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Oxygen and placental development; parallels and differences with tumour biology

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ABSTRACT

Human placentation involves the invasion of the conceptus into the wall of the uterus, and establishment of a blood supply from the maternal spiral arteries. The placenta has therefore been likened to a malignant tumour, albeit a highly regulated one. Oxygen plays an important role in controlling both placental development and tumour behaviour. In the placenta, early development takes place in a physiological low oxygen environment, which undergoes a transition with onset of the full maternal arterial circulation towards the end of the first trimester. By comparison, in tumours there is often a progressive hypoxia as the mass outgrows its blood supply. Both early placental tissues and tumour cells show high rates of proliferation, and the energy required to support these comes principally from glycolysis. Glycolysis is maintained in placental tissues by reoxidation of pyridine nucleotides through the polyol pathways, whereas in tumours there is fermentation to lactate, Warburg metabolism. In both cases, the reliance on glycolysis rather than oxidative phosphorylation preserves carbon skeletons that can be utilised in the synthesis of nucleotides, cell membranes and organelles, and that would otherwise be excreted as carbon dioxide. In the placenta, this reliance may also protect the embryo from free radical-mediated teratogenesis. Local oxygen gradients within both sets of tissues may influence the cell behaviour. In particular, they may induce an epithelial-mesenchymal transition, promoting extravillous trophoblast invasion in the placenta and metastasis in a tumour. Further investigations into the two scenarios may provide new insights of benefit to these contrasting, but similar, fields of cellular biology.

1. Introduction

Placental development displays many of the same growth characteristics as are seen in malignant tumour progression, such as a high proliferative rate, invasion into the host tissue, and immunological modulation [1]. There are parallels too in terms of oxygenation and tissue metabolism, but also significant divergences. Here, we review the major similarities and differences.

2. The first trimester placental environment

Fertilization and early development of the conceptus occur in the Fallopian tube, supported by the oviductal secretions. In the human, measurements performed during the non-pregnant cycle indicate an oxygen tension of 15–19 mmHg [2,3], and it is likely that similar conditions prevail during early pregnancy. Data from the mouse show that oxygen consumption by the early conceptus is low, at approximately 4 μl/mg dry weight per hour, prior to implantation, although it peaks transiently at the time of blastocyst formation due to the higher energy demands associated with ionic pumping and protein synthesis [4]. This low level of oxygen consumption has been coined 'quiet metabolism' [5], and is considered to be beneficial as it limits the production of potentially harmful reactive oxygen species. These species, and their non-radical intermediates, may cause damage to diverse biomolecules, including lipid peroxidation, protein carbonylation and DNA strand breaks. Indeed, more active 'noisy' metabolism is associated with higher levels of DNA damage, and with poorer outcomes in assisted reproductive technologies [6].

Early placental development can be seen as a continuation of this 'quiet metabolism', for the oxygen concentration within the

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intervillous space and the embryonic compartments remains at approximately 20 mmHg during most of the first trimester [7,8]. Following implantation, the conceptus lies within the superficial endometrium, and as the trophoblast mantle expands it erodes into neighbouring capillaries and into the endometrial glands. Maternal arterial inflow into the placenta only occurs towards the end of the first trimester, as initially the endovascular trophoblast invasion that occurs as part of remodelling of the spiral arteries is sufficiently voluminous to occlude the mouths of most of the vessels [9,10]. A network of narrow intercellular spaces exists between the endovascular trophoblast cells, however, enabling maternal plasma to pass into the placenta at a slow rate. Consequently, there is a continual supply of oxygen, albeit at a low partial pressure and content as it is carried principally in solution in the absence of maternal erythrocytes.

The distribution of this oxygen to the deeper placental and fetal tissues must initially occur by simple diffusion, for the fetal heart does not start beating until the 5th week of pregnancy, and an effective circulation through the placental villi is only achieved towards the end of the first trimester. Diffusion is facilitated by the large surface area provided by the villous morphology of the placenta, and presence of fluid-filled stromal channels within the villi that communicate with the extra-embryonic coelom [11]. The oxygen within the exocoelomic fluid is able reach the deeper tissues within the embryo as the intra- and extra-embryonic coeloms are in free communication before the anterior body folds fuse at around 6 weeks post-fertilization. When the fetal-placental circulation is established, oxygen transport is achieved during the first three months of pregnancy by high-affinity embryonic haemoglobin (Hb) located inside red cells which are mainly nucleated. The oxygen binding characteristics of embryonic Hb and the high viscosity of circulating blood containing a high proportion of nucleated red cells contribute to limiting oxygen transfer to the fetal tissues [12–14].

By comparison, although the oxygen tension in many tumours is low, and indeed lower than that inside the early placenta, the situation has a very different ontology. The pattern in tumour masses is one of increasing hypoxia, compared to the steady state seen within the early placenta. In tumours, the initiating growth normally occurs at ordinary tissue oxygen levels, but with expansion the tumour gradually outstrips its blood supply. In solid tumours the opportunity for diffusion is limited, and as a result the central core becomes increasingly hypoxic [15]. Although angiogenesis is stimulated through the release of VEGF, the degree of hypoxia may be sufficient to induce necrosis in the core, an event never seen in first trimester placental tissues or in fetal development. In fact, variation in blood flow distribution to the periphery of the early placenta leads to a high level of oxygen exposure inducing apoptosis and degeneration of two-thirds of the original placental mass, a process which is pivotal for the formation of the membranes.

3. Early placental metabolism

Early placental tissues display a high proliferative rate, as do tumour cells, although the drivers are different. In the placenta, proliferation is thought to be stimulated exogenously by mitogens secreted by the endometrial glands [16]. Both epidermal growth factor and the insulin-like growth factors promote proliferation of the cytotrophoblast cells when applied to first trimester villous explants [17,18]. These mitogens are presumably transported through the syncytiotrophoblast by the same endocytotic/exocytotic pathways that lead to the accumulation of other gland products, such as glycodelin, in the amniotic fluid [19]. By contrast, in tumour cells the drive for proliferation arises as the result of endogenous mutations within growth promoting pathways. However, unlike in a tumour, the placental tissues display no evidence of hypoxic stress. Hypoxia cannot be defined simply by the prevailing partial pressure that cells are exposed to, but rather by whether the oxygen supply is sufficient to meet the metabolic requirements of the cells. Hence, it is notable that the ATP/ADP ratio in placental tissues is the same during the first trimester as it is later in the second trimester and at term [20]. Furthermore, there is no stabilisation of either hypoxia inducible factors (HIF-1 and HIF-2) in villi removed by a chorionic villous sampling technique, which avoids any confounding stress induced by exposure to maternal blood as occurs during curettage [20]. These differences with the tumour situation most likely reflect the replenishment of oxygen through the perfusion of the intervillous chamber with maternal plasma, and also the different ontological progressions. In addition, the placental tissues are provided with a rich source of glucose for glycolysis by the endometrial glands, along with lipid and proteinaceous substrates [21].

The exocoelomic fluid is in free communication with the placenta tissues, and so its metabolic profile predominantly reflects placental metabolism. Analysis of the fluid indicates evidence of limited anaerobic metabolism, in that the pH of the fluid at 7–10 weeks of gestation is approximately 7.17, with a base excess of −8.9 mmol/l [22]. The concentration of lactate is, however, not excessively high (0.6 mmol/l). In part, this may be due to metabolism of lactate by the fetus, but it also reflects the reliance of the placenta on phylogenetically old carbohydrate metabolic pathways involving the formation of polyols [23].

4. The importance of glycolysis

One of the most striking similarities between the early placenta and tumours is their reliance on glycolysis for energy production, although the pathways involved in enabling this are quite different. In the case of the placenta, glycolysis is closely interlinked with the polyol and pentose-phosphate pathways. Conversion of glucose to pyruvate generates two molecules of ATP, and requires a supply of NAD^+. Under full aerobic conditions that NAD^+ is normally regenerated via the tricarboxylic acid (TCA) cycle, whereas in adult tissues under anaerobic conditions NAD^+ is regenerated by fermentation of pyruvate to lactate (Fig. 1). The polyol pathways provide an alternative mechanism for maintaining the oxidation-reduction balance of pyridine nucleotides. Conversion of ribose 5-phosphate created from glucose in the pentose-phosphate pathway to ribitol regenerates NAD^+. Similarly, formation of erythritol and sorbitol regenerates $NADP^+$. The concentrations of these polyols are much higher in the coelomic fluid than in maternal serum during early pregnancy [23].

By contrast, in tumours fermentation to lactate appears to be the principal method for regeneration of NAD^+, even under conditions of adequate oxygenation. This process is therefore referred to as aerobic glycolysis, or eponymously as the Warburg effect. In hypoxic cells and tissues, such as the tumour, glycolysis is directly stimulated following HIF-1 stabilisation, with the upregulation of most, if not all, glycolytic enzymes [24]. Notably, aerobic glycolysis is also specifically promoted, and mitochondrial pyruvate oxidation bypassed, via inhibition of pyruvate dehydrogenase (PDH) activity (Fig. 1). HIF-1 dependent upregulation of PDH kinase 1 (PDK-1) [25,26] leads to the phosphorylation of the E1 subunit of PDH, and thus its inhibition. Under such conditions, pyruvate is therefore not converted into acetyl-CoA, and the TCA cycle cannot be fuelled, leading to a fall in mitochondrial oxygen consumption [26], which promotes survival in the face of hypoxia. Hypoxic cells instead accumulate pyruvate, some of which is converted to lactate under the action of lactate dehydrogenase (LDH), another HIF-1 regulated

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