The role of adrenomedullin on placental development during early pregnancy and its association with early-onset preeclampsia

Zhang QQ, Lee CL, Duan YG, Yeung WSB, Chiu PCN
Department of Obstetrics & Gynaecology, Li Ka Shing Faculty of Medicine, The University of Hong Kong
Shenzhen Key Laboratory of Fertility Regulation, The University of Hong Kong-Shenzhen Hospital

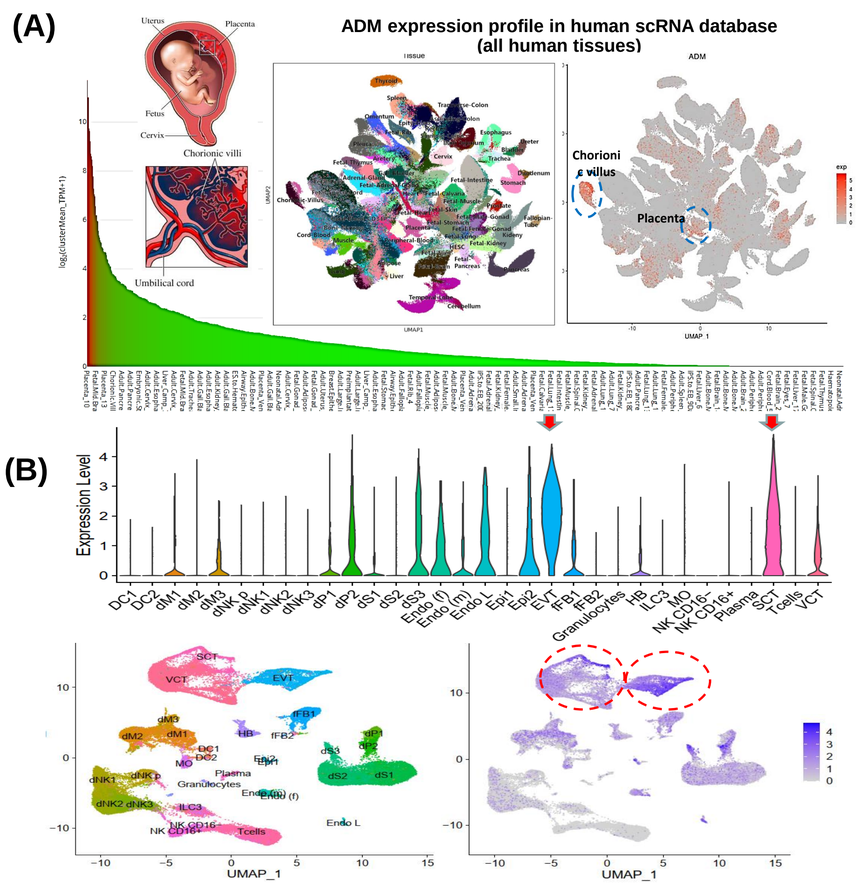
INTRODUCTION

Adrenomedullin (ADM) is a peptide hormone belonging to the calcitonin/calcitonin-gene-related peptide (CGRP)/amylin peptide family. In human, plasma ADM level is elevated after implantation and peaks in early pregnancy but is decreased at term, suggesting the involvement of the molecule in early placentation. However, the exact role of ADM on the functions of first trimester pregnancy is unknown. Pre-eclampsia (PE) is a common human pregnancy complication affecting 2-5% of pregnancies worldwide and is the leading cause of maternal mortality, preterm birth, and consequent neonatal morbidity and mortality. In this study, we hypothesis that ADM insufficiency may contribute to the pathophysiology of PE by altering trophoblast functions.

Hypothesis:

We hypothesize that adrenomedullin regulates the placental vascular remodeling process in humans by modulating the activities of trophoblast during early pregnancy and the down-regulation of adrenomedullin contributes to the pathophysiology of preeclampsia.

Results



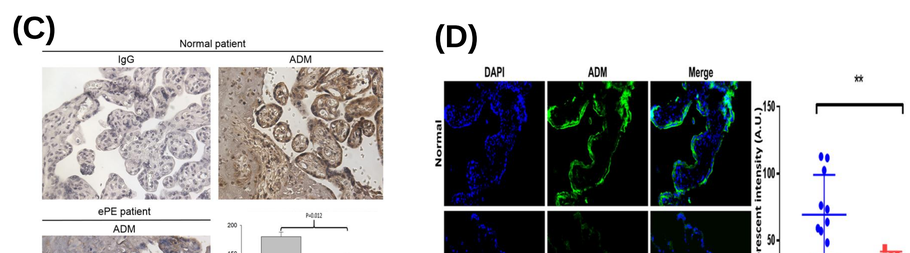


Figure 1: Reduced ADM expression in the term placenta and 1st trimester CVS sample in PE patients. (A) ADM expression profile in human scRNA database (all human tissues). (B) ADM expression profile in human scRNA database (maternal-fetal interphase). (C) Reduced ADM expression in the term placenta of ePE patients.(D) The expression of ADM was reduced in PE 1st trimester CVS tissue compare with normal pregnancy control.

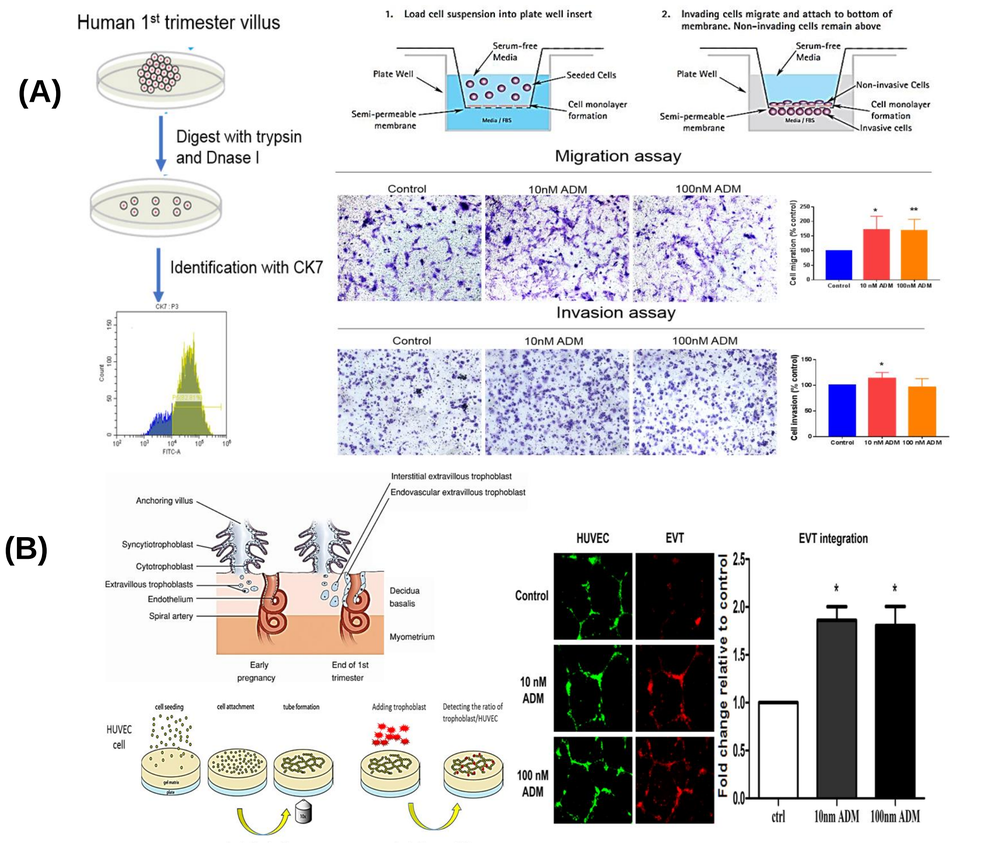
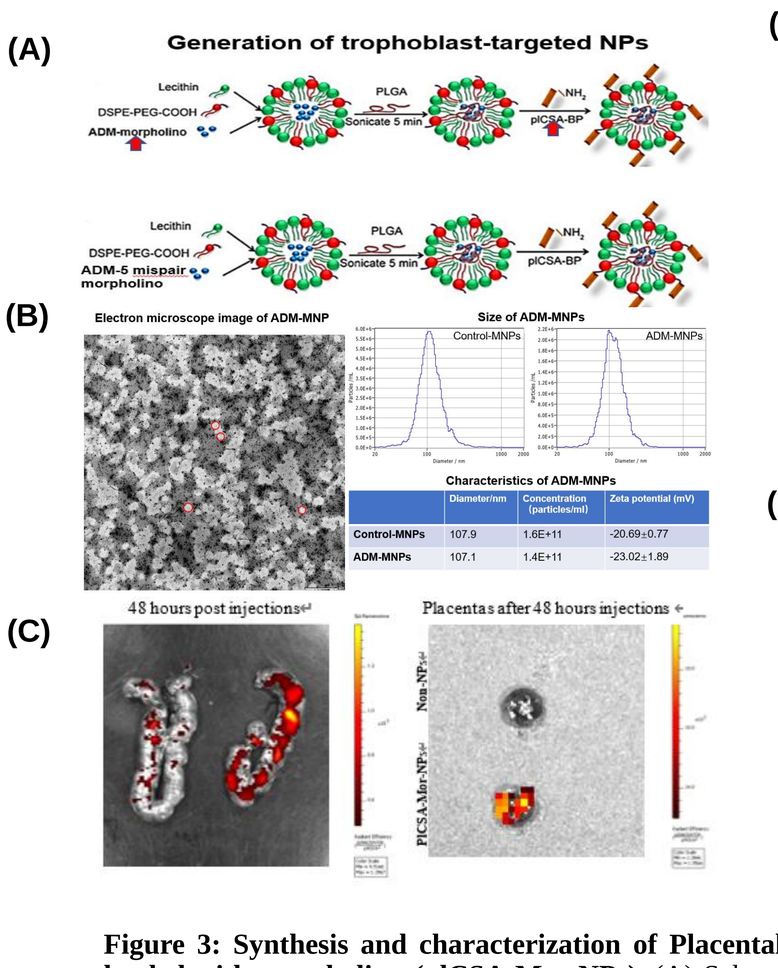


Figure 2: The effect of ADM *in vitro* study(A) ADM enhances migration and invasion of primary EVT. (B) ADM induces the EVTs to integrate along the endothelial lining of the tubes formed by endothelial (HUVEC) cells (C) ADM promotes angiogenesis of endothelial cells.(D) ADM diminishes endothelial permeability. ADM stabilized the endothelial barrier



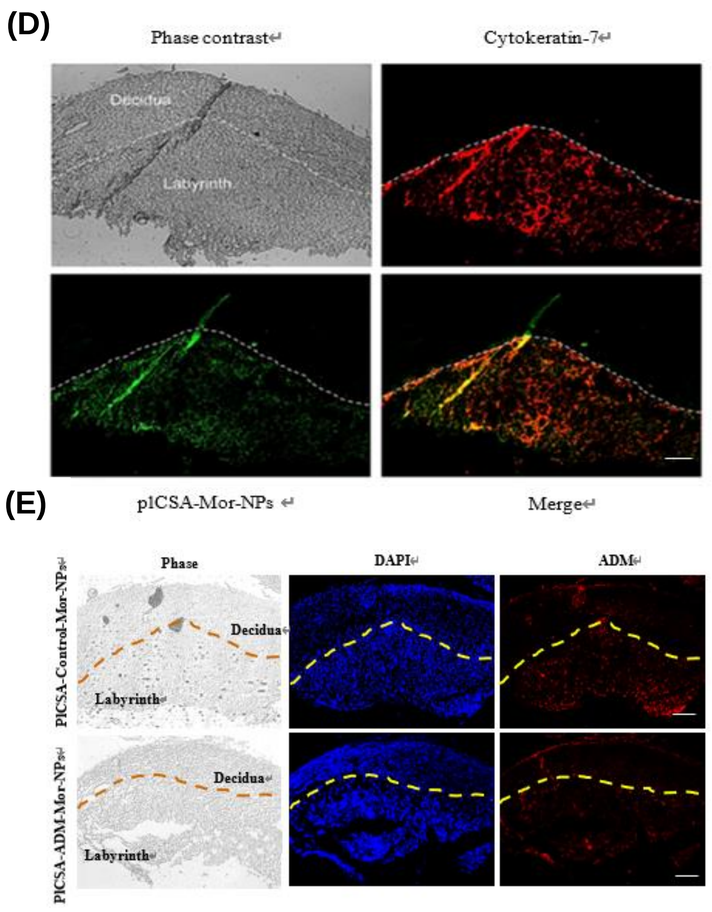


Figure 3: Synthesis and characterization of Placental Chondroitin Sulfate A (plCSA)-binding Nanoparticles loaded with morpholinos(plCSA-Mor-NPs). (A) Schematic illustration of placental chondroitin sulfate A (plCSA)-binding nanoparticles loaded with morpholinos(plCSA-Mor-NPs) used a single-step sonication method. (B)) Characterization of plCSA-Mor-NPs. (C) The carboxyfluorescein signal in uteri and placentas were detected by IVIS at E14.5.(D) The plCSA-Mor-NPs specifically targeted to mouse trophoblast *in vivo*.(E) The ADM expression was downregulated in the mouse placenta post plCSA-ADM-Mor-NPs injection.

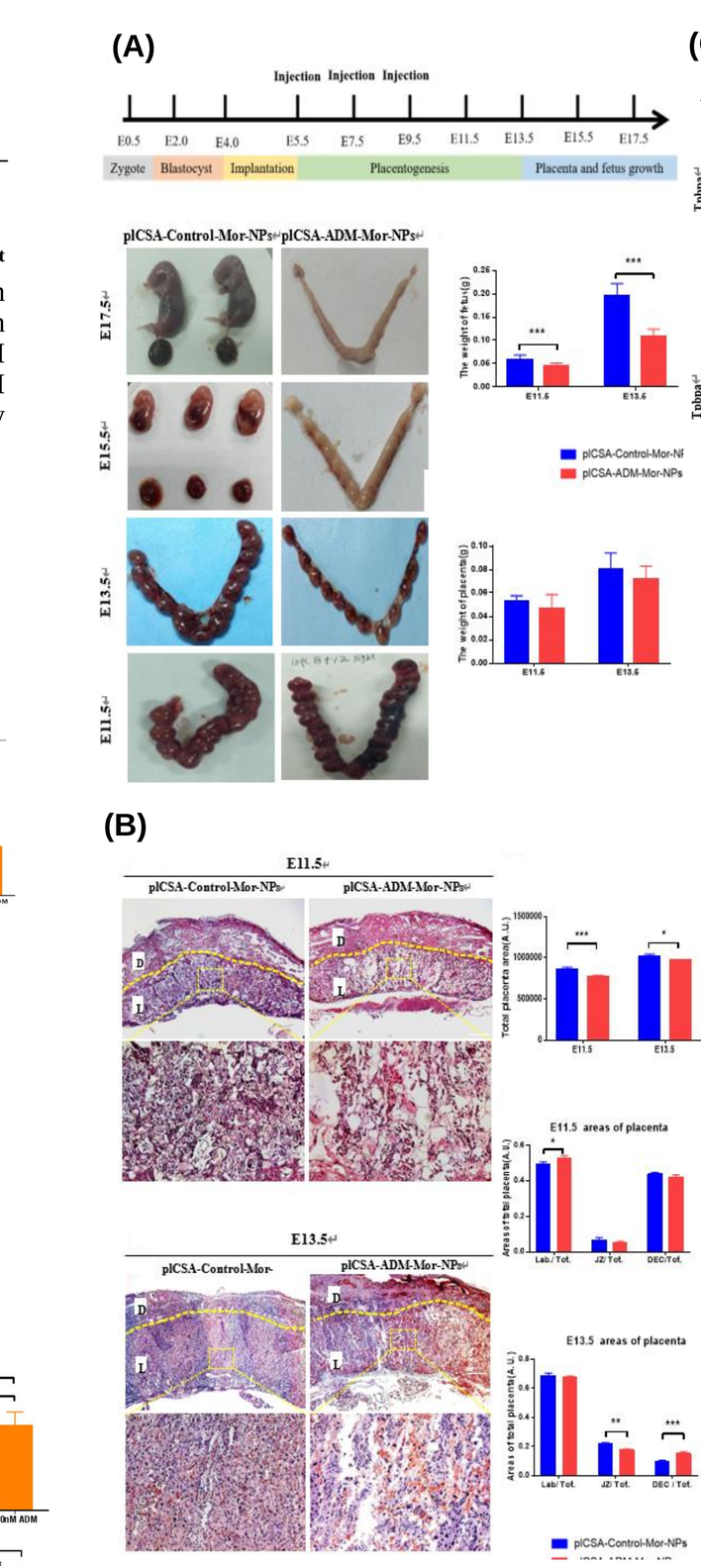


Figure 4: Trophoblast specific ADM knockdown increases the abortion rate and decreases embryo development. (A) Trophoblast-specific ADM knockdown induced adverse pregnancy outcome in mice. (B) Trophoblast-specific ADM knockdown induced adverse pregnancy outcome in mice. (C) Loss of ADM hampered the development of glycogen trophoblast cells and spongiotrophoblast . (D) 8ADM knockdown reduced differentiation of syncytiotrophoblast II . (E) ADM knockdown reduced fetal blood formation in the labyrinthine zone. (F) Summary of trophoblast specific ADM knockdown *in vivo* model. (n=3 each, *p<0.05 **p<0.01, ***p<0.001)

SUMMARY

Reduced expression of ADM in first trimester and term placental tissues of PE patients. Our data further revealed that ADM regulates the trophoblast migration, invasion and integration into the endothelial network in vitro. Consistently, poor placental angiogenesis and increased abortion rate in pregnant mice were demonstrated to be associated with the trophoblast-specific knockdown of ADM in vivo. This study provides the first genetic evidence to our knowledge to suggest that a modest reduction in human trophoblast specific ADM expression during pregnancy may have an unfavorable impact on reproduction.

ACKNOWLEDGMENT

This work was supported in part by grants from the Health and Medical Research Fund (Project code: 02131786).