COMMENT

CD81, a new actor in the development of preeclampsia

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CD81 is a widely expressed transmembrane protein that provides a scaffold for signaling molecules and orchestrates interactions among membrane-associated proteins to initiate signaling cascades related to cell migration, adhesion, and fusion¹. CD81 exerts a wide range of regulatory effects on immune cells. In B cells, CD81 facilitates the assembly of CD19-CR2/CD21 and B-cell receptor complexes at tetraspanin-enriched signaling microdomains, lowering the threshold dose of antigen required to trigger B-cell clonal expansion and antibody production. Moreover, CD81 strengthens multivalent VLA-4 contacts within subsecond integrin occupancy, thus promoting the adhesion of B cells to the vessel wall². In T cells, CD81 controls temporal progression of the immune synapse and the permanence of CD3 in the membrane contact area, contributing to sustained T-cell receptor-CD3-mediated signaling, which is important for T-cell activation³. In NK cells, the crosslinking of CD81 induces phosphorylation of the ezrin/radixin/moesin (ERM) protein, and CD81 colocalizes with phosphorylated ERM at the uropod, which is associated with increased cell polarization and migration toward chemoattractants⁴. With respect to the regulatory effect of CD81 on virus infection, CD81 participates in the cell-surface assembly of both human immunodeficiency virus and influenza A virus and is essential for the entry of hepatitis C virus into hepatocytes^{5–7}.

CD81 may also play important roles in early placentation. We demonstrated that CD81 is preferentially expressed in cytotrophoblast cell columns, and CD81 expression is gradually down-regulated in syncytiotrophoblasts and extravillous trophoblasts; CD81 is then barely expressed in these cells in the third trimester during normal pregnancy, so CD81 appears to act as a cytotrophoblast differentiation suppressor in placentation⁸. However, in patients with early-onset severe preeclampsia, CD81 expression is consistently upregulated in syncytiotrophoblasts and cytotrophoblasts, which results in increased CD81 levels in maternal plasma. This increase in plasma CD81 may mediate dysfunction of the endothelium and drive development of the maternal manifestations of preeclampsia⁸.

Maternal immune tolerance to the fetus is a prerequisite for a successful pregnancy. As an invader, the trophoblast plays an important role in inducing maternal-fetal tolerance⁹. Since preeclampsia is a typical disease of maternal immune intolerance to the fetus, we investigated the effect of CD81 upregulation in trophoblasts on T-cell differentiation. We found that CD81 promotes T-cell differentiation to Th17 cells and inhibits Treg differentiation¹⁰, indicating that overexpression of CD81 in trophoblasts contributes to the abnormal maternal-fetal-tolerant environment.

While we are beginning to understand the effects of CD81 on the pathogenesis of preeclampsia, further study is required to

clarify the association between CD81 overexpression in trophoblasts and other immune cells, such as decidual NK cells and macrophages, which play important roles in maintaining maternal-fetal tolerance, especially in regulating fetal growth^{11,12}. Moreover, transgenic mice with placenta-restricted high CD81 expression need to be constructed to explore the molecular mechanisms of CD81 in the development of preeclampsia. Clinically, whether the upregulation of CD81 in maternal circulation may serve as a biomarker to predict the occurrence of preeclampsia merits more exploration based on the development of quantitative CD81 assays with high sensitivity and specificity.

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ADDITIONAL INFORMATION

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