



ICGEB International SEMINAR PROGRAMME 2017

Wednesday, 24 May 2017 | 3:00 pm | ICGEB Seminar Room, W building | Padriciano, 99, Trieste, ITALY



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Peripartum cardiomyopathy (PPCM) is a life-threatening pregnancy-associated cardiomyopathy in previously healthy women driven in part by the anti-angiogenic 16kDa N-terminal prolactin fragment (16K PRL). The 16K PRL is generated from the nursing hormone prolactin by proteolytic cleavage via Cathepsin D and/or metalloproteases (MMP)-8, -13, -3, -1 and -2 in part as a response to unbalanced postpartum oxidative stress. The 16K PRL forms a complex with the plasminogen activator inhibitor-1 (PAI-1)/uPAR and thereby activates NF- κ B signaling in endothelial cells. Subsequently, miR-146a is upregulated in endothelial cells, which by down-regulating the target gene NRAS mediates anti-angiogenic effects. In addition, miR-146a-loaded exosomes are released from endothelial cells, which are absorbed by cardiomyocytes where they increase endogenous miR-146a levels and subsequently target proteins such as ErbB4 and Notch1. Down-regulation of ErbB4 signaling in the heart per se leads to heart failure. For Notch1, we showed that a cardiomyocyte-specific knockout of Notch1 causes peripartum heart failure indicating that the expression of both genes is essential for protection of the peripartum maternal heart. Complete prolactin blockade by the dopamin-2D agonist bromocriptine stops lactation, reduces circulating and cardiac miR-146a levels and prevents onset of disease in an experimental mouse model of PPCM (a cardiomyocyte-restricted knockout of Stat3, CKO). Blocking miR-146a with LNAs or antagomiRs attenuates PPCM in CKO mice but in contrast bromocriptine allows CKO females to nurse their offspring. Finally, PAI-1 and miR-146a are specifically elevated in plasma of PPCM patients and are decreased in patients recovered from PPCM after treatment with bromocriptine making them to potential disease specific diagnostic biomarkers as well as novel therapeutic targets for PPCM.

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“Pathophysiology of Peripartum Cardiomyopathy links Prolactin to the PAI-1/uPAR system: Modulation of NF- κ B signaling and miR146a as therapeutic options”

Host: M. Giacca

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