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.

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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.

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 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-fertilisation. 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.

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).

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 (Figure 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 (Figure 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 enzyme (24), and lactate is in turn transported out of the cell (27). The build-up of pyruvate also favours transformation of fructose-6-phosphate to D-ribose-5-phosphate, promoting the synthesis of nucleic acids to support cell proliferation (Figure 1). At present it is unclear whether glycolysis is promoted by mitochondrial inhibition in a similar fashion in the case of the placenta, though in the apparent absence of HIF-1 stabilisation this would seem unlikely. Instead, placental glycolysis may possibly be promoted early in pregnancy as a necessary means of supporting ATP-synthesis in the absence of significant mitochondrial activity. The time-course of changes in placental mitochondrial density has not yet been established; however, the initiation of significant mitochondrial biogenesis may only coincide with the rise in oxygenation towards the end of the first trimester.

It might be supposed that in both situations metabolism is relatively inefficient, and does not take advantage of the higher yield of ATP that can be gained through oxidative phosphorylation. However, unlike differentiated cells in adult tissues the rapidly proliferating cells of the placenta and a tumour have additional requirements. There is a need for carbon skeletons that can be incorporated into nucleotides, amino acids and sterols that support synthesis of DNA, cell and organelle membranes, and proteins. Instead of breaking glucose down completely and excreting the carbon atoms as carbon dioxide, maintaining the carbon skeletons as lactate or through the pentose-phosphate pathways allows them to be incorporated into the biomass (28).

There are other potential benefits for the fetal-placental unit derived through reliance on the polyol pathways. Firstly, conversion of glucose to ribose 5-phosphate produces two molecules of NADPH. NADPH is required for the regeneration of reduced glutathione from its oxidised form, and hence is key to the antioxidant defences of a cell. Developing systems are highly prone to perturbation by oxidative stress, which can lead to severe congenital abnormalities (29, 30). Adequate antioxidant defences are therefore crucial. Secondly, polyols such as sorbitol are incapable of crossing cell membranes and so act as powerful osmolytes. Sorbitol is produced from glucose by the action of aldose reductase, one of the first enzymes to be expressed in the sheep conceptus. In this species there is a rapid expansion of the embryonic sac into a thread-like structure, and sorbitol may assist in driving this process by drawing water across the trophoblast epithelium. In the human there is a similar, though less extensive, need to expand the extra-embryonic coelom.

The benefits of a low oxygen environment for fetal-placental development

Although at first sight the reliance on glycolysis for energy production in the early placenta and tumours may appear to be inefficient, there is no reason to assume that it cannot meet the cells' requirements as long as there is a sufficient supply of glucose (31). In the case of the placenta there is a plentiful supply in the secretions derived from the endometrial glands, and accumulation of glycogen within the syncytioplasm is a conspicuous feature during early pregnancy (21, 32).

Thus, these metabolic pathways enable a high rate of proliferation to be maintained under a relatively low oxygen concentration. The rise in oxygen concentration within

the placenta and the embryonic compartments at the end of the first trimester notably coincides with the completion of organogenesis. At this stage of development the risk of teratogenesis falls sharply, as differentiation of the major organ systems is completed. The risks from oxygen free radicals therefore falls somewhat, and so the metabolic balance may tip in favour of oxidative phosphorylation. Evidence for such a shift comes from the rapid fall in placental glycogen content at the end of the first trimester (33), and it may explain the rise in growth rate of the embryo seen at this stage (34).

Increasing evidence from the field of stem cell biology indicates that adult stem cell niches are located in low oxygen environments, roughly equivalent to the intraplacental oxygen concentration during the first trimester (35). Consistent with this, studies have revealed that culture of primary cytotrophoblast cells under low oxygen conditions favours proliferation, whereas higher concentrations promote differentiation and invasion (36, 37). With respect to this finding, it is notable that levels of CDX2 and ELF5, two transcription factors that act as gate-keepers of the trophoblast lineage, drop sharply at the end of the first trimester (38). This suggests a reduction in the proliferative potential of the placenta, but whether this is due to the three-fold rise in intra-placental oxygen concentration that occurs at the start of the second trimester (8), or the loss of growth factors from the endometrial glands with the switch from histotrophic to haemotrophic nutrition has not yet been clarified.

Oxygen and cell differentiation

Within the placenta, a sub-population of trophoblast cells, the extravillous trophoblast, undergo a partial epithelial-mesenchymal transition and migrate from the outer surface of the cytotrophoblastic shell into the endometrium (39). In doing so they adopt a

pleiotrophic phenotype and move into an area of higher oxygen concentration, for the decidua is always better oxygenated than the placenta (8). In many ways this resembles the process of metastasis, albeit a highly regulated one, but the influence of oxygen on the transition is still unclear. Experimental studies of first trimester explant cultures have demonstrated that oxygen may be a significant factor, for culture under low oxygen conditions (3% v 21%) inhibits invasion. This effect is mediated through the HIF-1 and transforming growth factor beta (TGFß) pathways, and is associated with changes in matrix metalloproteinase activity (40).

Local oxygen concentrations also appear to play a role in remodelling of the early placenta into its definitive form. Villi initially form over the entire surface of the chorionic sac, but later regress to leave the discoid placenta at the deep pole in contact with the endometrium, and the smooth membranes. This remodelling coincides with onset of the maternal arterial circulation to the placenta, which starts preferentially in the periphery and then extends centripetally, reflecting the degree of trophoblast invasion and arterial plugging across the placental bed (41). Villi sampled from the peripheral region display higher levels of oxidative stress and activation of the apoptotic cascade than their counterparts from the central region, and it has been proposed that these effects mediate the regression. Excessive regression at this stage of development may lead to placentas with eccentric insertions of the umbilical cord and more irregular margins (42, 43).

Even within the definitive placenta there will be oxygen gradients that reflect the pattern of maternal arterial blood flow. The placental villi are not arranged at random, but form 30-40 lobules, each centred over the opening of a maternal spiral artery. The

arteries deliver their blood into the relatively villus-free central cavities of a lobule. From there, the blood percolates through the network of intervillous clefts, exchanging oxygen with the fetal circulation as it does so, before draining into the openings of the uterine veins. Each lobule thus represents an individual maternal-fetal exchange unit, and the pattern of the circulation suggests an oxygen gradient from the arterial centre to the more venous periphery. This concept is supported by differences in the expression and activity of the principal antioxidant enzymes (44). These differences in oxygenation may explain regional variations in villous morphology and enzyme activities (45). Oxygen gradients similarly occur within tumours due to the limitations of diffusion (15), and again may mediate cell behaviours, such as resistance to radiotherapy, or predisposition to metastasis (46).

Conclusion

Early placental development occurs in a low oxygen environment, and as a rapidly proliferating tissue it shares many of the same metabolic requirements as tumours. However, in the placenta there is continual replenishment of oxygen due to plasma flowing at a slow rate through the intervillous space, and so the tissues do not experience the increasing drive towards hypoxia that typifies the central regions of tumours. Nonetheless, oxygen appears to be a major regulator of cell behaviour in both the placenta and tumours. A better understanding of the similarities and differences between the two may lead to new insights that are beneficial to these contrasting fields of biology.

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Conflict of interest

The authors have no conflicts of interest to declare.

References

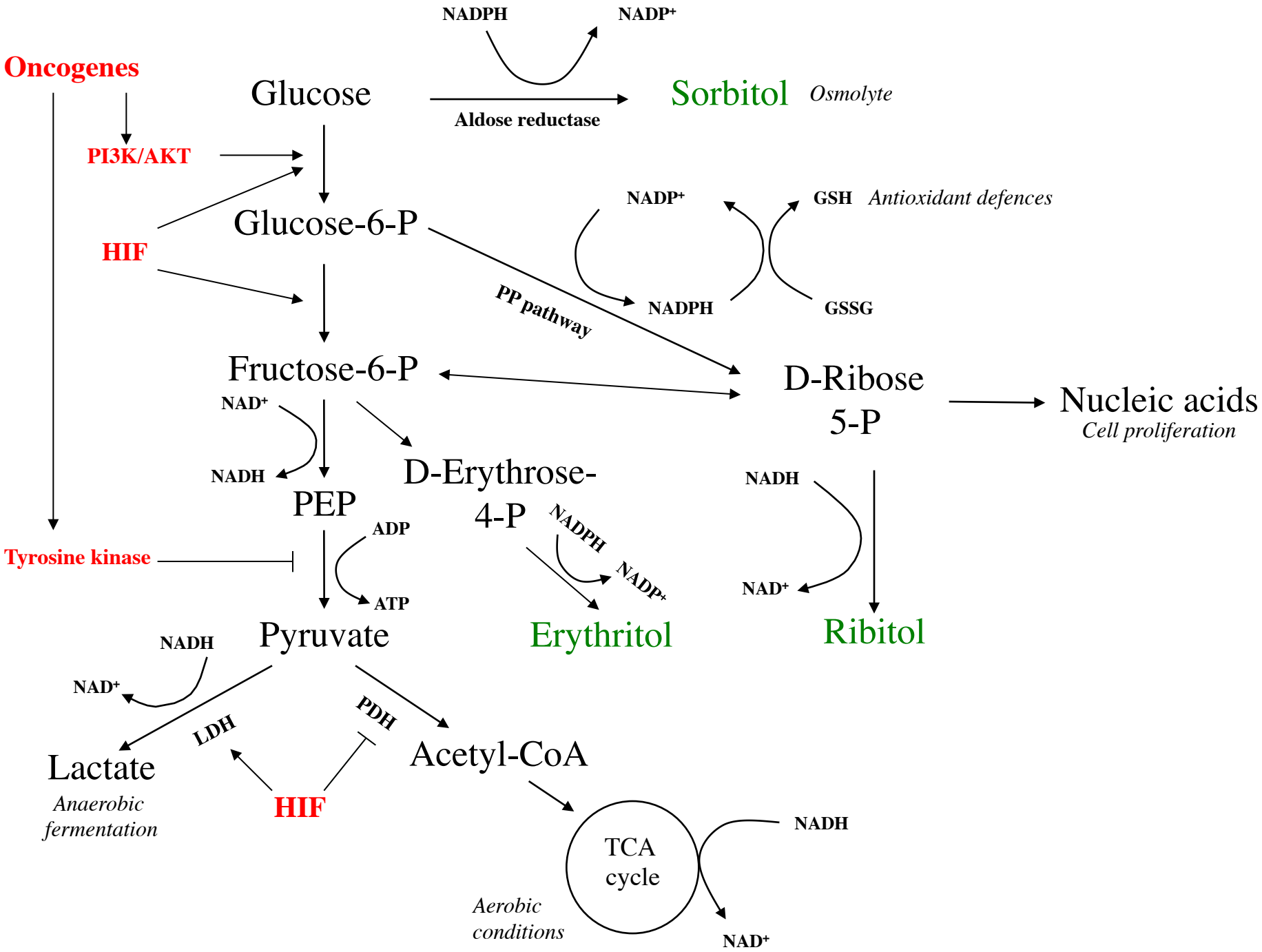
1. Holtan SG, Creedon DJ, Haluska P, Markovic SN. Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. Mayo Clin Proc. 2009;84(11):985-1000.
2. Yedwab GA, Paz G, Homonnai TZ, David MP, Kraicer PF. The temperature, pH, and partial pressure of oxygen in the cervix and uterus of women and uterus of rats during the cycle. Fertil Steril. 1976;27(3):304-9.
3. Ottosen LD, Hindkaer J, Husth M, Petersen DE, Kirk J, Ingerslev HJ. Observations on intrauterine oxygen tension measured by fibre-optic microsensors. Reprod Biomed Online. 2006;13(3):380-5.
4. Houghton FD, Thompson JG, Kennedy CJ, Leese HJ. Oxygen consumption and energy metabolism of the early mouse embryo. Mol Reprod Dev. 1996;44(4):476-85.
5. Leese HJ. Quiet please, do not disturb; a hypothesis of embryo metabolism and viability. BioEssays. 2002;24:845-9.
6. Sturmey RG, Hawkhead JA, Barker EA, Leese HJ. DNA damage and metabolic activity in the preimplantation embryo. Hum Reprod. 2009;24(1):81-91.
7. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. Obstetrics and Gynecology. 1992;80:283-5.
8. Jauniaux E, Watson AL, Hempstock J, Bao Y-P, Skepper JN, Burton GJ. Onset of maternal arterial bloodflow and placental oxidative stress; a possible factor in human early pregnancy failure. American Journal of Pathology. 2000;157:2111-22.
9. Hustin J, Schaaps JP. Echographic and anatomic studies of the maternotrophoblastic border during the first trimester of pregnancy. American Journal of Obstetrics and Gynecology. 1987;157:162-8.
10. Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy; the Boyd Collection revisited. Am J Obstet Gynecol. 1999;181:718-24.
11. Castellucci M, Kaufmann P. A three-dimensional study of the normal human placental villous core: II. Stromal architecture. Placenta. 1982;3:269-86.

12. Jauniaux E, Jurkovic D, Campbell S. In vivo investigations of anatomy and physiology of early human placental circulations. Ultrasound in Obstetrics and Gynecology. 1991;1:435-45.
13. Hofmann OM, Brittain T. Partitioning of oxygen and carbon monoxide in the three human embryonic hemoglobins. Hemoglobin. 1998;22(4):313-9.
14. Carter AM. Evolution of factors affecting placental oxygen transfer. Placenta. 2009;30 Suppl A:S19-25.
15. Bertuzzi A, Gandolfi A. Cell kinetics in a tumour cord. J Theor Biol. 2000;204(4):587-99.
16. Burton GJ, Jauniaux E, Charnock-Jones DS. Human early placental development: potential roles of the endometrial glands. Placenta. 2007;28 Suppl A:S64-9.
17. Maruo T, Matsuo H, Murata K, Mochizuki M. Gestational age-dependent dual action of epidermal growth factor on human placenta early in gestation. J Clin Endocrinol Metab. 1992;75:1362-7.
18. Forbes K, Westwood M, Baker PN, Aplin JD. Insulin-like growth factor I and II regulate the life cycle of trophoblast in the developing human placenta. Am J Physiol Cell Physiol. 2008;294(6):C1313-22.
19. Seppälä M, Jukunen M, Riitinen L, Koistinen R. Endometrial proteins: a reappraisal. Human Reproduction. 1992;7 Suppl. 1:31-8.
20. Cindrova-Davies T, van Patot MT, Gardner L, Jauniaux E, Burton GJ, Charnock-Jones DS. Energy status and HIF signalling in chorionic villi show no evidence of hypoxic stress during human early placental development. Mol Hum Reprod. 2015;21(3):296-308.
21. Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E. Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. J Clin Endocrinol Metab. 2002;87:2954-9.
22. Jauniaux E, Watson AL, Burton GJ. Evaluation of respiratory gases and acid-base gradients in fetal fluids and uteroplacental tissue between 7 and 16 weeks. American Journal of Obstetrics and Gynecology. 2001;184:998-1003.
23. Jauniaux E, Hempstock J, Teng C, Battaglia F, Burton GJ. Polyol concentrations in the fluid compartments of the human conceptus during the first trimester of pregnancy; maintenance of redox potential in a low oxygen environment. J Clin Endocrinol Metab. 2005;90:1171-5.
24. Semenza GL, Roth PH, Fang HM, Wang GL. Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. J Biol Chem. 1994;269(38):23757-63.
25. Kim JW, Tchernyshyov I, Semenza GL, Dang CV. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. Cell Metab. 2006;3(3):177-85.
26. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab. 2006;3(3):187-97.
27. Simon MC. Coming up for air: HIF-1 and mitochondrial oxygen consumption. Cell Metab. 2006;3(3):150-1.
28. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.
29. Eriksson UJ. Oxidative DNA damage and embryo development. Nature Medicine. 1999;5:715.

30. Nicol CJ, Zielenski J, Tsui L-C, Wells PG. An embryoprotective role for glucose-6-phosphate dehydrogenase in developmental oxidative stress and chemical teratogenesis. FASEB Journal. 2000;14:111-27.
31. Coller HA. Is cancer a metabolic disease? Am J Pathol. 2014;184(1):4-17.
32. Boyd JD. Glycogen in early human implantation sites. Memoirs of the Society for Endocrinology. 1959;6:26-34.
33. Robb SA, Hytten FE. Placental glycogen. Br J Obstet Gynaecol. 1976;83(1):43-53.
34. van Uitert EM, Exalto N, Burton GJ, Willemsen SP, Koning AH, Eilers PH, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod. 2013;28(7):1753-61.
35. Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell. 2010;7(2):150-61.
36. Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development by oxygen tension. Science. 1997;277:1669-72.
37. Zhou S, Xie Y, Puscheck EE, Rappolee DA. Oxygen levels that optimize TSC culture are identified by maximizing growth rates and minimizing stress. Placenta. 2011;32(6):475-81.
38. Hemberger M, Udayashankar R, Tesar P, Moore H, Burton GJ. ELF5-enforced transcriptonal networks define an epigentically regulated trophoblast stem cell compartment in the human placenta. Mol Hum Genet. 2010;19:2456-67.
39. Davies JE, Pollheimer J, Yong HE, Kokkinos MI, Kalionis B, Knofler M, et al. Epithelial-mesenchymal transition during extravillous trophoblast differentiation. Cell Adh Migr. 2016;10(3):310-21.
40. Caniggia I, Mostachfi H, Winter J, Gassmann M, Lye SJ, Kuliszewski M, et al. Hypoxia-inducible factor-1 mediates the biological effects of oxygen on human trophoblast differentiation through TGFbeta(3). J Clin Invest. 2000;105(5):577-87.
41. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. American Journal of Pathology. 2003;162:115-25.
42. Burton GJ, Jauniaux E, Charnock-Jones DS. The influence of the intrauterine environment on human placental development. Int J Dev Biol. 2010;54:303-12.
43. Salafia CM, Yampolsky M, Shlakhter A, Mandel DH, Schwartz N. Variety in placental shape: when does it originate? Placenta. 2012;33(3):164-70.
44. Hempstock J, Bao Y-P, Bar-Issac M, Segaren N, Watson AL, Charnock Jones DS, et al. Intralobular differences in antioxidant enzyme expression and activity reflect oxygen gradients within the human placenta. Placenta. 2003;24:517-23.
45. Schuhmann RA. Placentone structure of the human placenta. Bibliotheca Anatomica. 1982;22:46-57.
46. Lewis DM, Park KM, Tang V, Xu Y, Pak K, Eisinger-Mathason TS, et al. Intratumoral oxygen gradients mediate sarcoma cell invasion. Proc Natl Acad Sci U S A. 2016;113(33):9292-7.

Figure legend

Figure 1. Schematic representation of the interconnections between glycolysis and some of the polyol pathways. Polyols that are at high concentrations in the first trimester placenta are shown in green, and their synthesis enables the regeneration of NAD^+ and $NADP^+$ under low oxygen conditions independent of the TCA acid cycle. NAD^+ is required to maintain glycolysis and production of ATP, whereas $NADP^+$ is important for the generation of reduced glutathione. By contrast, in tumours NAD^+ is regenerated principally through fermentation of pyruvate to lactate under the action of lactate dehydrogenase (LDH). Pathways activated in tumours are shown in red, and include stabilisation of HIF through increasing hypoxia. HIF promotes glycolysis and LDH, but inhibits pyruvate dehydrogenase (PDH) and so blocks the conversion of pyruvate to acetyl-CoA. Consequently, there is a build-up of intermediates in the glycolytic pathway, favouring the diversion of carbon skeletons for synthesis of nucleic acids. Some oncogenes promote cell proliferation through similar effects. PEP; phosphoenolpyruvate.


NADPH
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Osmolyte
Aldose reductase
PI3K/AKT
HIF
Glucose-6-P
NADP+
GSH
Antioxidant defences
NADPH
GSSG
PP pathway
Fructose-6-P
D-Ribose
5-P
Nucleic acids
Cell proliferation
NAD+
NADH
PEP
D-Erythrose-
4-P
NADPH
NADP+
NADH
Tyrosine kinase
ADP
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NAD+
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Erythritol
Ribitol
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NAD+
LDH
PDH
Acetyl-CoA
Lactate
Anaerobic
fermentation
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