Role of decidual natural killer cells, interleukin-15, and interferon-γ in placental development and preeclampsia

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IN RODENTS AND HUMANS, implantation is the first coordinated encounter between mother and baby (7). The process of decidualization is defined as the differentiation of uterine stromal cells into epithelial-like decidual tissue, beginning during the periimplantation period at embryonic day (e) 4.5 in mice (7). This transitory process is characterized by significant vascular remodeling of the uterus (e5.5–e7.5) to ensure proper placental blood flow (7). The decidua also modulates critical local immune responses (9).

Coincident with decidualization in humans and mice is the appearance of decidual natural killer (dNK) cells, the predominant immune cell at the maternal-fetal interface (4, 9, 10). Activation of dNK cells has been linked to uterine interleukin (IL)-15 (4). IL-15<sup>−/−</sup> mice show inappropriate decidualization, lack mature dNK cells, and, interestingly, produce low-birthweight pups (3). Exogenous IL-15 administration in these mice restores dNK cell populations, thus confirming its importance in dNK cell maturation. In mice, mature dNK cells are recognized histologically by their lymphoid shape and cytoplasmic granules that react with Dolichos biflorus agglutinin (DBA) (5). DBA<sup>+</sup> cells have been identified as early as e5.5 in the decidua (12). They continue to proliferate and accumulate at the base of the placenta, obtaining peak numbers at midgestation (~e12.5) and declining thereafter (5). Mature dNK cells maintain decidual integrity and produce factors that directly modify decidual vessels (10). Upon stimulation by IL-15, dNK cells begin secreting key angiogenic factors, including interferon-γ (IFN-γ) (12) (Fig 1). In mice, IFN-γ provides the signals that transiently change spiral arteries from constricted to dilated high-capacitance vessels necessary for adequate placental perfusion (4). Endometrial IFN-γ expression mirrors dNK cell localization in the uterus (12). This expression profile was not observed in a mouse strain (tg<sup>e26; NK<sup>b<sup>−/−</sup>T<sup>b</sup>+</sup>) having much reduced levels (only 1%) of normal dNK cell numbers (1). IFN-γ is also thought to promote senescent decline of dNK cells after midgestation (5). Implantation sites from Ifng null mice exhibit excessive numbers of incompletely differentiated dNK cells, widespread decidual necrosis, inappropriate spiral artery modifications (12), and significant fetal loss (1). Treatment of alymphoid mice with recombinant IFN-γ results in normal decidual and arterial morphology (12). Therefore, the production of IFN-γ by dNK cells is critical for gestational changes in the decidua and uterine vasculature.

Increased decidual IL-15 expression has been linked to recurrent miscarriage in women, suggesting impaired implantation and vascularization of the placenta (15). Other reports have demonstrated increased circulating IL-15 levels in the serum of preeclamptic mothers compared with healthy controls, where IL-15 levels were proportional to severity of disease presentation (11). These findings provide evidence that IL-15 may be involved in poor pregnancy outcomes. IFN-γ may also play a role in preeclampsia, since it is reported to be elevated in plasma, circulating leukocytes, and decidua from patients with preeclampsia (12). There is conflicting evidence regarding the significance of dNK cells in pregnancy outcomes. Some reports state that dNK cells are increased in...
Decidual natural killer (dNK) cell recruitment during decidualization is necessary for establishing blood flow to the placenta. A: window of implantation in mice is between embryonic days (e) e3.5 and e5.5 (rectangle). Decidualization begins at e4.5, peaks at e7.5, and declines thereafter as the placental unit is formed by e10.5 (trapezoid). B: coincident with decidualization is the appearance of dNK cells into the uterus at e5.5 with cell numbers increasing to reach maximum between e10.5 and e12.5. C: pre-dNK cells are activated by uterine IL-15 to mature dNK cells that produce angiogenic factors, including IFN-γ, which is important in spiral artery remodeling for adequate placental blood flow. Evidence in human preeclamptic pregnancies and our BPH/5 mouse model of preeclampsia indicates dysregulation in mature dNKs, IL-15, and IFN-γ (bold arrows). M, mesometrial pole; AM, anti-mesometrial pole; E, embryo; D, decidua; P, placenta; F, fetus.

Perspectives and Significance

Both dNK cell activation by IL-15 and dNK secretion of IFN-γ are crucial for placental development. Interestingly, BPH/5 mice show elevations in IL-15 and IFN-γ mRNA as well as a dramatic reduction in mature dNK cells. Other mouse models lacking dNK cells, IL-15, or IFN-γ have significant placental and/or fetal abnormalities. Furthermore, women with pregnancy-related disorders also show dysregulation in IL-15, IFN-γ, and dNK cells. Therefore, understanding the significance of dNK cells and related cytokines in preeclampsia and other pathological pregnancies with abnormal placenta formation is of utmost importance. Mouse models such as the BPH/5 offer critical tools for investigating this at the earliest stages of pregnancy.

REFERENCES


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DISCLOSURES

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AUTHOR CONTRIBUTIONS


pecreclampsia, albeit with an altered phenotype (2), whereas others show dNK cells are decreased in preeclamptic placental samples (17). Interestingly, others propose that dNK cell function, rather than number, may be altered in preeclampsia (16).

Because dNK cells are critical for uterine angiogenesis and spiral artery remodeling, gestational processes that are often pathological in preeclamptic pregnancies, we asked whether dNK cell activation and function were dysregulated before placenta formation in our model of preeclampsia, BPH/5. These mice spontaneously develop the maternal signs of preeclampsia, including hypertension and proteinuria, as well as similar placental defects observed in human preeclamptic placentae such as inadequate remodeling of spiral arteries (6, 8). We found dNK cell mRNA expression in BPH/5 implantation sites was similar to C57Bl/6 controls at e4.5 but dramatically reduced at e5.5. This finding was confirmed by a marked decrease in mature dNK cell numbers at e5.5 in BPH/5 implantation sites as measured by flow cytometry and immuno-

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