understanding of how VEGF-induced vascular hyperpermeability is promoted and how it can be mechanistically separated from VEGF-induced angiogenesis.

P.2.1-003
Cooperation of transport and sensing in C4-dicarboxylate signaling by DcuS sensor kinase of *E. coli*

G. Unden, M. Stopp
University of Mainz, Mainz, Germany

Bacteria depend on sensors for interaction and communication with their environment. Membrane bound sensor kinases (His kinases) of two-component systems represent the major device for signal perception and transmembrane signaling by bacteria [1]. Typically, the sensor kinases become activated by phosphorylation after binding of the stimuli to extra-cytoplasmic sensor domains. Rotational, scissors- and piston-type conformational changes are supposed to transfer the signal across the membrane.

The DcuS-DcuR two-component system of *E. coli* is a member of the CitA family of sensor kinases and controls expression of genes related to C4-dicarboxylate catabolism. The sensor kinase DcuS contains an extra-cytoplasmic PAS domain for fumarate binding. Transmembrane helices TM1 and TM2 constitute the membrane anchor of DcuS. Fumarate binding at the extra-cytoplasmic PAS domain triggers a long-range piston type movement of TM2 within the membrane whereas the position of TM1 is not affected [2]. The driving force for the shift of TM2 is provided by fumarate binding which causes contraction of the PAS domain [3, 4]. DcuS requires in addition the C4-dicarboxylate transporters DctA or DcuB for function [5]. The transporters form sensor complexes with DcuS and convert DcuS to the C4-dicarboxylate responsive state whereas free DcuS is in the permanent ON state. Details of TM1/TM2 interaction and dynamics during fumarate activation and signal transduction will be shown.

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P.2.1-004
Nicotine facilitates nicotinic acetylcholine receptor targeting to mitochondria but makes them less susceptible to specific ligands

K. Uspenska, O. Lykhmus, M. Skok
Palladin Institute of Biochemistry, Kyiv, Ukraine

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels, which mediate fast synaptic transmission and regulate cell viability and proliferation. Previously we discovered the presence of nAChRs in mitochondria, where they regulate the early stages of mitochondria-driven apoptosis through activation of intramitochondrial kinases. However, the mechanism of nAChR functioning in and targeting to mitochondria is still unknown.

Nicotine has been shown to enhance maturation of nAChRs on the way of biosynthesis. We studied the content, state of glycosylation and functioning of nAChRs in the liver mitochondria of mice, which consumed nicotine with the drinking water during 7 days. The level of nAChR subunits in mitochondria *vs* non-mitochondria fractions and cytochrome c release from live mitochondria under the effect of Ca2+ were studied by Sandwich-ELISAs, and the nAChR-attached carbohydrate residues were identified by lectin-ELISA.

It was found that nicotine consumption stimulated targeting of nAChRs to mitochondria: the ratio of mitochondrial *vs* non-mitochondrial nAChRs enhanced from 0.78 ± 0.06 to 1.09 ± 0.08. Nicotine facilitated glycosylation of liver nAChRs: the non-mitochondrial a7 nAChR subunits contained more sialic acid, while mitochondrial a7 nAChRs were extra fucosylated compared to corresponding nAChRs of control mice. Finally, mitochondria of nicotine-consuming mice released more cytochrome c in response to 0.05–0.1 μM Ca2+ and were less sensitive to protective effects of a7 nAChR agonist PNU282987 and positive allosteric modulator PNU120956.

It is concluded that nicotine-induced extra-glycosylation facilitates the nAChR targeting to mitochondria but makes the nAChR molecules less susceptible to the binding or effects of specific ligands.

P.2.1-005
Glutamate transport systems in the spinal cord: new mechanistic targets for pharmacological modulation of excitatory signalling

G. Gegelashvili
School of Natural Sciences and Engineering, Institute of Chemical Biology, Ilia State University, Tbilisi, Georgia

High-affinity glutamate transporters, GluTs (GLAST / EAAT1, GLT1 / EAAT2, EAAC1 / EAAT3, and EAAT4), as well as glutamate/cystine exchanger, xCT, are differentially expressed in sensory neurons, dorsal root ganglia (DRG) and surrounding glial cells in the spinal cord. Several pharmacological agents, believed to affect GluTs, including therapeutically promising new compounds, have been studied in co-cultures of DRG neurons and spinal glial cells. In such *in vitro* model system, that partially

recapitulates primary pain signaling path, both glial and neuronal GluTs and xCT undergo expressional changes, as well as post-translational modifications. Thus, for the first time, altered expression of a rare splice variant, GLT1c, has been demonstrated, both in rat and human spinal astroglia. Direct signaling through GluTs, a phenomenon recently reported by us, was also found to be involved in the modulation of pain signaling. Thus, physiological doses of some pro-nociceptive agents (e.g. capsaicin, cytokines) activate pro-apoptosis proteases, caspases, that precisely cleave spinal GluTs at their cytoplasmic C-terminal domains, but do not cause cell death. Both truncated C-terminal domains and bioactive peptides produced by the caspase-dependent cleavage functionally interact with other cytoplasmic or nuclear signaling complexes participating in aberrant pain signaling. For example, soluble C-terminal fragments of EAAT4 interfere with protein translation machinery via phosphorylation of PHAS1, and thus modulate the quantity of active GluT molecules in DRG neurons. In case of GLAST, C-terminus functionally interacts with the modulatory FXYD2/ gamma-subunit of Na+, K+ ATPase in spinal astrocytes and thus provides its targeting to the cell surface, while protelolytic cleavage reverses this process. The elucidated bioactive agents and regulatory pathways affecting glutamate signaling in the spinal cord can thus emerge as prospective drug prototypes/therapeutic targets.

P.2.1-007
Production of functional Kir1.1b channels in protein-lipid nanodiscs

A. Kielbasa, M. Krajewska, P. Koprowski, A. Szewczyk
Nencki Institute of Experimental Biology, Warsaw, Poland

Inwardly rectifying (Kir) potassium channels share similar topology with only two transmembrane helices per subunit and a large cytoplasmic C-terminus that tetramerizes into a cage that binds various ligands (e.g. phosphatidylinositol 4,5-bisphosphate, ATP or G-proteins) to regulate channel activity. Kir1.1b is a splice variant of KCNJ1 gene, which forms mitochondrial potassium channel inhibited by ATP (mitoK_{ATP}). Since mitoK_{ATP} resides in the mitochondrial inner membrane, it provides a potential way to regulate mitochondrial membrane potential and ROS production. Studies on mitoK_{ATP} are difficult due to very low amount of protein that could be obtained from mitochondria. We attempted to produce mitoK_{ATP} in lipid-protein membrane nanodiscs. These nanodiscs are build of truncated forms of apolipoprotein (apo) A-I which wrap around a patch of a lipid bilayer to form a disc-like particles, which allow for cotranslational insertion of membrane proteins into native environment. We were able to produce Kir1.1b channels i*n vitro* as native tetramers in membrane nanodiscs indicating for proper channel assembly.