1 **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.

48

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).

74 Early placental development can be seen as a continuation of this 'quiet metabolism', for

75 the oxygen concentration within the intervillous space and the embryonic

76 compartments remains at approximately 20 mmHg during most of the first trimester (7,

77 8). Following implantation, the conceptus lies within the superficial endometrium, and

78 as the trophoblast mantle expands it erodes into neighbouring capillaries and into the

79 endometrial glands. Maternal arterial inflow into the placenta only occurs towards the

80 end of the first trimester, as initially the endovascular trophoblast invasion that occurs

81 as part of remodelling of the spiral arteries is sufficiently voluminous to occlude the

82 mouths of most of the vessels (9, 10). A network of narrow intercellular spaces exists

83 between the endovascular trophoblast cells, however, enabling maternal plasma to pass

84 into the placenta at a slow rate. Consequently, there is a continual supply of oxygen,

85 albeit at a low partial pressure and content as it is carried principally in solution in the

86 absence of maternal erythrocytes.

87

88 The distribution of this oxygen to the deeper placental and fetal tissues must initially

89 occur by simple diffusion, for the fetal heart does not start beating until the 5th week of

90 pregnancy, and an effective circulation through the placental villi is only achieved

91 towards the end of the first trimester. Diffusion is facilitated by the large surface area

92 provided by the villous morphology of the placenta, and presence of fluid-filled stromal

93 channels within the villi that communicate with the extra-embryonic coelom (11). The

94 oxygen within the exocoelomic fluid is able reach the deeper tissues within the embryo

95 as the intra- and extra-embryonic coeloms are in free communication before the

96 anterior body folds fuse at around 6 weeks post-fertilisation. When the fetal-placental

97 circulation is established, oxygen transport is achieved during the first three months of

98 pregnancy by high-affinity embryonic haemoglobin (Hb) located inside red cells which

99   are mainly nucleated. The oxygen binding characteristics of embryonic Hb and the high

100   viscosity of circulating blood containing a high proportion of nucleated red cells

101   contribute to limiting oxygen transfer to the fetal tissues (12-14).

102

103   By comparison, although the oxygen tension in many tumours is low, and indeed lower

104   than that inside the early placenta, the situation has a very different ontology. The

105   pattern in tumour masses is one of increasing hypoxia, compared to the steady state

106   seen within the early placenta. In tumours, the initiating growth normally occurs at

107   ordinary tissue oxygen levels, but with expansion the tumour gradually outstrips its

108   blood supply. In solid tumours the opportunity for diffusion is limited, and as a result

109   the central core becomes increasingly hypoxic (15). Although angiogenesis is stimulated

110   through the release of VEGF, the degree of hypoxia may be sufficient to induce necrosis

111   in the core, an event never seen in first trimester placental tissues or in fetal

112   development. In fact, variation in blood flow distribution to the periphery of the early

113   placenta leads to a high level of oxygen exposure inducing apoptosis and degeneration

114   of two-thirds of the original placental mass, a process which is pivotal for the formation

115   of the membranes.

116

117   **Early placental metabolism**

118   Early placental tissues display a high proliferative rate, as do tumour cells, although the

119   drivers are different. In the placenta, proliferation is thought to be stimulated

120   exogenously by mitogens secreted by the endometrial glands (16). Both epidermal

121   growth factor and the insulin-like growth factors promote proliferation of the

122   cytotrophoblast cells when applied to first trimester villous explants (17, 18). These

123   mitogens are presumably transported through the syncytiotrophoblast by the same

124   endocytotic/exocytotic pathways that lead to the accumulation of other gland products,

125   such as glycodelin, in the amniotic fluid (19). By contrast, in tumour cells the drive for

126   proliferation arises as the result of endogenous mutations within growth promoting

127   pathways. However, unlike in a tumour, the placental tissues display no evidence of

128   hypoxic stress. Hypoxia cannot be defined simply by the prevailing partial pressure that

129   cells are exposed to, but rather by whether the oxygen supply is sufficient to meet the

130   metabolic requirements of the cells. Hence, it is notable that the ATP/ADP ratio in

131   placental tissues is the same during the first trimester as it is later in the second

132   trimester and at term (20). Furthermore, there is no stabilisation of either hypoxia

133   inducible factors (HIF-1 and HIF-2) in villi removed by a chorionic villous sampling

134   technique, which avoids any confounding stress induced by exposure to maternal blood

135   as occurs during curettage (20). These differences with the tumour situation most likely

136   reflect the replenishment of oxygen through the perfusion of the intervillous chamber

137   with maternal plasma, and also the different ontological progressions. In addition, the

138   placental tissues are provided with a rich source of glucose for glycolysis by the

139   endometrial glands, along with lipid and proteinaceous substrates (21).

140

141   The exocoelomic fluid is in free communication with the placenta tissues, and so its

142   metabolic profile predominantly reflects placental metabolism. Analysis of the fluid

143   indicates evidence of limited anaerobic metabolism, in that the pH of the fluid at 7-10

144   weeks of gestation is approximately 7.17, with a base excess of -8.9 mmol/l (22). The

145   concentration of lactate is, however, not excessively high (0.6 mmol/l). In part, this may

146   be due to metabolism of lactate by the fetus, but it also reflects the reliance of the

147   placenta on phylogenetically old carbohydrate metabolic pathways involving the

148   formation of polyols (23).

149

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).

164

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,

174   pyruvate is therefore not converted into acetyl-CoA, and the TCA cycle cannot be fuelled,

175   leading to a fall in mitochondrial oxygen consumption (26), which promotes survival in

176   the face of hypoxia. Hypoxic cells instead accumulate pyruvate, some of which is

177   converted to lactate under the action of lactate dehydrogenase (LDH), another HIF-1

178   regulated enzyme (24), and lactate is in turn transported out of the cell (27). The build-

179   up of pyruvate also favours transformation of fructose-6-phosphate to D-ribose-5-

180   phosphate, promoting the synthesis of nucleic acids to support cell proliferation (Figure

181   1). At present it is unclear whether glycolysis is promoted by mitochondrial inhibition

182   in a similar fashion in the case of the placenta, though in the apparent absence of HIF-1

183   stabilisation this would seem unlikely. Instead, placental glycolysis may possibly be

184   promoted early in pregnancy as a necessary means of supporting ATP-synthesis in the

185   absence of significant mitochondrial activity. The time-course of changes in placental

186   mitochondrial density has not yet been established; however, the initiation of significant

187   mitochondrial biogenesis may only coincide with the rise in oxygenation towards the

188   end of the first trimester.

189

190   It might be supposed that in both situations metabolism is relatively inefficient, and

191   does not take advantage of the higher yield of ATP that can be gained through oxidative

192   phosphorylation. However, unlike differentiated cells in adult tissues the rapidly

193   proliferating cells of the placenta and a tumour have additional requirements. There is a

194   need for carbon skeletons that can be incorporated into nucleotides, amino acids and

195   sterols that support synthesis of DNA, cell and organelle membranes, and proteins.

196   Instead of breaking glucose down completely and excreting the carbon atoms as carbon

197   dioxide, maintaining the carbon skeletons as lactate or through the pentose-phosphate

198   pathways allows them to be incorporated into the biomass (28).

199

200 There are other potential benefits for the fetal-placental unit derived through reliance

201 on the polyol pathways. Firstly, conversion of glucose to ribose 5-phosphate produces

202 two molecules of NADPH. NADPH is required for the regeneration of reduced

203 glutathione from its oxidised form, and hence is key to the antioxidant defences of a cell.

204 Developing systems are highly prone to perturbation by oxidative stress, which can lead

205 to severe congenital abnormalities (29, 30). Adequate antioxidant defences are

206 therefore crucial. Secondly, polyols such as sorbitol are incapable of crossing cell

207 membranes and so act as powerful osmolytes. Sorbitol is produced from glucose by the

208 action of aldose reductase, one of the first enzymes to be expressed in the sheep

209 conceptus. In this species there is a rapid expansion of the embryonic sac into a thread-

210 like structure, and sorbitol may assist in driving this process by drawing water across

211 the trophoblast epithelium. In the human there is a similar, though less extensive, need

212 to expand the extra-embryonic coelom.

213

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

215 Although at first sight the reliance on glycolysis for energy production in the early

216 placenta and tumours may appear to be inefficient, there is no reason to assume that it

217 cannot meet the cells' requirements as long as there is a sufficient supply of glucose

218 (31). In the case of the placenta there is a plentiful supply in the secretions derived from

219 the endometrial glands, and accumulation of glycogen within the syncytioplasm is a

220 conspicuous feature during early pregnancy (21, 32).

221

222 Thus, these metabolic pathways enable a high rate of proliferation to be maintained

223 under a relatively low oxygen concentration. The rise in oxygen concentration within

224 the placenta and the embryonic compartments at the end of the first trimester notably

225 coincides with the completion of organogenesis. At this stage of development the risk of

226 teratogenesis falls sharply, as differentiation of the major organ systems is completed.

227 The risks from oxygen free radicals therefore falls somewhat, and so the metabolic

228 balance may tip in favour of oxidative phosphorylation. Evidence for such a shift comes

229 from the rapid fall in placental glycogen content at the end of the first trimester (33),

230 and it may explain the rise in growth rate of the embryo seen at this stage (34).

231

232 Increasing evidence from the field of stem cell biology indicates that adult stem cell

233 niches are located in low oxygen environments, roughly equivalent to the intraplacental

234 oxygen concentration during the first trimester (35). Consistent with this, studies have

235 revealed that culture of primary cytotrophoblast cells under low oxygen conditions

236 favours proliferation, whereas higher concentrations promote differentiation and

237 invasion (36, 37). With respect to this finding, it is notable that levels of CDX2 and ELF5,

238 two transcription factors that act as gate-keepers of the trophoblast lineage, drop

239 sharply at the end of the first trimester (38). This suggests a reduction in the

240 proliferative potential of the placenta, but whether this is due to the three-fold rise in

241 intra-placental oxygen concentration that occurs at the start of the second trimester (8),

242 or the loss of growth factors from the endometrial glands with the switch from

243 histotrophic to haemotrophic nutrition has not yet been clarified.

244

245 **Oxygen and cell differentiation**

246 Within the placenta, a sub-population of trophoblast cells, the extravillous trophoblast,

247 undergo a partial epithelial-mesenchymal transition and migrate from the outer surface

248 of the cytotrophoblastic shell into the endometrium (39). In doing so they adopt a

249 pleiotrophic phenotype and move into an area of higher oxygen concentration, for the

250 decidua is always better oxygenated than the placenta (8). In many ways this resembles

251 the process of metastasis, albeit a highly regulated one, but the influence of oxygen on

252 the transition is still unclear. Experimental studies of first trimester explant cultures

253 have demonstrated that oxygen may be a significant factor, for culture under low oxygen

254 conditions (3% v 21%) inhibits invasion. This effect is mediated through the HIF-1 and

255 transforming growth factor beta (TGFß) pathways, and is associated with changes in

256 matrix metalloproteinase activity (40).

257

258 Local oxygen concentrations also appear to play a role in remodelling of the early

259 placenta into its definitive form. Villi initially form over the entire surface of the

260 chorionic sac, but later regress to leave the discoid placenta at the deep pole in contact

261 with the endometrium, and the smooth membranes. This remodelling coincides with

262 onset of the maternal arterial circulation to the placenta, which starts preferentially in

263 the periphery and then extends centripetally, reflecting the degree of trophoblast

264 invasion and arterial plugging across the placental bed (41). Villi sampled from the

265 peripheral region display higher levels of oxidative stress and activation of the apoptotic

266 cascade than their counterparts from the central region, and it has been proposed that

267 these effects mediate the regression. Excessive regression at this stage of development

268 may lead to placentas with eccentric insertions of the umbilical cord and more irregular

269 margins (42, 43).

270

271 Even within the definitive placenta there will be oxygen gradients that reflect the

272 pattern of maternal arterial blood flow. The placental villi are not arranged at random,

273 but form 30-40 lobules, each centred over the opening of a maternal spiral artery. The

274   arteries deliver their blood into the relatively villus-free central cavities of a lobule.

275   From there, the blood percolates through the network of intervillous clefts, exchanging

276   oxygen with the fetal circulation as it does so, before draining into the openings of the

277   uterine veins. Each lobule thus represents an individual maternal-fetal exchange unit,

278   and the pattern of the circulation suggests an oxygen gradient from the arterial centre to

279   the more venous periphery. This concept is supported by differences in the expression

280   and activity of the principal antioxidant enzymes (44). These differences in oxygenation

281   may explain regional variations in villous morphology and enzyme activities (45).

282   Oxygen gradients similarly occur within tumours due to the limitations of diffusion (15),

283   and again may mediate cell behaviours, such as resistance to radiotherapy, or

284   predisposition to metastasis (46).

285

286   **Conclusion**

287   Early placental development occurs in a low oxygen environment, and as a rapidly

288   proliferating tissue it shares many of the same metabolic requirements as tumours.

289   However, in the placenta there is continual replenishment of oxygen due to plasma

290   flowing at a slow rate through the intervillous space, and so the tissues do not

291   experience the increasing drive towards hypoxia that typifies the central regions of

292   tumours. Nonetheless, oxygen appears to be a major regulator of cell behaviour in both

293   the placenta and tumours. A better understanding of the similarities and differences

294   between the two may lead to new insights that are beneficial to these contrasting fields

295   of biology.

296

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301   **Conflict of interest**

302   The authors have no conflicts of interest to declare.

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428 **Figure legend**

429   Figure 1. Schematic representation of the interconnections between glycolysis and some

430   of the polyol pathways. Polyols that are at high concentrations in the first trimester

431   placenta are shown in green, and their synthesis enables the regeneration of NAD^+ and

432    $NADP^+$ under low oxygen conditions independent of the TCA acid cycle. NAD^+ is required

433   to maintain glycolysis and production of ATP, whereas $NADP^+$ is important for the

434   generation of reduced glutathione. By contrast, in tumours NAD^+ is regenerated

435   principally through fermentation of pyruvate to lactate under the action of lactate

436   dehydrogenase (LDH). Pathways activated in tumours are shown in red, and include

437   stabilisation of HIF through increasing hypoxia. HIF promotes glycolysis and LDH, but

438   inhibits pyruvate dehydrogenase (PDH) and so blocks the conversion of pyruvate to

439   acetyl-CoA. Consequently, there is a build-up of intermediates in the glycolytic pathway,

440   favouring the diversion of carbon skeletons for synthesis of nucleic acids. Some

441   oncogenes promote cell proliferation through similar effects. PEP;

442   phosphoenolpyruvate.