MACROPHAGE INHIBITORY CYTOKINE-1 AT THE MATERNAL–FETAL INTERFACE IN EARLY HUMAN PREGNANCY

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Macrophage inhibitory cytokine-1 (MIC-1) is a transforming growth factor-β (TGF-β) superfamily member, first isolated from activated macrophages and subsequently localised in the human placenta. We previously reported that decreased circulating levels in very early pregnancy are associated with subsequent miscarriage. We undertook these current *in vitro* studies to investigate possible roles for MIC-1 in early pregnancy: *(1)* regulation of placental matrix metalloproteinase-2 and -9 (MMP-2 and -9); *(2)* effect on placental apoptosis; and *(3)* regulation of endometrial stromal cell decidualisation. *(1)* First trimester placental explant cultures were treated with 100–200 ng/mL MIC-1 ± 1/1000 (v/v) anti-MIC-1 antibody. MMP-2 and -9 were measured by gelatin zymography. MMP activation via the plasminogen activation pathway was examined by measuring mRNA expression for urokinase plasminogen activator and its receptor (uPA, uPAR) and type-1 plasminogen activation inhibitor (PAI-1). *(2)* In first trimester trophoblast explants, apoptosis was induced *in vitro* with tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) ± 200 ng/mL MIC-1. The pro-apoptosis factor caspase-3 was localised by immunohistochemistry. *(3)* Using an established model of oestrogen and progesterone induced endometrial stromal cell decidualisation, MIC-1 production was measured and correlated with morphological changes. Cultures were also treated with 20 ng/mL MIC-1. MIC-1 treatment inhibited activation of both MMP-2 and MMP-9 while treatment with anti-MIC-1 antibody blocked the inhibition. uPA, uPAR and PAI-1 mRNA did not change with either treatment. MIC-1 treatment mitigated TNF-α/IFN-γ induced trophoblast apoptosis. MIC-1 production increased during induced decidualisation and MIC-1 treatment facilitates further decidualisation in this model. MIC-1 appears to have a number of potentially important functions in the human placenta and decidua consistent with physiological roles in normal placentation. Whether these functions are key to successful pregnancy remains to be studied.

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