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### Commentary

Human developmental biology has been stirred by the emergence of evidence that the early placental environment is hypoxic (1). Plugs of cytotrophoblasts block maternal spiral arteries that supply the placental site (2), and when the intervillous space is observed through a hysteroscope, it appears devoid of maternal erythrocytes. At about the 11th week of gestation, however, the plugs are displaced and blood flow begins. As a result, the local partial pressure of oxygen increases from about 18 to 60 mm (3), whereupon the placenta develops enhanced mechanisms for protection against oxidative damage (4). Pathways of regulation of trophoblast function by oxygen are not well known, but in this issue of the JCI, Caniggia and colleagues (5) investigate a transcription factor that appears to participate in physiological changes during this transition. This transcription factor, hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), belongs to the basic helix-loop-helix family and functions as a heterodimer with its constitutively expressed partner HIF-1 $\beta$ , or ARNT, to bind gene regulatory regions. As Caniggia et al. now show, HIF-1 $\alpha$  is present in the placenta before 10 weeks, but not at 11–14 weeks of gestation. Most placental villi float freely in the intervillous space, but specialized anchoring villi at the periphery attach the placenta to the decidual surface (6). These anchoring villi also act as feeder sites for the many migratory [...]

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Human developmental biology has been stirred by the emergence of evidence that the early placental environment is hypoxic (1). Plugs of cytotrophoblasts block maternal spiral arteries that supply the placental site (2), and when the intervillous space is observed through a hysteroscope, it appears devoid of maternal erythrocytes. At about the 11th week of gestation, however, the plugs are displaced and blood flow begins. As a result, the local partial pressure of oxygen increases from about 18 to 60 mm (3), whereupon the placenta develops enhanced mechanisms for protection against oxidative damage (4). Pathways of regulation of trophoblast function by oxygen are not well known, but in this issue of the *JCI*, Caniggia and colleagues (5) investigate a transcription factor that appears to participate in physiological changes during this transition. This transcription factor, hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), belongs to the basic helix-loop-helix family and functions as a heterodimer with its constitutively expressed partner HIF-1 $\beta$ , or ARNT, to bind gene regulatory regions. As Caniggia et al. now show, HIF-1 $\alpha$  is present in the placenta before 10 weeks, but not at 11–14 weeks of gestation.

Most placental villi float freely in the intervillous space, but specialized anchoring villi at the periphery attach the placenta to the decidual surface (6). These anchoring villi also act as feeder sites for the many migratory extravillous cytotrophoblasts (EVT) that infiltrate the decidual interstitium and spiral arteries (6, 7). These cells transform the arterial walls, allowing expansion, so that the blood supply can increase with fetal demands. Transformation proceeds from very early stages until about the 18th week, suggesting that trophoblast must be recruited into this lineage in both the first and second trimester. Similarly, to sustain placental growth, differentiation along another major

pathway, from stem cytotrophoblast into villous syncytiotrophoblast, must occur efficiently both before and after the oxygen transition.

The mechanism of anchoring villus formation has been illuminated by several groups using placental explants cultured *ex vivo* under varying concentrations of oxygen. First trimester villi, explanted onto a 3-dimensional extracellular matrix in 20% oxygen, form new sites spontaneously at their tips (8–10), whereas explants cultured in 2 or 3% oxygen show increased EVT production (5, 10, 11). Cytotrophoblast proliferation has long been known to be higher in hypoxia (12, 13), although the placental oxygen sensor still remains to be identified. Furthermore, as predicted from observations *in vivo*, HIF-1 $\alpha$  mRNA levels are several-fold higher after culture in low oxygen. Now, following up on their earlier finding that TGF- $\beta$ 3 mRNA levels decline after the oxygen transition (14), the Caniggia group shows that TGF- $\beta$ 3 levels decline when HIF-1 $\alpha$  mRNA is reduced by antisense treatment. Because reduction of TGF- $\beta$ 3 has no effect on HIF-1 $\alpha$  levels (5), they conclude that TGF- $\beta$ 3 lies downstream of HIF-1 $\alpha$ .

Beyond its effects on TGF- $\beta$ 3, HIF-1 $\alpha$  inhibits the expression of integrin  $\alpha$ 1 $\beta$ 1 and MMP9, which are required for migration (5, 11). Caniggia and colleagues argue that TGF- $\beta$ 3 acts in an autocrine fashion to regulate these events. Certainly, TGF- $\beta$  inhibits trophoblast migration in culture (15), but for several reasons interpretation of the new data is not straightforward. First, cytotrophoblast proliferation, migration, and colonization of decidua occur *in vivo* both before and after the oxygen transition (7, 16). Second, *de novo* column formation occurs in cultures in 20% oxygen (9, 10). Third, TGF- $\beta$  is abundantly expressed in decidua (17), the very environment through which trophoblast migration occurs. Thus, observations made both *in vivo* and *in*

*vitro* suggest that the placenta adapts to a changing oxygen environment by maintaining its core functions — anchorage, EVT migration, hormone production, and nutrient transfer — but that it adjusts the rate of each process to meet fetal requirements at specific developmental stages.

Placental hypoxia, prolonged beyond the first trimester, is now recognized as a probable cause of pregnancy pathology (12, 13). Thus, for example, preeclampsia is associated with failed transformation of maternal spiral arteries by EVT (18). TGF- $\beta$ 3 overexpression has been reported in preeclamptic placenta (14). Some authors have linked preeclampsia to a failure of EVT migration, and Caniggia et al. (14) suggest

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that elevated TGF- $\beta$ 3 and a consequent inhibition of cell differentiation may be responsible for this failure. However, interstitially migrating EVT are abundant in the preeclamptic placental bed (18). Hence, the inability of these cells to enter and transform the arteries remains unexplained.

The TGF $\beta$  family is controlled by proteases, binding proteins, and receptors, and more information is needed about the availability and activity of these molecules at the maternal-fetal interface. The explant model of EVT differentiation represents a significant technical advance. Assays of this kind that reflect, as faithfully as possible, the gravid uterine environment will play a vital role in elucidating developmental mechanisms and should lead to earlier and more effective treatments for pregnancy pathology.

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