

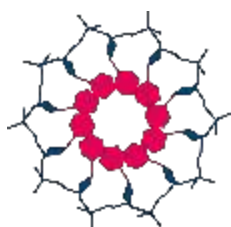
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ment of a functional tumor-associated stroma. In this talk, I present data strongly suggesting the pro-tumorigenic effect of HOFI by a complex mechanism that includes regulation of endothel cell functions, cell proliferation and the immune compartment of tumor-associated stroma. This work was supported by grants from the Hungarian Research Fund OTKA K 109444 (Hungarian Academy of Science), and by the Romanian Ministry of Education, Executive Agency For Higher Education, Research, Development and Innovation Funding, PNCDI II, project no. 119/2014. PN-II-PT-PCCA-2013-4 1583.

E3-2

The emerging role of Ring1 and Yy1 binding proteins in stem cell differentiation

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Polycomb Repressive Complexes (PRCs) are transcriptional repressors that control stem cell identity, differentiation and tumorigenesis. Their activity is divided between two multi-protein complexes called PRC1 and PRC2. The notion of the polycomb recruitment is that there is a strict hierarchical order, where PRC2 recruits PRC1 to initiate chromatin compaction and gene repression. From past years this hypothesis was turned upside-down by showing that the recruitment of PRC1 can occur also independently of PRC2. Recent findings also described the presence of alternate, canonical and non-canonical PRCs, which opened up a number of interesting new questions in this field. Polycomb-group Ring1 and Yy1 Binding Protein (Rybp) are newly discovered components of the recently identified non-canonical PRC1 complex (nc-PRC1) and the role of Rybp in this context is unknown. Work from our laboratory has demonstrated that Rybp itself is essential for mouse embryonic development since *rybp homozygous null (KO)* mouse embryos die at the time of implantation. Furthermore, *rybp KO* embryonic stem (ES) cells have limited developmental potential; they can not form beating cardiomyocytes (CMCs) and mature neuronal cell types *in vitro*. Our findings demonstrate that Rybp is essential for embryonic development, the proper execution of differentiation and its function can not be compensated by other PRC1-related complexes. Current results and possible mechanisms of Rybp action in PcG recruitment, lineage commitment during embryonic development and disease conditions will be addressed. This work was supported by TÁMOP-4.1.1.C-13/1/KONV-2014-0001 and TÁMOP-4.2.6.A-15/1-2015-0002.

E3-3

E3-deficiency mediated by the pathogenic mutations of the human dihydrolipoamide dehydrogenase (hE3): elucidation of the molecular pathomechanism by a multifaceted structural approach

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The α -ketoglutarate dehydrogenase complex (KGDHc) represents a rate-limiting step in the Krebs cycle catalyzing the oxidative decarboxylation of α -ketoglutarate while generating succinyl-CoA and NADH. The KGDHc is one of the major generators of oxidative stress in the mitochondrion under pathological conditions; malfunctioning of and reactive oxygen species (ROS) generation by KGDHc are implicated in the progression of senescence/aging, neurodegenerative diseases, ischemia-reperfusion, hypoxia- and glutamate-induced cerebral damage, E3-deficiency, among others. ROS generation by KGDHc is attributed to the homodimeric flavoenzyme E3 component, which is also part of the pyruvate dehydrogenase complex (PDHc) and selected other dehydrogenase complexes. Pathogenic mutations of hE3 (h for human) lead to an inherited, often lethal disease known as E3-deficiency; the clinical course of E3-deficiency is greatly diversified and often involves cardiological and/or neurological symptoms. Selected pathogenic mutations of hE3 stimulate the ROS generation by hE3 and hKGDHc or impair the recruitment of hE3 to the harboring complexes, which are likely to be important factors in the respective molecular pathogenesis. Structural alterations of the 14 pathogenic variants of hE3 and their role in the respective molecular pathogenesis have been investigated in our laboratory by a multifaceted structural approach, which involves CD spectroscopy, MD simulation, H/D-exchange mass spectrometry, electron microscopy and x-ray crystallography. The biophysical approaches are accompanied by biochemical assays for assessing *i.*, FAD-content, *ii.*, superoxide- or H₂O₂-generating capacities and enzymatic activities in the forward or the reverse catalytic directions as a function of pH, *in vivo* effectors or reconstructing with other recombinant hPDHc or hKGDHc components (E1, E2), and *iii.*, monomerization *via* calibrated size-exclusion chromatography coupled to nano-LC MS. Funding: OTKA, NAP, MTA.