COLLOQUIA IN CELLULAR SIGNALLING

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**".
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Friday **06.12.2013 11:00 s.t.** **Klaus Groschner** **(host: Th. Stockner)**

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"From understanding of TRPC3 structure-function relations towards novel therapeutic concepts "

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Abstract: TRPC3 is a lipid-regulated member of the family of canonical transient receptor potential channels. TRPC3 forms nonselective cation channels that generate Ca^{2+} signals crucially involved in maladaptive remodeling of the cardiovascular system. Consequently, these nonselective channels have been suggested as a potential target for therapeutic intervention. Our recent attempts to uncover structure-function relations within the TRPC3 pore complex led to the development of genetic tools, suitable for identification of specific molecular functions of TRPC3 in native cells (Lichtenegger et al., 2013). We identified TRPC3 as a multifunctional signaling molecule in cardiovascular cells that determines excitability, contractility as ell as Ca^{2+} transcription coupling. TRPC3 channels are proposed to generate dynamic alterations in Ca^{2+} and Na^{+} levels in the vicinity of the Na^{+}-Ca^{2+} exchanger (NCX1), thereby governing myocyte Ca^{2+} loading, excitability and contractility. Moreover, regulated targeting of calcineurin into TRPC3 complexes was uncovered as a key mechanism of transcriptional control hypertrophic remodeling (Poteser et al., 2011). By use of recently availability selective pharmacological tools, we confirmed the pathophysiological significance of TRPC3 in myocytes, and provided a first prove of concept, demonstrating efficient prevention of mechanical stress-induced vascular remodeling of human arteries by inhibition of TRPC3 activity (Koenig et al., 2013). Therapeutic perspectives of the recent gain in knowledge on molecular pathophysiology and pharmacology of TRPC3 will be discussed.

Koenig S, Schernthaner M, Maechler H, Kappe CO, Glasnov TN, Hoefler G, Braune M, Wittchow E, Groschner K. 2013. A TRPC3 blocker, ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-c arboxylate (Pyr3), prevents stent-induced arterial remodeling. J Pharmacol Exp Ther 344(1):33-40.

Lichtenegger M, Stockner T, Poteser M, Schleifer H, Platzer D, Romanin C, Groschner K. 2013. A novel homology model of TRPC3 reveals allosteric coupling between gate and selectivity filter. Cell Calcium.

Poteser M, Schleifer H, Lichtenegger M, Schernthaner M, Stockner T, Kappe CO, Glasnov TN, Romanin C, Groschner K. 2011. PKC-dependent coupling of calcium permeation through transient receptor potential canonical 3 (TRPC3) to calcineurin signaling in HL-1 myocytes. Proc Natl Acad Sci U S A 108(26):10556-10561.