PREP1 NEGATIVELY REGULATES VASCULAR FUNCTION THROUGH NITRIC OXIDE-MEDIATED PATHWAY

Ilaria Cimmino[1], Claudio Cerchione[2], Mariangela De Rosa[1], Michela Celardo[1], Carmine Del Giudice[3], Antonella Fiordelisi[3], Michele Ciccarelli[4], Guido Iaccarino[4,] , Pietro Formisano[1], Francesco Beguinot[1], Francesco Oriente[1]

1 URT-GDD, National Council of Research - Department of Translational Medicine, "Federico II" University of Naples, Naples, Italy; 2 Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Naples, Italy; 3 Department of Advanced Biomedical Sciences, "Federico II" University of Naples, Naples, Italy; 4 Department of Medicine and Surgery, University of Salerno, Salerno, Italy.

FIRST AUTHOR:
Ilaria Cimmino
Post graduate School in Clinical Pathology and Clinical Biochemistry
URT-GDD, National Council of Research - Department of Translational Medicine, "Federico II" University of Naples, 5, S. Pansini street, 80131 Naples, Italy
ilariacimmino@hotmail.it

- Thematic Area: 1. Diabetes
- Introduction: Diabetes is an indipendent risk factor for cardiovascular disease (CVD), individuals with diabetes have a 2-to 4-fold increased risk of myocardial infarction and stroke that accounts for over 65% of diabetic mortality. Endothelial dysfunction may play a primary role in the development of the vascular complication of type 2 diabetes. In particular, endothelial cells maintain the balance between vasodilation and vasoconstriction, through the production of vasodilator factors, such as Nitric oxide (NO) produced by eNOS which is regulated by several protein kinases on different specific sites. Moreover, epidemiological and clinical studies have shown consistent relationships between markers of inflammation and risk of cardiovascular events.

Prep1 is an homeodomain transcription factor known to play an essential role in hematopoiesis, development and metabolism. Previous studies carried out in our laboratory have indicated Prep1 as a key regulator of insulin signaling, glucose homeostasis and regulation of insulin-action in muscle and liver using a Prep1 heterozygous mouse (*Prep1*$^{i/+}$) which expresses only 55-57% of protein.

- Aim: In this study, we aimed to evaluated the role of Prep1 in the regulation of vascular function.
-Methods: Blood Pressure has been performed in WT and *Prep1i/+* mice using a pressure transducer catheter. NO production has been measured by a colorimetric assay. Aortas and Mouse aortic endothelial cells (MAEC), transfected with *Prep1* cDNA, were analyzed by Western blot and Real Time RT-PCR.
- Results: Prep1 deficiency in mice display a significant decrease of blood pressure, and a 40% decrease of residual vasoconstriction in *Prep1*$^{i/+}$mice upon phenylephrine stimulation compared to WT. Moreover, *Prep1*$^{i/+}$mice show a 20% increase of serum NO release, paralleled by a significant decrease of eNOSThr495 and an increase of eNOSSer1177 phosphorylation, compared to the WT mice. Experiments performed in MAEC cells overexpressing Prep1 have, in part, confirmed the data obtained *in vivo*, as NO production is strongly reduced. Moreover Prep1 overexpression leads to a significant increase of IL6, TNFα and IL1β compared to control cells.
-Conclusions: These data suggest Prep1 as a novel molecular determinant for a better knowledge of vascular complication of type 2 diabetes.