**The Tumor Suppressor Gene Tip30 Supports Cardiac Compensation During Overload and Inhibits Myocardial Protein Synthesis**

Andrea Grund, Malgorzata Szaroszyk, Mortimer Korf-Klingebiel, Christopher Tiedje, Matthias Gaestel, Sandor Batkai, Thomas Thum, Medische Hochschule Hannover, Hannover, Germany; Andreas Jungmann, Ralf Bauer, Univsklinikum Heidelberg, Heidelberg, Germany; Xiaoke Yin, Manuel Mayr, King`s Coll, London, United Kingdom; Kai C. Wollert, Andreas Pich, Medische Hochschule Hannover, Hannover, Germany; Hua Xiao, Michigan State Univ, East Lansing, MI; Hugo A. Katus, Univsklinikum Heidelberg, Heidelberg, Germany; Johann Bauersachs, Medische Hochschule Hannover, Hannover, Germany; Oliver J Müller, Univsklinikum Heidelberg, Heidelberg, Germany; **Joerg Heineke**, Medische Hochschule Hannover, Hannover, Germany

**Background:** Here, we examined the currently unknown cardiac expression and function of Tip30, which has previously emerged as a tumor suppressor gene.
**Results:** Myocardial TIP30 mRNA and protein were significantly upregulated in response to experimental transverse aortic constriction (TAC). TIP30 contributed to cardiac compensation, since a reduction of cardiac TIP30 in heterozygous Tip30 knock-out mice (HET) led to exaggerated hypertrophy and cardiac dysfunction compared to wild-type mice (WT) after TAC. In turn, TIP30 overexpression by an adenovirus in isolated neonatal cardiomyocytes or by an adeno-associated-virus (AAV9) in mouse hearts led to reduced hypertrophy after pro-hypertrophic stimulation in cells and reduced hypertrophy and improved cardiac function after TAC in mice. Interestingly, cardiac TIP30 levels were strongly diminished in mouse models of genetic cardiomyopathy (mdx mice) and in endstage human cardiomyopathy. Reduced cardiac TIP30 contributed to disease progression, since reconstitution of myocardial TIP30 via AAV9 in mdx mice prevented hypertrophy and improved cardiac function. A protein interaction screen and subsequent characterization showed that TIP30 interacts with the middle domain of the eukaryotic translation factor 1A1 (eEF1A1). As revealed by immunoprecipitation and in situ proximity ligation assay, the cellular interaction of eEF1A1 and its essential cofactor eEF1B was diminished by TIP30 overexpression, but enhanced in cardiomyocytes isolated from HET mice after pro-hypertrophic stimulation. Because eEF1A1 is a crucial mediator of translational elongation, we hypothesized that TIP30 regulates cardiac hypertrophy by interfering with protein synthesis. Indeed, overexpression of TIP30 inhibited cardiac protein synthesis during pro-hypertrophic stimulation, while reduced TIP30 levels in HET (vs. WT) mice triggered enhanced protein synthesis after TAC. Interestingly, administration of the eEF1A1 inhibitor narciclasine ablated the increased hypertrophy in HET mice after TAC.
**Conclusion:** TIP30 inhibits protein synthesis by binding to eEF1A1 and inhibiting its interaction with eEF1B. It thereby reduces pathological hypertrophy and supports cardiac compensation during overload.

Disclosure Block:
**A. Grund:** None. **M. Szaroszyk:** None. **M. Korf-Klingebiel:** None. **C. Tiedje:** None. **M. Gaestel:** None. **S. Batkai:** None. **T. Thum:** None. **A. Jungmann:** None. **R. Bauer:** None. **X.**

**Yin:** None. **M. Mayr:** None. **K.C. Wollert:** None. **A. Pich:** None. **H. Xiao:** None. **H.A. Katus:** None. **J. Bauersachs:** None. **O.J. Müller:** None. **J. Heineke:** None.