The effect of pregnancy hormones and trophoblast-derived factors on IL-10 producing regulatory B cells

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Objective

IL-10 competent regulatory B cells (Breg) possess immune regulatory properties in humans and mice. In human pregnancies, we have recently demonstrated that CD19+CD24hiCD27+IL-10+ Breg increase with healthy pregnancy onset but not in the case of spontaneous abortions. Physiological triggers and mechanisms involved in Breg expansion are yet to be discovered. Pregnancy hormones such as human chorionic gonadotropin (hCG), progesterone (P4) and estradiol (E2) have eminent immune modulatory properties. Thus, our main objective was to identify hormones and other pregnancy factors that promote the generation of Breg.

Method

Peripheral B cells were isolated from healthy nulliparous women of reproductive age and cultured for 24h in hormone-stripped medium. Thereafter, stimulated B cells were co-cultured with recombinant hCG, P4, E2 or hCG-producing trophoblast cells (JEG-3) for further 24h. In a murine study naive and pregnant female C57BL/6 mice were sacrificed and total B cells isolated. Unstimulated and stimulated B cells were co-cultured with murine trophoblast cells (SM9-2) and placental explants from pregnant female Swiss Webster mice for 24h. The generation of Breg was calculated by evaluating IL-10 production in total B cells using flow cytometry. IL-10 levels in cell culture supernatants were analyzed by enzyme-linked immunosorbent assay.

Results

We found a significant increase in the human CD19+CD24hiCD27+IL-10+ Breg population when co-cultured with recombinant hCG or hCG-producing JEG-3 cells. The addition of P4 and E2 did not provoke any changes. Correspondingly, we observed a significant IL-10+ Breg expansion in murine co-culture studies with trophoblast SM9-2 cells or placental explants.

Conclusion

Trophoblast-associated factors, in particular hCG are key contributors towards the immune tolerance in pregnancy by means of promoting Breg generation.