The role of endothelin and metalloproteinases in the first trimester placenta

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Introduction: Trophoblast invasion is crucial in early pregnancy in order to anchor the placenta and the fetus in the uterus and to establish adequate utero-placental blood flow by remodelling the spiral arteries. These processes are mediated by matrix degrading enzymes such as metalloproteinases (MMPs). Impaired invasion of trophoblasts has been implicated in severe pregnancy complications such as missed abortions, pre-eclampsia (PE) or fetal growth restriction (FGR). Increased levels of ET-1, a regulator of trophoblast invasion, were found in patients with PE and FGR. The present study tested the hypothesis that MMPs and their inhibitors (TIMPs) are expressed in the first trimester placenta and are modified by ET-1.

Methods: The human first trimester trophoblast cell line ACH-3P was cultured on various matrices (laminin, fibronectin, collagen-1, gelatine and uncoated plates) for five days and the expression of MMPs and TIMPs was determined by semiquantitative RT-PCR. Expression signals were normalized to the ribosomal protein L-30. Expression levels were compared in various human organs (placenta, heart, uterus, brain; Clontech No:636643) which served as positive controls. Cells (plated on gelatine) were incubated in the presence or absence of ET-1 (1-100 nM) for 24 hours and the expression of those MMPs and TIMPs that had shown highest expression in the previous experiments was determined. The activity of the gelatinases (MMP-2 and -9) in the supernatants was examined by gelatine-zymography.

Results: The different matrices did not effect the expression of MMPs and TIMPs. MMP-2, -14, -15 and -19 and TIMPs 1-4 showed the highest expression in ACH-3P cells. MMP-11 and MMP-24 were only weakly expressed. All other MMPs could not be detected. ET-1 (100 nM) caused a significant down-regulation in expression of MMP-14 (30%, p=0.03), -15 (25%, p=0.02), and -19 (8%, p=0.05) while TIMP-1 (39%, p=0.001), -2 (8%, p=0.05)), -3 (25%, p=0.05) and -4 (17%, p=0.04) were up-regulated. No significant changes in MMP-2 activity could be determined by gelatine-zymography of the cell supernatants.
Conclusion: ET-1 results in a disbalance of MMPs and TIMPs, their inhibitors, favoring invasion inhibiting enzymes. Therefore elevated levels of ET-1 may contribute to impaired trophoblast invasion observed in PE and FGR.

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