CONTROL OF THE INFLAMMATORY RESPONSE DURING PREGNANCY: WHY VIP IS A VERY IMPORTANT PEPTIDE

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Normal pregnancy and fetal growth entails successful immune-placental cooperation. Maternal leukocytes are recruited to the uterus from the beginning of pregnancy where they interact with trophoblast cells, modulating their functional profile to contribute to immune homeostasis maintenance. Cell-to-cell interaction as well as a wide variety of mediators in redundant loops sustain an anti-inflammatory microenvironment that ensures fetal growth. Defects in these processes are associated with pregnancy complications like preeclampsia or intrauterine growth restriction with high rates of maternal and neonatal morbidity and mortality. Among the factors that regulate trophoblast cell function and their interaction with immune cells, we have proposed that vasoactive intestinal peptide (VIP) and its high affinity receptors VPAC have a central role.

By means of *in vitro* approaches with human cells and *in vivo* murine models of pregnancy in VIP deficient mice, we present evidence to support the contribution of VIP/VPAC system in autocrine and paracrine interactions of trophoblast and immune cells. Human trophoblast derived cell lines Swan 71 and HTR8 transfected with a VIP siRNA were co-cultured with blood monocytes or neutrophils from healthy donors to assess immune and trophoblast cell functional profiles. VIP deficient trophoblastic cells failed to promote a predominant M2 macrophage polarization profile, as well as to deactivate neutrophils primed with pro-inflammatory stimuli. Accordingly, in murine pregnancy, VIP deficient trophoblast cells displayed a less invasive phenotype with lower expression of metalloprotease-9, failed to promote Treg cell recruitment to the implantation sites, and were associated with an impaired pregnancy outcome.

New approaches are required to understand the mechanisms of deep placentation disorders and to identify potential therapeutic targets. Our results point to the role of VIP acting on different loops for immune homeostasis maintenance throughout pregnancy.