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Role of HLA-G and other immune mechanisms in pregnancy

Mini-Review

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Abstract: Pregnancy loss (abortion) and pre-eclampsia represent the most common disorders in pregnant women. Besides infection, there are anatomical, endocrinological, genetic and immunological factors that can induce pregnancy disorders. Because the exact mechanisms of physiological pregnancy maintenance are still not clearly understood, the search for genes and proteins fulfilling this role is still in progress. One of the immune molecules that plays a beneficial role in pregnancy is the non-classical HLA-G molecule. The molecule is mainly expressed on trophoblast cells in the foetal placenta and induces the immune tolerance of the foetus *via* its interaction with inhibitory receptors on maternal NK cells and $CD8^+$ T lymphocytes. In relation to pregnancy disorders, associations between HLA-G polymorphism, HLA-G level and HLA-G function were described. Thus, the HLA-G molecule can be used as a new diagnostic marker and, potentially, for the future therapy of pregnancy disorders.

Keywords: *HLA-G • Immunity • Human genetics • Spontaneous abortion • Pre-eclampsia • Pregnancy*

1. Introduction

Spontaneous miscarriage and pre-eclampsia are major disorders appearing during pregnancy. Spontaneous miscarriage affects 50–60% of pregnant women and pre-eclampsia about 6-8%. It is also estimated that 1 to 3% of women may develop recurrent pregnancy loss (RPL). Its known etiologic factors are chromosomal anomalies, hormonal problems, uterine abnormalities, infections and immune disorders. Just impaired immune mechanisms account for the etiology of less than half of all cases of RPL [1]. Pre-eclampsia, another serious pregnancy complication, is a multisystemic disorder that is manifested by hypertension, proteinuria and abnormal blood clotting. Advanced clinical symptoms include seizures, renal failure, IUGR (intrauterine growth restriction) and/or HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome. Finally, generalized damage of the maternal endothelium, kidneys and liver can develop, leading to increased mortality risk for the mother as well as the foetus. The clinical symptoms of pre-eclampsia can be observed in the second or third trimester in pregnancy, and are the most common in primiparas [2]. Despite many research studies, the pathology of pre-eclampsia is not fully understood. One cause may originate in an insufficiently developed placenta, referred to as poor placentation. It is characterised by impaired remodelling of spiral arteries of the uterus (endothelial dysfunction) caused by an imbalance of circulating angiogenic factors. High circulating levels of soluble Fms like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng), a circulating receptor or TGF-β (both anti-angiogenic factors), and low levels of circulating vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (both pro-angiogenic factors) have been described [3]. VEGF is the main factor that supports angiogenesis. sFlt1 (a splice variant of VEGF receptor FLT-1) acts as a VEGF and PlGF antagonist by binding these molecules in the circulatory system and in target tissues such as those

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