The role of decidual macrophages in early human pregnancy

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Investigation of the role of decidual macrophages in spiral artery transformation in early human pregnancy and their involvement in trophoblast invasion

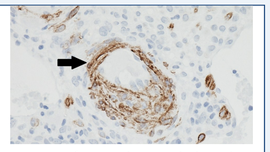
Aims

To determine whether MMP-2, MMP-9 and uPA are secreted by decidual macrophages in early pregnancy and whether this can be linked to extravillous trophoblast cell invasion and thus spiral artery remodelling

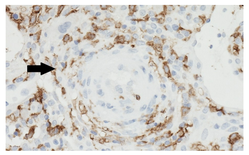
Background

Spiral artery remodelling is an essential processes that takes place in the early stages of human pregnancy to allow for sufficient blood flow to the fetus.

Previous work has highlighted the importance of immune cells in spiral artery remodelling and extravillous trophoblast (EVT) invasion. However, the mechanisms involved in this are still largely unknown.



Untransformed vessel showing vascular smooth muscle



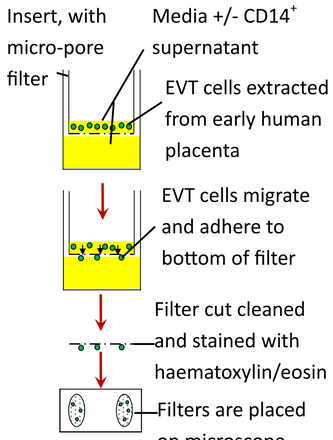
Untransformed vessel showing macrophage association

Methods

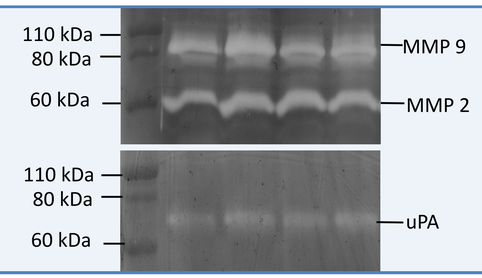
① MMP and uPA Zymograms

- Gelatin and casein zymogram gels were made.
- Decidual macrophage samples (11 'early' [8-10 wks] and 10 'late' [12-14 wks]) containing 10µg protein loaded with non-reducing buffer and subjected to electrophoresis. This was also done for 4 EVT samples.
- Gels were washed and then incubated overnight in 50mM Tris and 5mM $CaCl_2$.
- Gels were stained with 0.4% Coomassie blue and dried.
- Bands shown indicate zymogen activity.

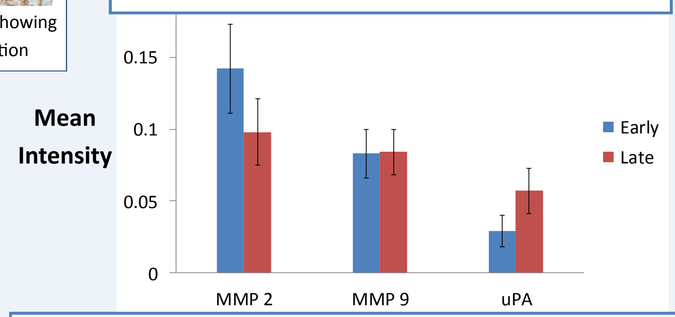
② EVT Invasion Assay



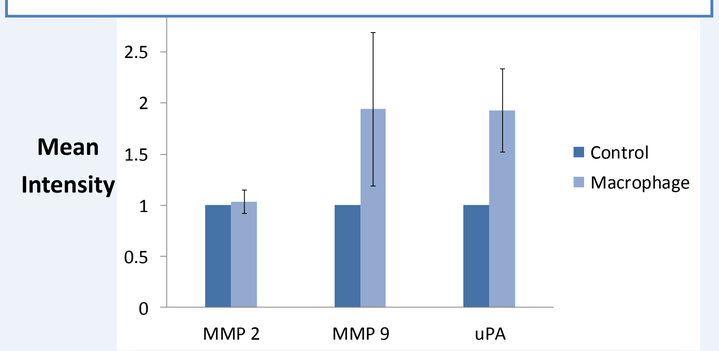
Scanned zymograms for (A) MMP and (B) uPA in the EVT invasion assay media show that these zymogens were present



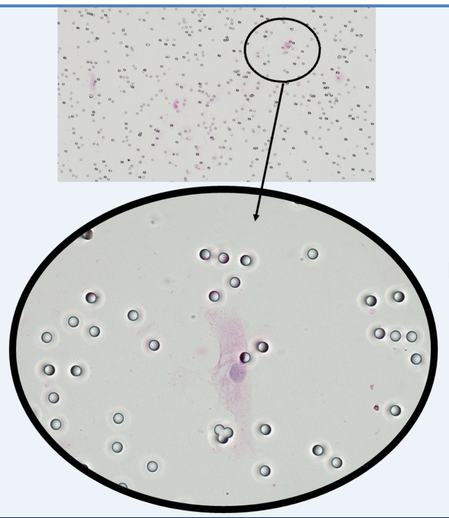
No significant difference between 8-10 wk and 12-14 wk decidual macrophage MMP 2, MMP 9 and uPA production



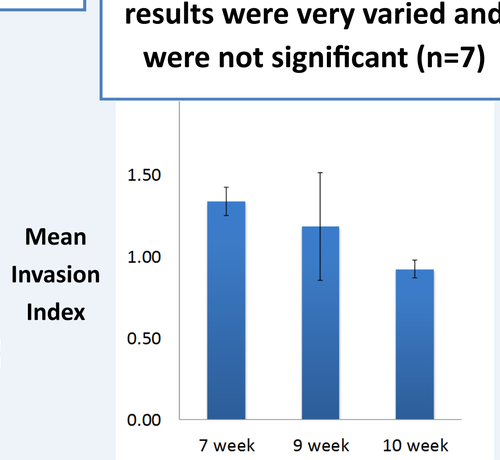
Decidual macrophage supernatant increased trophoblast production of uPA and MMP 9 but not significantly; no increase was seen for MMP 2



EVT cells were present in the invasion assays and migrated through the filter during the 48 hr incubation period



An invasion index >1 indicates stimulation of invasion; the results were very varied and were not significant (n=7)



Conclusion

- MMPs and uPA are secreted by decidual macrophages in early human pregnancy and the levels are not significantly altered by gestational age.
- Levels of uPA and MMP 9 increased when EVT cells were treated with decidual macrophage supernatants but this was not significant and did not significantly alter EVT invasion. We can speculate that uPA involvement is important as it works via a complex pathway which requires inhibitors and activators. These inhibitors could have been present/active which would have prevented the uPA from affecting EVT invasion.
- Assessment of the spiral arteries clearly showed that remodelling was linked to the invading EVT cells, which could be found in interstitial, intramural and endovascular locations.

Future Work?

Further investigation using the different MMPs would be beneficial as it is possible that other MMPs have different effects on EVT invasion and spiral artery remodelling. To form a strong conclusion, further studies would need to asses the presence/secretion of these inhibitors and determine whether they have an influence in preventing uPA from increasing EVT invasion.

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