Reproductive BioMedicine Online (2015) ■■, ■■–■■

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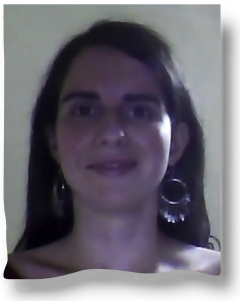
REVIEW

The endocrine function of human placenta: an overview

Marian A Costa *,[1]

Faculdade de Farmácia, Universidade do Porto, Porto, Portugal
* *E-mail address:* marianaac@sapo.pt. [1] Mariana A Costa obtained her PhD degree in Pharmaceutical Sciences at Faculdade de Farmácia Universidade do Porto, though she is not currently linked to this institution.



Mariana Costa holds a PhD in Pharmaceutical Sciences, Specialty of Biochemistry, by the Faculty of Pharmacy University of Porto. Her PhD work contributed significantly to unveil the importance of endocannabinoid signaling in apoptosis and differentiation of human trophoblasts, as well as in protein synthesis by these cells.

Abstract During pregnancy, several tightly coordinated and regulated processes take place to enable proper fetal development and gestational success. The formation and development of the placenta is one of these critical pregnancy events. This organ plays essential roles during gestation, including fetal nourishment, support and protection, gas exchange and production of several hormones and other mediators. Placental hormones are mainly secreted by the syncytiotrophoblast, in a highly and tightly regulated way. These hormones are important for pregnancy establishment and maintenance, exerting autocrine and paracrine effects that regulate decidualization, placental development, angiogenesis, endometrial receptivity, embryo implantation, immunotolerance and fetal development. In addition, because they are released into maternal circulation, the profile of their blood levels throughout pregnancy has been the target of intense research towards finding potential robust and reliable biomarkers to predict and diagnose pregnancy-associated complications. In fact, altered levels of these hormones have been associated with some pathologies, such as chromosomal anomalies or pre-eclampsia. This review proposes to revise and update the main pregnancy-related hormones, addressing their major characteristics, molecular targets, function throughout pregnancy, regulators of their expression and their potential clinical interest.

KEYWORDS: placental hormones, peptide hormones, pregnancy, steroid hormones, syncytiotrophoblast

Introduction

The human placenta is a specialized pregnancy organ that is responsible for essential functions for gestational success, including fetal support, nourishment and protection. The most characteristic placental cells are the trophoblasts. These epithelial cells have different phenotypes and form the in chorionic villi, finger-shaped structures present in the placenta. Cytotrophoblasts are mononucleated cells that are able to proliferate and differentiate into other trophoblast

http://dx.doi.org/10.1016/j.rbmo.2015.10.005
1472-6483/

Please cite this article in press as: Marian A Costa, The endocrine function of human placenta: an overview, Reproductive BioMedicine Online (2015), doi: 10.1016/j.rbmo.2015.10.005

subtypes, functioning as a precursor pool for the syncytiotrophoblast and extravillous trophoblasts (EVT). In fact, cytotrophoblasts fuse and undergo biochemical differentiation, giving rise to the multinucleated syncytiotrophoblast. The syncytial layer has no proliferative capacity and is in intimate contact with maternal blood, participating in fetal nourishment, gas exchange and also playing important roles in other placental functions, mainly in protein biosynthesis. Cytotrophoblasts may also acquire invasive properties, forming the EVT. These trophoblasts are able to invade and remodel maternal tissues (interstitial EVT) and uterine spiral artery (endovascular EVT), reducing the resistance against blood flow that irrigates the fetus. EVT may also invade and remodel uterine glands (endoglandular EVT), which is important to provide histiotrophic nutrition to the embryo. All these trophoblast subtypes interact with each other and with the other cell types in the placental milieu, e.g. decidual cells, Hofbaüer cells, endothelial cells, vascular smooth muscle cells, providing a unique microenvironment that is crucial for pregnancy outcome and fetal development (Huppertz et al., 2014; Lunghi et al., 2007). The human trophoblast phenotypes at the maternal–fetal interface are represented in **Figure 1**.

One of the major functions of the human placenta is the capacity to synthesize important hormones and other mediators, as this placental endocrine function is crucial for gestational success. In fact, placental hormones are important throughout gestation, as they play different roles in pregnancy establishment and maintenance, fetal development and labour. The major source of placental hormones is the syncytiotrophoblast layer, which expresses the enzymatic machinery and other requirements for the biosynthesis of several hormones that intervene in numerous pregnancy-related events. Other trophoblast phenotypes, however, may also produce some placental hormones and affect the gestational course. For instance, the hormones produced by EVT contribute to vascular and uterine tissue remodelling and to regulate EVT migration and invasion (Lunghi et al., 2007; Ji et al., 2013).

The release of placental hormones into maternal circulation has been the target of intense research into their potential as biomarkers for predicting and diagnosing pregnancy-related diseases. Nevertheless, the study of hormone production by human placenta and the function of each hormone in different gestational events represent a challenge. In fact, because of ethical reasons, studies in human models are limited and are susceptible to great inter-individual variability. Currently, human placental explants or isolated primary human cytotrophoblasts are used to assess the endocrine function of human placenta. Alternatively, immortalized trophoblast cell lines have been used as models to study the human trophoblast. The choriocarcinoma-derived cell line BeWo is the most commonly used model to represent the cytotrophoblast, as these cells have the main characteristics of human cytotrophoblast cells, including the synthesis of placental hormones, e.g. human chorionic gonadotrophin (HCG), progesterone, oestrogens (Orendi et al., 2011). BeWo cells, however, still keep tumour cell properties, which raises questions about their true representation of normal human trophoblasts. On the other hand, animal models, namely mice, are frequently used to study placentation (Carter, 2007) but considerable differences are denoted between mice and human placentas. In fact, although both have haemochorial placentation, trophoblast invasion in mice is much more restricted, and placental hormone production is considerably different. For example, in mice, progesterone synthesis by corpus luteum is required throughout pregnancy, and mouse placental lactogens regulate corpus luteum function. In humans, placenta assumes progesterone synthesis from 6–8 weeks of gestation until the labour, and HCG maintains corpus luteum. Also, human trophoblasts secrete higher amounts of steroid hormones than trophoblasts of other mammals (Malassine et al., 2003). Therefore, this interspecies variability also limits the study of human placental hormones in animal models.

In this review, the main placental hormones and their functions, mechanisms of action, regulators and the most consistent evidence linking altered levels of these hormones and

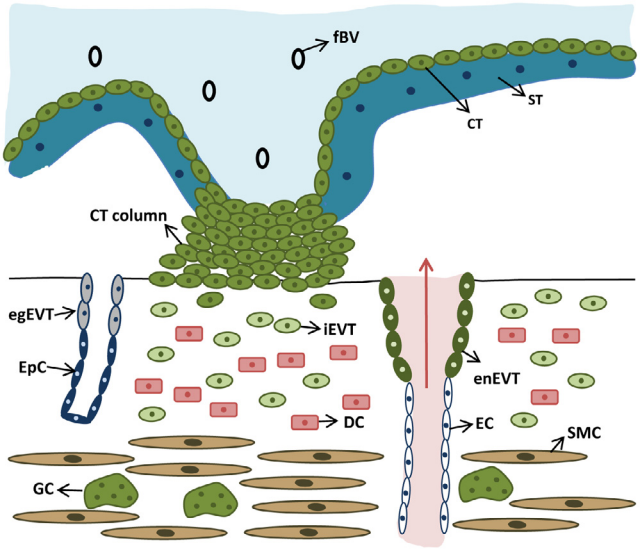


Figure 1 Placental cells at the maternal–fetal interface. Cytotrophoblasts are mononucleated cells that proliferate and undergo fusion and biochemical differentiation to originate the syncytiotrophoblast. The syncytiotrophoblast is a multinucleated cell layer devoid of proliferative activity, which is in intimate contact with the maternal blood. The cytotrophoblasts may also acquire invasive capacity, invading maternal decidua (decidual cell) and part of the myometrium (smooth muscle cell), blood vessels, and uterine glands forming the interstitial extravillous trophoblast, endovascular extravillous trophoblasts, and endoglandular extravillous trophoblasts respectively. Endovascular extravillous trophoblasts replace the endothelial cells of spiral artery, leading to the widening of artery lumen, which decreases the resistance against blood flow that irrigates the fetus (pink arrow). Interstitial extravillous trophoblast fuse and form the multinucleated giant trophoblast cells, which are unable to further invade the uterine tissues. CT = cytotrophoblast; DC = decidual cell; EC = endothelial cell; egEVT = endoglandular extravillous trophoblast; enEVTs = endovascular EpC = epithelial cell; EVT = extravillous trophoblast; fBV = fetal blood vessel; GC = giant trophoblast cells; iEVT = interstitial extravillous trophoblast; SMC = smooth muscle cell; ST = syncytiotrophoblast.

Please cite this article in press as: Marian A Costa, The endocrine function of human placenta: an overview, Reproductive BioMedicine Online (2015), doi: 10.1016/j.rbmo.2015.10.005