Abstract: 46O

Transthyretin binds to soluble endoglin: a possible role for transthyretin in the prevention of preeclampsia?

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Background: Preeclampsia is a common but life-threatening pregnancy condition, affecting 5-8% of pregnancies worldwide. The condition presents as hypertension, proteinuria and edema in pregnancy. It is caused by poor placentation resulting in release of trophoblast material, including soluble endoglin (sEng), into the maternal circulation (Margioula-Siarkou G *et al.* 2022). sEng is proposed to bind to circulating transforming growth factor beta 1 (TGF-β1), blocking its normal functions, leading to maternal vascular dysfunction and ultimately to eclampsia, a life-threatening condition (Venkatesha S *et al.* 2006). The only cure is delivery of the placenta which can have lifelong consequences for the premature infant. The thyroid hormone binding protein transthyretin (TTR) is also dysregulated in preeclampsia, it is responsible for the transport of thyroid hormone and may also play a role in clearing endo- and xenobiotics from the circulation (Kalkunte *et al.* 2013).

Aim: To determine whether functional transthyretin binds to sEng and abrogate its negative effects by facilitating the removal of sEng from the maternal circulation.

Methods: Molecular dynamic simulations and molecular docking computational methods were utilised to predict if and how sEng and TTR interact. TTR was immobilised on CnBr-Sepharose beads and incubated with either recombinant sEng or protein lysates prepared from human placental tissue to confirm the interaction of TTR and sEng. Alexa-sEng was incubated with hepatocytes with and without TTR present to determine if TTR altered uptake of Alexa-sEng by cells.

Results: Molecular dynamic modelling predicted that a TTR dimer interacts with two individual sEng molecules. The interaction of sEng and TTR was confirmed by the binding of pure recombinant sEng, and also placental endoglin, to immobilised TTR. Alexa-sEng was endocytosed by hepatocytes and addition of TTR increased the uptake of Alexa-sEng.

Conclusion: Functional TTR may play a protective role in the pathogenesis of preeclampsia by binding to sEng and removing it from the maternal circulation.

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