

Reproductive Biology

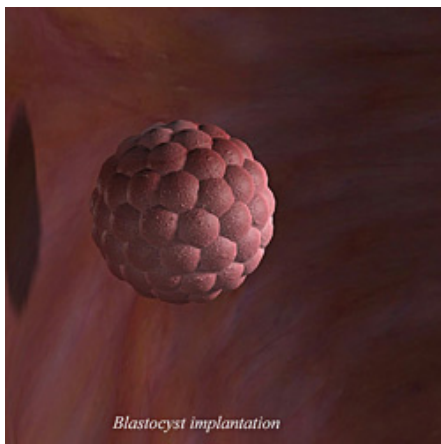
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www.sgul.ac.uk/dept/immunology/~dash We are interested in the

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We are interested in the regulation of the early stages of pregnancy, particular those involving trophoblast invasion of the uterus, remodelling of the maternal environment and the development of the placenta. Problems with these processes is thought to be associated with complications of pregnancy such as pre-eclampsia. Our interest in reproductive biology is focussed on the events that occur after the implantation of the blastocyst (shown below).



Trophoblast cells form the outer layer of the blastocyst and following implantation they are responsible for forming the placenta. The formation of the placenta is a highly complex and tightly regulated process that is essential for the establishment of a healthy pregnancy. Despite this the factors that regulate this process are still poorly understood, and it is this that forms one of our major research interests.

Trophoblasts

Following implantation of the blastocyst, trophoblast cells begin to differentiate. Cytotrophoblast cells differentiate, migrate and invade into the uterine stroma in early pregnancy. The cytotrophoblast stem cells either fuse to form syncytiotrophoblasts or aggregate to form anchoring villous trophoblasts. The latter give rise to a sub-population known as extravillous trophoblasts which invade the uterine wall and its blood vessels, particularly the spiral arteries. The extravillous trophoblast cells remodel the maternal spiral arteries, displacing smooth muscle and endothelial cells, in order to produce a blood vessel with a larger diameter, increased blood flow and reduced resistance. This is an essential step in establishing and maintaining a normal pregnancy and is necessary for the higher blood requirement of the fetus later in pregnancy.

The process of implantation, differentiation and invasion is illustrated in Figure 1.

Spiral Artery Invasion

Following implantation of the blastocyst into the endometrium the trophoblasts continue to invade the uterine endometrium until they reach the spiral arteries, by which time they have differentiated into an endothelial-like cell type. The trophoblasts then begin to remodel the spiral arteries by replacing the smooth muscle and endothelial cells. The result is an increase in vessel diameter and the creation of a high blood flow, low resistance zone. This process is illustrated below. The increased blood flow is essential for the developing embryo and a lack of spiral artery modification has been implicated in complications of pregnancy such as pre-eclampsia and intra-uterine growth retardation. The process of spiral artery remodelling is illustrated in Figure 2.

As with any complex tissue, the development of the placenta is a highly regulated process. Nitric oxide is thought to be involved in many aspects of this regulation,

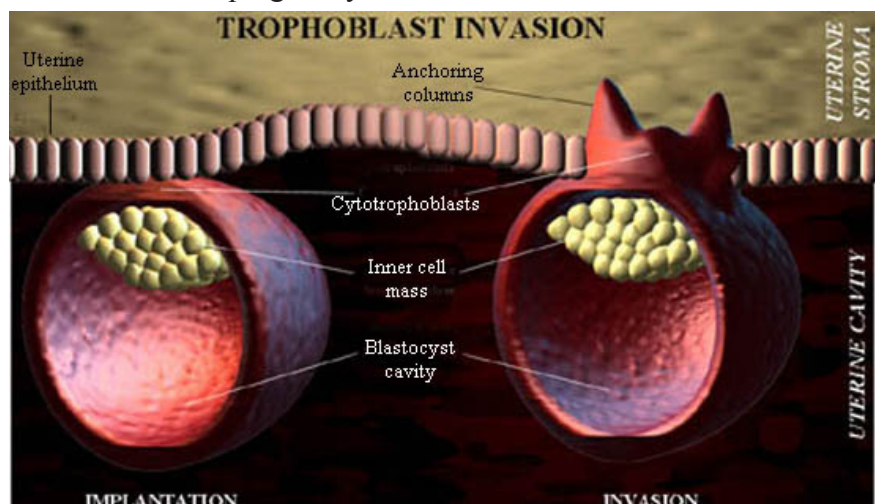
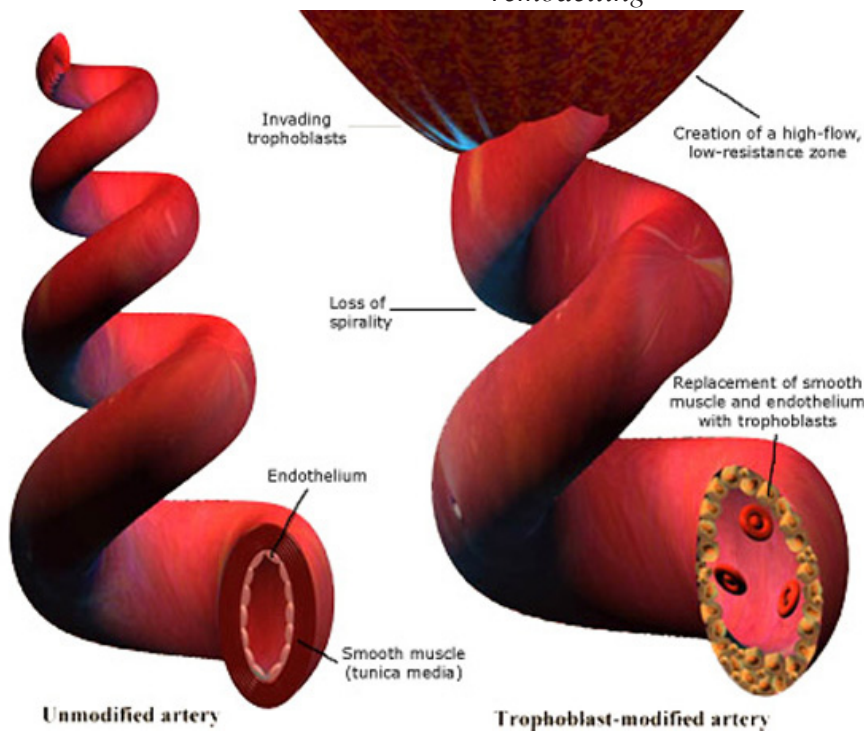


Figure 1: Illustration of trophoblast invasion

including trophoblast apoptosis and motility.

Figure 2: Spiral artery remodelling



Vessel Re-modelling

Vascular remodelling of resistance arteries typically involves medial thickening through hyperplasia of smooth muscle cells (SMC) and deposition of extra-cellular matrix. The result is a reduction in lumen diameter and increased resistance. In human pregnancy the opposite occurs when the uterine spiral arteries are remodelled. There is loss of both endothelium and SMC resulting in medial ablation, luminal expansion and a decrease in resistance. The factors that influence vessel remodelling can be classified as cellular, micro-environmental or genetic. In pregnancy, the cellular effect, namely the presence of the trophoblast, is the most important factor that determines the outcome of remodelling. Due to the scarcity of appropriate tissue and models, little work has been done to understand the basics

of spiral artery remodelling in human pregnancy. Recent work on pregnant rats has identified features that suggest they could be a useful model for future investigations into the fundamental mechanisms of remodelling in human pregnancy.

Shallow or incomplete trophoblast invasion with limited vessel remodelling have been associated with complications of human pregnancy such as pre-eclampsia. Work on spiral artery remodelling has focussed on defects that may lead to this outcome however little is known about the basis of remodelling in normal pregnancy. Our laboratory has been able to demonstrate that primary cytotrophoblast can initiate SMC apoptosis in spiral arteries via the Fas/Fas ligand pathway. A trophoblast-dependent apoptotic mechanism could thus contribute

to SMC loss during remodelling. Apoptosis is a slow and gradual event, typically involving single cells which can take upwards of 24 hours to die following an initial apoptotic signal. Apoptosis thus proceeds in an asynchronous manner leading to a cumulative effect. This is in keeping with the time course of spiral artery remodelling in vivo which is a gradual process occurring over a period of weeks.

Many factors will affect the interactions between trophoblast and SMC. Secreted chemokines may attract trophoblast to SMC and recent work has identified a role for the eph/ephrin family in stimulating trophoblast invasion. Placental hormones such as human placental lactogen and human chorionic gonadotropin (hCG) may act to positively or negatively regulate SMC apoptosis. hCG has been reported to both protect cells from apoptosis and to increase apoptosis. Cytokines found in the maternal-fetal environment can alter expression of apoptotic ligands such as TNF-related apoptosis-inducing ligand (TRAIL) which is produced by trophoblast and is up-regulated by TNF-alpha and IFN-gamma stimulation.

Spiral artery remodelling in pregnancy thus relies on a complex co-ordination of micro-environmental factors, cell-cell interactions and apoptotic events over an extended time frame that maintains vessel integrity. The end result is a unique transformation of maternal vessels which is essential for the maintenance of a successful pregnancy.

Pre-eclampsia

Pre-eclampsia is a multi-systemic disorder characterised by hypertension (high blood pressure) and proteinuria (the presence of protein in urine). It has been the leading cause of maternal mortality in the UK over recent decades. Worldwidethe disease is responsible for approximately 150,000 deaths per year. Pre-eclampsia also leads to considerable mortality and morbidity in newborn children and can carry health implications in adult life, including increased risk of hypertension, heart disease and diabetes.

Examination of the placenta from normal and pre-eclamptic pregnancies has revealed that pre-eclampsia is associated with an apparent failure of trophoblast cells to invade and remodel the maternal environment. A failure to remodel the maternal spiral arteries, for example, is thought to restrict the blood flow to the developing foetus and may be a contributing factor to the onset of pre-eclampsia.

There are a number of reasons for the failure of trophoblasts to perform their normal function during pre-eclamptic pregnancies. For example, an increased incidence of trophoblast cell death (apoptosis) has been detected in these pregnancies. It is also possible that the motility and invasiveness of trophoblast cells is compromised. Our research aims to investigate the factors, such as nitric oxide, that regulate trophoblast function in order to determine how and why some pregnancies are complicated with pre-eclampsia.