PP13, Decidual Zones of Necrosis, and Spiral Artery Remodeling—Preeclampsia Revisited?

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Placental protein 13 (PP13) is predominantly produced by the syncytiotrophoblast, which secretes this placenta-specific galectin (galectin 13) into the maternal circulation. PP13 expression is decreased in severe, preterm preeclampsia and HELLP syndrome, also reflected by decreased first-trimester maternal serum PP13 concentrations.^{1,2} In spite of the extensive research, the relationship between reduced PP13 expression and serum concentrations and the pathogenesis of preeclampsia remains a mystery. In this issue of *Reproductive Sciences*, Kliman et al, who present interesting insights into the behavior of PP13 in early pregnancy, more importantly may help us to understand early placentation events and pieces of the puzzle that is called preeclampsia.

Kliman et al systematically examined placental specimens collected between 6 and 15 weeks of gestation from elective terminations of normal pregnancies for immunostaining patterns of PP13 and various trophoblast, leukocyte, and apoptosis markers. A primary observation was made on zones of apoptotic and necrotic decidual cells, T cells, neutrophils, and macrophages, which were always localized around decidual veins but not arterioles. The occurrence of these “ZONES” peaked at 7 to 8 weeks of gestation and declined by the end of the first trimester, corroborating earlier findings of McCombs and Craig on zones of decidual necrosis in the first trimester,³ and suggesting that this phenomenon is part of the physiologic events in early placentation.

The present article makes another remarkable observation about the immunolocalization of PP13 using a new monoclonal antibody whose performance is superior to former clones on formalin-fixed tissues. Consistent with previous findings for the third trimester,² strong PP13 immunopositive staining of the syncytiotrophoblast was documented. Interestingly, weak immunopositivity of some luminal trophoblasts was found within converted decidual spiral arteries, while no immunopositivity was found for other trophoblast subpopulations. Importantly, large extracellular PP13 deposits and phagocytized PP13 debris were detected coincident with the ZONES, and the temporal and spatial distributions of these PP13 aggregates paralleled ZONE formation, decidual inflammation, and necrosis. This is consistent with PP13 belonging to the group of β -

galactoside-binding galectins, which are key controllers of fundamental biological processes (e.g., apoptosis) and participate in the activation and resolution of innate and adaptive immune responses.^{1,2,4} These data, previous findings for the apoptosis-inducing effect of PP13 on immune cells,¹ and current functional evidence showing that PP13 induces secretion of interleukin (IL)-1 α and IL-6 in peripheral blood mononuclear cells *in vitro* prompted Kliman et al to propose that PP13, secreted by the syncytiotrophoblast, drains through the veins of decidua basalis, forms perivenous crystal-like aggregates, and then attracts, activates, and sinks maternal immune cells, diverting them from spiral arterioles and invading trophoblasts.

According to the article’s third chief observation, the number of ZONES and the percentage of converted spiral arterioles in the investigated normal pregnancy specimens changed in parallel. Notably, invasive trophoblasts, converted spiral arterioles, and ZONES were only rarely seen in specimens taken from women who had low maternal serum PP13 MoMs. Therefore, it was hypothesized that a decreased PP13 expression may lead to deficient ZONE formation along with decreased trophoblast invasion and failure of spiral arteriole conversion.

The data presented here are also interesting from an evolutionary point of view since PP13 belongs to an anthropoid primate-specific subgroup of galectins uniquely expressed by the placenta.^{1,2} Among these, PP13 evolved in Old World primates that have more intense trophoblast invasion than do other anthropoids. Although, similar to other galectins, PP13 may exert various cell-dependent and developmental stage-

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dependent intra- and extra-cellular functions, emerging data suggest that it may belong to a set of primate-specific molecules, e.g. HLA-C (human leukocyte antigen C) and KIRs (killer-cell immunoglobulin-like receptors), that regulate immune mechanisms related to invasive placentation in these species.^{1,2,5} It is not surprising that the dysregulation or certain combinations of these molecules has been implicated in the development of preeclampsia, a multistage syndrome originating from the failure of deep trophoblast invasion in anthropoid primates.⁶⁻¹⁰ How the evolutionary “arms race” involving these molecules has led to deep placentation along with vulnerability to preeclampsia in anthropoids remains an exciting field to be explored.

Declaration of Conflicting Interests

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