

vivo into athyroid mice, substantial reconstitution of functional thyroid tissue was observed at the grafting site. Moreover, athyroid mice grafted with follicular organoids displayed normalization of thyroid hormone plasma levels as well as symptomatic recovery.

S6-C2

Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions

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The primary central regulator of the hypothalamic-pituitary-thyroid (HPT) axis is the thyrotropin-releasing hormone (TRH), a tripeptide amide that functions as a neurotransmitter but also serves as a neurohormone. Hypophysiotropic TRH neurons involved in this neuroendocrine process are located in the hypothalamic paraventricular nucleus and secrete TRH into the pericapillary space of the external zone of the median eminence for conveyance to anterior pituitary thyrotrophs. The released TRH controls the activity of thyroid gland through the regulation of TSH synthesis, glucosylation and release in the anterior pituitary. The activity of hypophysiotropic TRH neurons is regulated by the negative feedback effects of thyroid hormone to ensure stable concentration of circulating level of thyroid hormone. This mechanism involves complex interactions between hypophysiotropic TRH neurons and the vascular system, cerebrospinal fluid, and specialized glial cells called tanycytes. The set point of this feedback regulation, however, can be altered under certain conditions to adjust the circulating thyroid hormone concentration to the actual demand. This mechanism facilitates adaptation of the organism to changing environmental conditions, including the shortage of food and a cold environment. Circulating hormones, neuronal inputs and the tanycytes play critical role in this adaptation. Adverse conditions such as infection, also alter the feedback regulation of this axis, however, it is not completely understood whether the illness induced central hypothyroidism is an adaptive or maladaptive response.

S6-C3

Regulation of cell cycle by microRNAs and its implication in the pathogenesis of endocrine tumors

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Dysregulation of cell cycle has been implicated in the pathogenesis of various tumors including tumors originating from endocrine glands. MicroRNAs (miRNAs) are small

noncoding RNAs that negatively regulate gene expression. Their role has been demonstrated in the regulation of numerous physiological and pathophysiological processes including regulation of cell cycle.

Our group studied the pathogenesis of adrenal and pituitary tumors. Multi-omics approach was used for integrating data obtained from various high-throughput technologies including whole comparative genomic hybridization, gene, miRNA and protein expression data.

Our data revealed that both in adrenal and pituitary gland tumors a dysregulation of cell cycle by aberrant miRNA expression might have an important role in the pathogenesis of these tumors. In adrenocortical cancer dysregulation of the G2/M transition of cell cycle by aberrant mRNA and miRNA expression was confirmed. In pituitary tumors underexpression of Wee1 kinase and overexpression of CDC25 phosphatases (both key regulators of cell cycle G2/M transition) together with the opposite expression of their 3' UTR targeting miRNAs were demonstrated. In addition, CDC25A targeting miRNAs showed a strong negative correlation with tumor size suggesting that these miRNAs may have an important role in tumor growth.

Our data suggest that tumors of endocrine glands have differentially expressed miRNAs compared to their normal counterparts and these miRNAs are involved in the regulation of G2/M checkpoint of cell cycle.

S6-C4

The roll of microRNAs in preimplantation embryos and pluripotent stem cells

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MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate multiple biological processes. Increasing experimental evidence implies an important regulatory role of miRNAs during early embryonic development and in embryonic stem cell biology.

We analyzed the expression profile of pluripotency-associated miRNAs in rabbit embryos and embryonic stem-like (ES-like) cells. The rabbit specific ocu-miR-302, ocu-miR-290 clusters and three homologs of human C19MC cluster (ocu-miR-512, ocu-miR-520e and ocu-miR-498) were identified in rabbit preimplantation embryos and ES-like cells. Ocu-miR-498, ocu-miR-520e and ocu-miR-512-5p exhibited an interesting expression pattern, because gene cluster members are extensively expressed in extra-embryonic tissues.

The ocu-miR-302 cluster was highly similar to its human homolog, while ocu-miR-290 revealed a low level of evolutionary conservation with its mouse homologous cluster. The expression of ocu-miR-302 cluster members began at 3.5 dpc early blastocyst stage and they stayed highly expressed in rabbit ES-like cells. In contrast, high expression level of ocu-miR-290 cluster members was detected during preimplantation embryonic development, but low level of expression was found in rabbit ES-like cells. This results show that the expression of ocu-miR-302 cluster is characteristic for the rabbit ES-like cell, while the ocu-miR-290 cluster may play a crucial role during early embryonic development.

It has been recently demonstrated that miR-99a modulates TGF- β induced epithelial to mesenchymal transition. Therefore expression of ocu-miR-99a-5p and ocu-miR-125b-5p in epiblast cells of 6 dpc blastocysts might have a direct correlation with epithelial-mesenchymal transition of epiblast cells and formation of mesoderm cells prior to implantation. In the future we would like to examine the expression of ocu-miR-99a-5p and ocu-miR-125b-5p in epiblast cells compared to hypoblast and trophoblast cells in 6 day old rabbit embryos.

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S6-C5

Novel insight in the regulation of the brainrenin-angiotensin system and its connection with hypertension

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The hyperactivity of the brainrenin-angiotensin system (RAS) has been implicated in the development and maintenance of arterial hypertension (HTA). We first demonstrated that aminopeptidase A (APA) and aminopeptidase N (APN), two membrane-bound zinc metalloproteases, are involved in the formation and metabolism of brain angiotensin III (AngIII), respectively. Then, we designed the specific and selective APA and APN inhibitors, EC33 and PC18. By blocking in vivo brain APA and APN with these compounds, we showed that AngIII and not AngII, as established in the periphery, is one of the main effector peptides of the brain RAS, exerting a tonic stimulatory control over blood pressure (BP) in hypertensive rats. Central injection of EC33 blocks the formation of brain AngIII and normalizes BP in hypertensive rats, suggesting that brain APA may be potential therapeutic target for HTA treatment.

For a clinical use of APA inhibitors, we, therefore, designed 4,4'-dithio[bis[(3S)-3-aminobutyl sulfonic acid]] (RB150), a systemically active prodrug of EC33 obtained by disulfide bridge mediated dimerization. RB150, given orally in conscious DOCA-salt rats or spontaneously hypertensive rats (SHRs), crosses the intestinal, hepatic and blood-brain barriers, enters the brain, where it is cleaved by brain reductases, generating two active molecules of EC33 which inhibit brain APA activity, block the formation of brain AngIII and induce a marked and sustained decrease in BP. The RB150-induced BP decrease is due to a decreased vasopressin release in the blood circulation, which results in increased diuresis, thus reducing extracellular volume and to a decrease in sympathetic tone, leading to a reduction of vascular resistances. Furthermore, in SHRs, concomitant RB150 oral administration with enalapril, a systemic RAS blocker, potentiates the RB150-induced BP decrease. RB150 also named QGC001 was then evaluated in humans and Phase I clinical trials have shown that this compound is clinically and biologically well-tolerated in

healthy normotensive male subjects after a single oral dose up to 2,000 mg or after repeated doses up to 750 mg b.i.d. for 7 days.

RB150 is the first drug candidate of a new class of antihypertensive agents targeting the brain RAS, the clinical efficacy of which will be soon evaluated in hypertensive patients.

S6-C6

Mutation of the palmitoylation site of Estrogen Receptor ER α in vivo reveals tissue-specific roles for membrane versus nuclear actions

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Estrogen Receptor alpha (ER α) activation functions AF-1 and AF-2 classically mediate gene transcription in response to estradiol (E2). A fraction of ER α is targeted to plasma membrane and elicits membrane-initiated steroid signalling (MISS), but the physiological roles of MISS in vivo are poorly understood. We therefore generated a mouse with a point mutation of the palmitoylation site of ER α (C451A-ER α) to obtain membrane-specific loss-of-function of ER α .

The abrogation of membrane localization of ER α in vivo was confirmed in primary hepatocytes, and it resulted in female infertility with abnormal ovaries lacking corpora lutea and increase in luteinizing hormone levels. In contrast, E2 action in the uterus was preserved in C451A-ER α mice and endometrial epithelial proliferation was similar to wild-type. However, E2 vascular actions such as rapid dilatation, the acceleration of endothelial repair and endothelial NO synthase phosphorylation were abrogated in C451A-ER α mice. A complementary mutant mouse lacking the transactivation function AF-2 of ER α (ER α -AF2^o) provided selective loss-of-function of nuclear ER α actions. In ER α -AF2^o, the acceleration of endothelial repair in response to estrogen-dendrimer conjugate, which is a membrane-selective ER ligand, was unaltered, demonstrating integrity of MISS actions. In genome-wide analysis of uterine gene expression, the vast majority of E2-dependent gene regulation was abrogated in ER α -AF2^o whereas in C451A-ER α it was nearly fully preserved, indicating that membrane-to-nuclear receptor crosstalk in vivo is modest in the uterus.

Thus, this work is the first to genetically segregate membrane versus nuclear actions of a steroid hormone receptor and to demonstrate their in vivo tissue-specific roles.

BÉKÉSY GYÖRGY ROOM

10:15-12:15

S6-C Basic Research Meets Clinical Endocrinology

Chairs: **Károly Rácz**, *Hungary* and **Attila Patócs**, *Hungary*

10:15 S6-C1

Organogenesis in a petridish - How to generate functional thyroid tissue from mouse embryonic stem cells

Robert Opitz

IRIBHM, ULB Brussels, *Belgium*

10:40 S6-C2

Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions

Csaba Fekete

Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, *Hungary*

11:00 S6-C3

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Attila Patócs

Semmelweis University, Budapest and MTA-SE „Lendület” Hereditary Endocrine Tumors Research Group, Hungarian Academy of Sciences, *Hungary*

11:20 S6-C4

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11:40 S6-C5

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12:00 S6-C6

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12:15

BREAK



27-30 August

Budapest, Hungary

**Joint Meeting of the
Federation of European Physiological
Societies (FEPS)
and the Hungarian Physiological Society**



PROGRAMME



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