singly used in antimutual therapies and mTOR inhibition with rapamycin was shown to be cardioprotective during aging and cardiac stress. Studies in genetic mice models have shown that mTOR is essential for heart development and cardiac function in adult. However, mTOR functions during postnatal cardiac development are not fully elucidated. We have therefore generated a cardiac-specific mTOR knockout mouse using α-MHC-Cre mice leading to mTOR inactivation in early postnatal mouse myocardium. The mutant mice develop a severe lethal dilated cardiomyopathy due to defects in cardiomyocyte growth, survival and subsequent fibrosis. In contrast to adult myocardium, both mTORC1 and mTORC2 activities are impaired in juvenile heart, as shown by hypophosphorylation of the translation initiation inhibitor 4E-BP1 and loss of the cardioprotective AKTS473 phosphorylation. We find that translation initiation defects and altered ribosome biogenesis both contribute to impaired cardiomyocyte growth. In addition, we show that increased apoptosis is associated with activation of JNK kinase and p53 accumulation. Moreover mTORcmKO hearts display a strong decreased expression of the primary oxygen carrier, myoglobin, and HIF1α accumulation suggesting hypoxia. However, mTORcmKO hearts do not display HIF1 hypoxic response consistently with mTOR being essential for HIF1-dependent transcriptional activity. These observations indicate that hypoxia-induced apoptosis likely contribute to DCM in mTORcmKO mice. Altogether, our results demonstrate that mTOR is a key regulator of cardiomyocyte growth, viability and oxygen supply in early postnatal myocardi. Our findings highlight potential cardiotoxicity of new mTOR inhibitors and the importance to set up optimal treatments in cardiology to both target mTOR hypertrophic functions and maintain adequate oxygen supply.

**0406**

Effects of FGF23 and Klotho on adult rat cardiomyocytes in culture

Hind Mehel (1), Véronique Mingué (1), Florence Lefebvre (2), David Bergerat (1), Gérard Friedlander (1), Rodolphe Fischmeister (2), Dominique Piqué (1)

(1) Hôpital Necker-Enfants Malades, Faculté de Médecine Paris Descartes, INEM U1151, Paris, France – (2) Université Paris Sud, Faculté de Pharmacie, INSERM U769, Chatenay-Malabry, France

The bone derived hormone fibroblast growth factor 23 (FGF23) and its coreceptor Klotho represent a novel endocrine axis regulating mineral metabolism in health and disease. FGF23-Klotho signaling inhibits renal phosphate reabsorption and activation of vitamin D, and reduces secretion of parathyroid hormone. Serum levels of FGF23 rise in chronic kidney disease (CKD). In contrast, tissue expression of Klotho decreases in parallel with CKD progression and reaches low or undetectable levels in end stage renal disease. Numerous studies identify elevated FGF23 as a predictor of adverse clinical outcome. In particular, elevated FGF23 has recently been associated with greater risks of major cardiovascular events and mortality.

However, there have been very few studies that have attempted to address the direct effects of FGF23 on myocardium. Moreover whether Klotho is involved in FGF23 – mediated actions on cardiomyocytes is still unclear.

In this context, we investigate the role of FGF23 and Klotho in adult rat ventricular myocytes (ARVMs). Using video-edge-detection, epifluorescent microscopy and an Ionoptix® system, performed in isolated cardiomyocytes subjected to FGF23 or Klotho alone, or in association, we showed that FGF23 increases cell size and cell shortening in ARVMs, and induces arrhythmia in the presence of Isoprenaline. In addition Klotho prevents FGF23 effects on adult cardiomyocytes. Indeed, ARVMs subjected to Klotho showed marked protection from FGF23- induced hypertrophic responses and from FGF23- induced arrhythmias in the presence of Isoprenaline.

Altogether these preliminary data provide a direct evidence of the role FGF23 in adult cardiomyocytes and suggest that Klotho may have a beneficial effect in preventing adverse cardiovascular outcomes in patients with or without CKD.