After implantation, human trophoblasts differentiate into two pathways: 1/ villous cytotrophoblasts (VCT) that fuse to form the syncytiotrophoblast (ST) involved in placental exchanges and endocrine function, and 2/ extravillous cytotrophoblasts (EVCT) that invade the uterus wall up to the upper third of the myometrium and participate to the remodelling of utero-placental vascularization.

Human chorionic gonadotropin (hCG) is the major pregnancy glycoprotein hormone, whose maternal concentration and glycan structure change all along pregnancy. It is well established that hCG is mainly secreted by the endocrine ST into the maternal compartment. We have reported in situ and in vitro that human invasive EVCT also produce and secrete hCG, suggesting an autocrine/paracrine function at the maternal-foetal interface (Handschuh et al, Placenta, 2007).

Thus, we investigated the activity and the role in trophoblast invasion of hCG secreted in vitro by primary cultures of human invasive EVCT in comparison with hCG produced by in vitro differentiated non invasive ST. LH/CG receptor (LHCGR) was present in EVCT in situ and in vitro as well as in the EVCT cell line HIPEC65 that we previously established and characterized (Pavan et al, Carcinogenesis, 2003). Incubation of HIPEC65, that do not secrete hCG, with EVCT supernatants containing 10-9 M hCG induced a 10-fold increase in cell invasion, as assayed in Matrigel-coated transwells, whereas ST supernatants containing the same concentration of hCG had no effect. This stimulating effect was strongly decreased by 85 % when hCG was depleted from EVCT supernatants by immunoprecipitation (Handschuh et al, Endocrinology, 2007).

We next quantified hyperglycosylated forms of hCG (hCG-H, mainly produced by choriocarcinoma JEG-3 cells) in each trophoblast subtype cell supernatants and found that hCG-H represent 20 % of total hCG in EVCT supernatant, whereas it was almost undetectable in the ST cell cultures. These results offer strong evidence that hCG secreted in vitro by the invasive EVCT, likely the hyperglycosylated forms of hCG, but not by the ST, promotes trophoblast invasion and may participate to the control of the trophoblast invasion process in an autocrine manner probably through a LHCGR independent pathway.

In situ, hCG-H immunostaining was strong in invasive and endovascular EVCT from 9 WG placenta tissue sections, weaker in mononucleated villous cytotrophoblasts but negative in the syncytiotrophoblast. In 539 maternal sera collected between 9 and 19 WG during normal pregnancies, hCG-H concentrations continuously decreased during pregnancy, whereas total hCG picked at 11WG and then decreased (Guibourdenche et al, JCEM, 2010).

Recently, we provided evidence that like hCG, hCG-H displayed a potent angiogenic effect. However, we demonstrated that hCG-H-induced angiogenesis was LHCGR independent. Indeed, using coimmunoprecipitation, competitive binding, TGF-β reporter gene assays, inhibitors and Smad immunoblotting, we demonstrated that Tß-RII was identified as the hCG-H receptor responsible for its angiogenic effect (Berndt et al, FASEB J, 2013).

All together, these results suggest that the high levels of hCG-H observed in first trimester maternal sera are mainly from invasive EVCT origin, reflecting the early trophoblast invasion process. Furthermore, unlike hCG, hCG-H do not signal through LHCGR but induces trophoblast invasion and angiogenesis via a Tß-RII signalling pathway.