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Successful embryo implantation requires complex interactions between the uterus and embryo, including the establishment of maternal immunologic tolerance of fetal material. The maternal-fetal interface is dynamically populated by a wide variety of innate immune cells; however, the relevance of uterine DCs (uDCs) within the decidua to the success of implantation has remained unclear. In this issue of the JCI, Plaks et al. show, in a transgenic mouse model, that uDCs are essential for pregnancy, as their ablation results in a failure of decidualization, impaired implantation, and embryonic resorption (see the related article beginning on page 3954). Depletion of uDCs altered decidual angiogenesis, suggesting that uDCs contribute to successful implantation via their effects on decidual tissue remodeling, including angiogenesis, and independent of their anticipated role in the establishment of maternal-fetal tolerance.

Placental viviparity, a mode of reproduction during which nutrients are supplied to the embryo directly from the mother via the placenta, poses a number of challenges. The first is the requirement for coordinated development of maternal and fetal tissue, while the second, in mammals, demands maternal immunologic tolerance of the fetus, which expresses foreign transplantation antigens. This latter requirement poses a significant immunological challenge.

Nonstandard abbreviations used: DT, diphtheria toxin; sFLT1, soluble FMS-like tyrosine kinase 1; uDC, uterine DC; uNK cell, uterine NK cell.

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Uterine DCs are essential for pregnancy

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required for successful embryo implantation and decidualization in mice (Figure 1). The authors used a suicide gene ablation approach to specifically delete uDCs during embryo implantation in these animals. As part of this approach, the human diphtheria toxin receptor (DTR) was expressed from the CD11c promoter, which made cells expressing the receptor uniquely sensitive to diphtheria toxin (DT); mice do not have the DTR and are thereby resistant to DT. Since CD11c is restricted to DCs, these cells were rapidly ablated with little to no ablation of other hematologic cells. The ablation of uDCs during implantation resulted in a failure of decidualization and embryo resorption. This effect was specific to the uterus and did not involve the embryo, since uDC ablation also blocked decidualization in an artificially induced model of decidualization in the absence of the embryo. Furthermore, this was a local effect and not secondary to a systemic effect, as administration of DT to one uterine horn resulted in retarded decidualization, while the contralateral control horn was unaffected. In addition, uDC ablation resulted in failed decidualization in both allogeneic and syngeneic pregnancies. These data indicate that uDCs are essential to implantation and decidualization, and this requirement did not have an immunological component, but rather represented trophic activities of uDCs.

**Decidual angiogenesis is regulated by uDCs**

These studies raise the question, By what mechanisms do DCs affect decidualization? One of the earliest events in the decidual response is an increase in vascular permeability, induced by the rapid expression of the angiogenic factor VEGF upon embryo attachment to a suitably hormone-primed uterus. This is in fact the basis for the earliest test of implantation, called blue spotting, which is the result of extravasation of i.v. administered pontamine blue dye at these sites of vascular permeability immediately below the attached blastocyst. After this increase in vascular permeability, there is rapid decidual cell proliferation and decidual transformation of the underlying stroma, giving rise to epithelioid-type cells that surround the invading blastocyst. These cells form the primary decidual zone, which is in turn surrounded by a diploid secondary decidual zone (Figure 1). After the decidua is formed, there is extensive vascularization via sprouting of the uterine artery at the mesometrial side (site of future placenta), which results in the formation of very dilated vessels and the bathing of the implantation nodule with maternal blood. Using sophisticated dynamic macromolecular contrast-enhanced MRI–assisted studies following partial uDC ablation that allowed some decidual response compared with controls, Plaks et al. show that these early vascular events were significantly perturbed following uDC ablation (7). Indeed, the data suggest that uDC depletion delayed the angiogenic response, increased vascular permeability, and inhibited blood vessel maturation.

In mice, uDCs are restricted to the outer decidual zones (Figure 1) and are often found associated with blood vessels, consistent with a role in angiogenesis. Taking a...
Figure 2
Proposed roles of uDCs in the regulation of angiogenesis and T cell action at the maternal-fetal interface. During pregnancy, monocytes are recruited to the uterus, where they differentiate into mature tolerogenic cells such as uDCs, under the influence of CSF-1, GM-CSF, and other cytokines (usually IL-4, although this cytokine has not been found in the uterus). uDCs produce sFLT1 and TGF-β1, which act to maintain the intricate balance of vascular development: sFLT1 modulates the actions of VEGF, and TGF-β1 influences endothelial cell viability and vascular maturation. A fine-tuning of angiogenesis is required for decidualization and embryo implantation. In addition, other studies have shown that TGF-β1 is presented by DCs at their surface on αvβ8 integrin. TGF-β1 suppresses cytotoxic CD8+ T cell function and promotes the development of Tregs. These data suggest that in addition to their role in decidual development, as shown in the present study by Plaks et al. (7), uDCs also play a role in immunoregulation. Together, these dual functions of uDCs contribute to successful implantation and the progression of an allogeneic pregnancy. This whole process is further coordinated during implantation and decidualization by the uterine synthesis of the growth factors VEGF and CSF-1 under the control of the ovarian hormones E2 and P4 (see Figure 1), which are the master regulators of pregnancy.

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Tumor metabolism: cancer cells give and take lactate

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Tumors contain well-oxygenated (aerobic) and poorly oxygenated (hypoxic) regions, which were thought to utilize glucose for oxidative and glycolytic metabolism, respectively. In this issue of the JCI, Sonveaux et al. show that human cancer cells cultured under hypoxic conditions convert glucose to lactate and extrude it, whereas aerobic cancer cells take up lactate via monocarboxylate transporter 1 (MCT1) and utilize it for oxidative phosphorylation (see the related article beginning on page 3930). When MCT1 is inhibited, aerobic cancer cells take up glucose rather than lactate, and hypoxic cancer cells die due to glucose deprivation. Treatment of tumor-bearing mice with an inhibitor of MCT1 retarded tumor growth. MCT1 expression was detected exclusively in nonhypoxic regions of human cancer biopsy samples, and in combination, these data suggest that MCT1 inhibition holds potential as a novel cancer therapy.

The pioneering work of Peter Vaupel and his colleagues established that the partial pressure of oxygen (pO₂) within human cancers is frequently much lower than that of the surrounding normal tissue and that intratumoral hypoxia is associated with an increased risk of local spread, metastasis, and patient mortality (1). Rakesh Jain’s laboratory demonstrated that in mouse tumor xenografts, the mean pO₂ and pH declined as distance from the nearest blood vessel increased (2), reflecting the switch from oxidative to glycolytic metabolism that occurs in response to reduced O₂ availability.

This metabolic reprogramming is orchestrated by HIF-1 through the transcriptional activation of key genes encoding metabolic enzymes, including: LDHA, encoding lactate dehydrogenase A, which converts pyruvate to lactate (3); PDK1, encoding pyruvate dehydrogenase kinase 1, which inactivates the enzyme responsible for conversion of pyruvate to acetyl-CoA, thereby shunting pyruvate away from the mitochondria (4, 5); and BNIP3, which encodes a member of the BCL2 family that triggers selective mitochondrial autophagy (6) (Figure 1). In addition, HIF-1 transactivates GLUT1 (7) — which encodes a glucose transporter that increases glucose uptake to compensate for the fact that, compared with oxidative phosphorylation, glycolysis generates approximately 19-fold less ATP per mole of glucose — and genes encoding the glycolytic enzymes that convert glucose to pyruvate (3). The extracellular acidosis associated with hypoxic tumor cells is due to both increased H+ production and increased H+ efflux through the HIF-1–mediated transactivation of: CA9, which encodes carbonic anhydrase IX (8); MCT4, which encodes monocarboxylate transporter 4 (9); and NHE1, which encodes sodium-hydrogen exchanger 1 (10).

Metabolic symbiosis

In this issue of the JCI, the elegant article by Sonveaux, Dewhirst, et al. makes a major contribution to the field of cancer biology (11).