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Immunological regulation of trophoblast invasion

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ABSTRACT

In investigating the immunological regulation of trophoblast invasion, emphasis is frequently placed on the constitution of the implantation site and its specific characteristics. However trophoblast cells are able of invading into not only the uterine tissue, but in the case of ectopic pregnancies also invade into other tissues, where they are actively involved in the creation of a beneficial local environment by expressing a range of membrane bound and soluble factors. The similarities and differences in trophoblast invasion in uterine and tubal pregnancies concerning trophoblast cells and maternal leukocytes and their interaction with each other are discussed in this review.

1. Trophoblast invasion

A tightly regulated transient invasion of the fetally derived trophoblast into the maternal decidua is a key process in placentation and consequently also one that is necessary for a successful pregnancy. Aberrant placentation due to extensive or shallow invasion of extravillous trophoblast cells causes important obstetric and neonatal complications, such as early abortion, preeclampsia, intrauterine growth restriction, prematurity or even maternal or fetal death (Benirschke et al., 2006; Hustin et al., 1990; Kaufmann et al., 2003; Lala and Chakraborty, 2003). Invasion takes part in the process of building placental architecture and establishes nutrition for the fetus by creating an adequate vascular connection between the intervillous space and the uterine spiral arteries.

Trophoblast invasion is not restricted to the uterus, but can – in the case of ectopic pregnancies – also take place in other organs, such as the fallopian tubes. Placenta may develop in many maternal organs (Benirschke et al., 2006) and there are numerous case reports of viable term fetuses from ectopic pregnancies, such as that described by Augensen (1983), where a mother with an unruptured tubal pregnancy delivered a healthy child. Ectopic pregnancy currently occurs in 1.9% of reported pregnancies, with 97% of them implanting in the fallopian tube (Della-Giustina and Denny, 2003).

There are many similarities and also some differences in trophoblast invasion in uterine and tubal pregnancies concerning trophoblast cells and maternal leukocytes and their interaction with each other. These will be discussed in this review.

2. Trophoblast

Trophoblast is derived from the external trophoectoderm layer of the blastocyst and differentiates after the initial phase of nidation along either the villous or the extravillous trophoblast pathway. Villous trophoblast consisting of the syncytiotrophoblast and villous cytotrophoblast cells covers the chorionic villi and is involved in the exchange of gas and nutrients between the mother and

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the fetus, once the blood circulation is established. Trophoblast outside the chorionic villi – termed extravillous trophoblast – consists of different subsets and invades the decidua to form the anchoring attachments of the placenta. Furthermore, extravillous trophoblast is implicated in the transformation of the spiral arteries into large flaccid vessels being incapable of responding to vasoactive stimuli.

2.1. Trophoblast in eutopic pregnancy

The first contact between extravillous cytotrophoblast and the maternal tissue of the endometrium occurs as early as the 14th day of pregnancy, when the first cytotrophoblast cells have penetrated through the syncytiotrophoblast and begin to invade the maternal tissue (Huppertz, 2007). In further development the syncytiotrophoblast cover becomes eroded and cell columns are formed, whose highly proliferative cells at the basal layer are the source for further invasion of the decidua by extravillous trophoblast, a discrete set of trophoblast cells, different in phenotype and function as compared to the villous type of trophoblast.

The extravillous trophoblast within the maternal tissue consists of several different trophoblast populations with different phenotypes regarding morphology and function. Frequently extravillous trophoblast cells are distinguished according to their location within the uterine tissue. The interstitial trophoblast is evenly distributed within the decidua and consists of two different trophoblast populations: the large polygonal extravillous trophoblast, which is thought to fix the placenta to the uterine wall by secreting matrix-type fibrinoid, and the small spindle-shaped type of extravillous trophoblast (Huppertz, 2007). The large polygonal extravillous trophoblast, which is rare in early pregnancy, but constitutes the prevailing phenotype in term placenta, is thought to be a differentiated not invasive cell type that arises from the small spindle-shaped type of extravillous trophoblast (Kemp et al., 2002). The latter one is thought to represent the highly invasive set of trophoblast cells and decreases in number as term approaches. The endovascular trophoblast infiltrates the vessel walls of the spiral arteries and replaces the smooth muscle cells in the media as well as the endothelial cells in the decidual part of the spiral arteries. By doing so, the distal ends of the spiral arteries are transformed into widely dilated, structureless conduits (Redman and Sargent, 2010). Furthermore, the endovascular trophoblast clots the spiral arteries until the end of the first trimester, thus preventing maternal blood flow into the intervillous space. Large multinucleated extravillous trophoblast cells, also termed giant cells, migrate as far as the inner third of the myometrium (Loke and King, 1995), where they tend to form a well-defined rather thin layer with the longitudinal axis oriented in parallel to the uterine wall (Kemp et al., 2002). Just recently a new subset of extravillous trophoblast, the endoglandular trophoblast, was described which replaces glandular epithelial cells similar to the endovascular trophoblast cells replacing the endothelial layer (Moser et al., 2010). This mechanism seems to provide nutrition to the fetus prior to onset of maternal blood flow within the placenta by opening the way for glandular secretion products to reach the intervillous space. To date, the different subsets of extravillous trophoblast have been characterized by location and by morphological phenotypes, but not according to immunological parameters.

2.2. Trophoblast in ectopic pregnancy

In ectopic pregnancies a principle difference has to be made between viable and not viable pregnancies, when comparing them with viable eutopic ones. The development of viable tubal pregnancies seems to be restricted to an implantation at the mesosalpingial half of the fallopian tube with its thickened wall (Benirschke et al., 2006).

In the case of viable tubal pregnancies the placental structures are formed with principally the same subset of trophoblast cells as in the uterus. Compared with uterine pregnancies, a difference is the large number of the highly invasive subset of small spindle shaped trophoblast and the rare presence of the large polygonal trophoblast (Kemp et al., 2002). Furthermore the large, multinucleated giant cells are very rare (Kemp et al., 2002). Several authors have commented on the highly invasive nature of trophoblast cells in viable tubal pregnancies (Kemp et al., 2002; Emmer et al., 2002; von Rango et al., 2003), which might in many cases penetrate the full thickness of the wall to reach the serosa (Kemp et al., 1999) thereby causing tubal rupture. Data describing endovascular trophoblast are rare. However, Randall et al. (1987) reported after investigating 105 tubal pregnancies that extravillous trophoblast invaded tubal vessels in the same fashion as it does into the spiral arteries in the uterus. Also Emmer et al. (2002) found endovascular trophoblast in lacune that resembled blood vessels and Kemp et al. (1999) describe an increased trophoblast invasion into the maternal tubal vessels, penetrating the vessel walls and forming intraluminal trophoblast plugs partly occluding the vessels.

3. Leukocytes

While migrating and invading the maternal uterine tissues (the entire endometrium and the inner third of the myometrium as well as the maternal spiral arteries) the trophoblast comes into intimate contact with maternal cells forming a zone of mixed cellular origin (Benirschke et al., 2006).

3.1. Leukocytes in eutopic pregnancy

The usual implantation site, the endometrium, consists of decidual cells, epithelial cells of the uterine glands, components of the spiral arteries, such as endothelial cells and smooth muscle cells, and maternal leukocytes. In the 1st trimester decidua immune cells constitute 40% of the cells in the human decidua (Whitelaw and Croy, 1996) and compared to other mucosal sites, the uterine mucosa shows a different and rather unusual distribution of leukocytes.

Granulocytes are absent and only a few B cells are present. In early pregnancy decidua, $CD3^+$ T cells constitute 5–20% of total $CD45^+$ decidual lymphocytes and this value increases with gestational age to 40–80% (Tilburgs et al., 2010). Decidual T cells comprise a heterogenic subset