Involvement of the Trail-Trail/eceptors (Trail-r) system in the model of gestational diabetes (GD)

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TRAIL is a member of the TNF family of cytokines that influences many functions including cell death, immune response and inflammation[1]. In a previous study on cultured HUVEC we demonstrated that TRAIL is able to activate eNOS and to increase NO release and prostanoid production[1] that play a crucial role in endothelial cells function[2]. Since hyperglycaemia can result in endothelial injury, due to a decreased bioavailability of NO[3], we investigated the effects of TRAIL and nitric oxide synthase/nitric oxide (NOS/NO) related pathways on the endothelial cells function in umbilical cords derived from Gestational Diabetic women, as a model of chronic *in vivo* exposure to hyperglycaemia in humans. The expression of sTRAIL and TRAIL-Rs was evaluated on paraffin-embedded sections of umbilical cords obtained from 10 healthy pregnant women (controls) and 10 women affected with GD as well as on mononuclear cells purified from PBMC of 6 controls and 6 GD women. The labelling for sTRAIL, TRAIL-R1 and TRAIL-R2 was found significantly higher in GD umbilical cords (venous endothelial layer) as compared with controls ($p<0.05$). Interestingly, cytofluorimetric analysis of mononuclear cells showed an up-regulation of TRAIL-R2 ($p<0.05$) and sTRAIL as well as a down-regulation of TRAIL-R3 ($p<0.05$) in GD women. In parallel experiments, a more intense positivity of eNOS and nitrotyrosine labelling was observed in GD umbilical cords (venous endothelial layer) as compared with control women. In addition, *in vitro* experiments, performed on cultured HUVEC derived from 4 GD umbilical cords and 4 healthy controls, displayed a significant increase in early apoptotic cells (Annexin V positive) in GD women ($30.3\%\pm10.8$ vs $21.1\%\pm5.0$, $p<0.001$) after 1 h treatment with 1000 ng/mL TRAIL. Our study shows that chronic hyperglycaemia induces eNOS expression and increases protein nitrosylation, suggesting that under these conditions most of the NO synthesized in excess is converted into peroxynitrite. In light of both *ex vivo* and *in vitro* observations, we may hypothesize a role for the TRAIL/TRAIL-R system in this model.

References

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Key words
TRAIL, NOS/NO, endothelial function, hyperglycaemia, gestational diabetes