ML-09.04.4-002
Serum glycomarkers of endoplasmic reticulum stress and lysosomal-endosomal functional disturbances in cardiovascular diseases

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Ischemia and hypertension cause stress of intracellular organelles leading to a disruption of their functions. The hallmark of the endoplasmic reticulum stress is alteration of protein homeostasis. This organelle triggers unfolded protein response to restore cellular homeostasis, in particular through activation of endoplasmic reticulum-associated degradation (ERAD) of misglycosylated and /or misfolded proteins. ERAD is one of the main intracellular sources of free oligosaccharides (FOS), unbound structural analogues of glycans of glycoconjugates. The lysosomal-endosomal degradation of glycoconjugates is a different source of their appearance. FOS structures and their alterations may reflect functional status of these organelles. Free oligosaccharides in plasma obtained from patients with cardiovascular diseases, before and after standard treatment, were investigated to evaluate this idea.

After plasma deproteinization and FOS purification the oligosaccharides were labeled with anthranilic acid, separated into the neutral and charged fractions with ion-exchange chromatography. FOS were analysed using high-performance liquid chromatography (HPLC).

HPLC profiles of FOS revealed a changing pattern of heterogeneity, depending on the severity of the disease.Three main enlarged glycan species in the neutral fraction and one peak in the charged fraction distinguished the FOS of the patients from those of the healthy volunteers. After treatment, the spectrum changes were observed in neutral fractions. The depth of these changes had individual features but a full profile recovery was not observed. There was no impact of the treatment on the charged fraction. That might indicate a stress prolongation of endosomal-lysosomal system in spite of the therapy.

The study of free oligosaccharides of blood plasma is a new field of Glycobiology allowing a non-invasive evaluation of an organism state at the level of the cell organelle functional status in norm and different diseases.

Thursday 8 September
9:00–11:00, Hall A

Intracellular organization

S-02.05.5-001
Microfilamanents dynamics and role in cell morphogenesis and migration

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The apex of intestinal epithelial absorptive cells is covered by a remarkable array of well-ordered finger-like membrane protrusions supported by an organized bundle of actin filaments. These microvillus arrays are settled on a complex terminal web area. Together they form the brush border, a functional unit specialized for secretion and absorption of salts and nutrients.. Rather than a structural entity of enterocytes, the brush border represents a crucial dynamic interface that modulates gut homeostasis. This exceptional structure implies the existence of precise regulatory mechanisms to control its assembly and dynamics. We will focus on molecular determinants involved in the regulation of enterocyte brush border morphogenesis. In addition, we will discuss the consequences of brush border misorganization and loss of integrity during wounding or due to pathogenic, inflammation and gentic disorders.

S-02.05.5-002
Biomechanical control of tissue morphogenesis

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Epithelial tissues exhibit a remarkable dual property of robustness and fluidity. This operates on different time scales and relies on unique mechanical properties of the cell cortex and on adhesive interactions between cells. We seek to understand the fundamental molecular mechanisms responsible for this property.

To that end we develop a range of approaches, from the genetic and pharmacological perturbations of molecular components, the quantitative imaging of proteins using a variety of photonic methods, probing of the physical properties of cells within intact tissues, and computational modelling of morphogenesis at different scales (molecular to tissue scales).

I will present our recent progress in understanding how adhesion and cortical tension control the dynamic remodelling of cell contacts in the primary epithelium of *Drosophila* embryos. I will also report recent findings delineating a novel GPCR signalling pathway responsible for the spatial regulation of cortical tension by the Rho1 pathway during tissue invagination and tissue extension.

S-02.05.5-003
VE-cadherin modulates YAP intracellular localization and signalling

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Besides promoting endothelial cell-to-cell adhesion, Vascular Endothelial (VE)-cadherin transfers intracellular signals contributing to vascular haemostasis. Signalling through VE-cadherin requires association and activity of different intracellular partners including beta catenin, p120 and many others. YAP/TAZ transcriptional co-factors are important regulators of cell growth, organ size, contact guidance and *intercellular junction* organization.

We found that EPS8, a signalling adapter regulating actin dynamics and the architectural organization of the cytoskeleton, is a novel partner of VE-cadherin and is able to modulate YAP transcriptional activity. By biochemical and imaging approaches in cultured endothelial cells we found that EPS8 associates to VE-cadherin in early confluent monolayers, when junctions are under remodelling.

Eps8 exerts a dual role: i) It binds to VE-cadherin and, by increasing its turnover, causes inhibition of PI(3)K-signalling and prevents, in this way, YAP phosphorylation and inactivation; ii) It directly interacts with α-catenin competing for the binding of the latter protein to 14-3-3/YAP complex, thus promoting YAP translocation to the nucleus and transcriptional activation. Junctional association of YAP inhibits nuclear translocation and inactivates its transcriptional activity both *in vitro* and *in vivo* in Eps8 null mice. Collectively, our data identify novel components of the adherens junction complex and introduce a new molecular mechanism through which AJ complex controls YAP transcriptional activity.

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