Killing the pathogen and sparing the placenta

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A healthy human pregnancy requires a careful balancing act: the maternal immune system must not reject the fetus — which is half foreign — and yet must be ready to attack pathogens such as bacteria and viruses.1 Decidual natural killer (NK) cells help to maintain this balance. These cells invade the maternal side of the placenta (i.e., the decidua). However, the classical lytic mode of NK activity, releasing cytotoxic granules that contain membrane-lysing peptides, would damage the host. Crespo and colleagues have recently described a new, more precise mechanism by which decidual NK cells attack pathogens without harming the placenta and fetus.2

The balancing act of maintaining immune tolerance of the fetus and protective immunity occurs at the maternal–fetal interface of the placenta. The placenta forms when embryo-derived cytotrophoblasts fuse to create multinucleated syncytiotrophoblasts, which mediate the maternal–fetal exchange of nutrients and gases. Cytotrophoblasts also make up the villi that anchor the embryo to the uterine wall. Moreover, they occupy the decidual space (and thus are extravillous trophoblasts) (Fig. 1), where they remodel the maternal spiral arteries, increasing the blood supply to the fetus. To evade recognition as “foreign” by maternal immune cells, extravillous trophoblasts express tolerogenic HLAs — HLA-G, HLA-E, and HLA-C. The expression of HLA-G by extravillous trophoblasts is critical to their ability to “educate” decidual NK cells to promote tolerance; this is achieved through filamentous projections that serve as synapses between the trophoblasts and the decidual NK cells.3 However, parasites, viruses, and the bacterium Listeria monocytogenes can subvert this mechanism in order to infect the placenta and fetus.4 Thus, tolerance of extravillous trophoblasts by decidual NK cells permits infection of the fetus by L. monocytogenes, resulting in fetal loss. Fortunately, the cytotoxic activity of decidual NK cells is often sufficient to kill L. monocytogenes. However, until now, the mechanism by which decidual NK cells are able to kill the bacterium without damaging placental cells was unclear.

Crespo et al. showed that decidual NK cells selectively kill L. monocytogenes in extravillous trophoblasts, without killing these cells, by injecting the protein granulysin into the trophoblasts through nanotubes (Fig. 1). The authors first showed that supernatants from decidual NK cells could kill intracellular L. monocytogenes in cultures of both a trophoblast cell line and primary extravillous trophoblasts. Treating decidual NK cells with an antigranulysin antibody...
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In the context of L. monocytogenes infection, the placenta plays a crucial role in protecting the fetus. The diagram illustrates the interactions between L. monocytogenes and the placenta, with a focus on the role of toleregenic HLA molecules expressed by extravillous trophoblasts to prevent the action of cytotoxic granules.

- **Cytotoxic granules** remain immobilized owing to the toleregenic effect of HLA expressed by trophoblasts.
- **Granulysin** permeabilizes cholesterol-poor phagosome and bacterial membranes, causing bacterial death without affecting host-cell plasma membrane.

The diagram highlights the complex interplay between bacterial infection and the maternal immune response, emphasizing the importance of toleregenic mechanisms in maintaining fetal health.

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or blocking their ability to secrete proteins prevented bacterial killing. However, bacterial killing did not require the decidual NK cells to release cytotoxic granules. Although decidual NK cells contain both granulysin and perforin (which makes pores in target cells) within the granules, they also contain cytosolic granulysin. Crespo et al. showed that decidual NK cells kill \textit{L. monocytogenes} in extravillous trophoblasts by directly transferring cytosolic granulysin to the trophoblasts through actin-containing nanotubes. Treating the infected cells with neuraminidase, a sialidase that cleaves glycosidic linkages, limited bacterial killing, which suggests that the recognition of sialylated moieties on extravillous trophoblasts triggers nanotube formation.

Crespo et al. showed that peripheral NK cells could also transfer granulysin to macrophages and dendritic cells without killing these cells. Thus, the authors may have uncovered a general mechanism by which NK cells selectively kill pathogens. Although previous work had shown that granulysin more effectively kills bacteria in the presence of perforin or granzyme, Crespo et al. showed that granulysin can kill \textit{L. monocytogenes} on its own — which could be considered a “stealth move” that destroys invading bacteria without raising alarm.

The authors then went a step further and asked whether this new mechanism occurs in vivo. To address this possibility, they used mice engineered to express human granulysin. (Although most mammals have \textit{GNLY}, the gene encoding granulysin, rodents do not.) Lieberman and colleagues have previously shown that \textit{GNLY}-transgenic mice were able to clear intracellular bacterial (\textit{L. monocytogenes}) infections more efficiently than control mice. In the current study, Crespo et al. found that pregnant \textit{GNLY}-transgenic mice were less susceptible to infection than control mice. Moreover, depletion of uterine NK cells (the murine counterparts of decidual NK cells) led to the resorption of fetuses in \textit{L. monocytogenes}-infected \textit{GNLY}-transgenic mice. However, because mice lack \textit{GNLY} and several other genes that mediate NK function in humans, caution is warranted in considering the implications of these data for understanding protection against bacterial infection in human pregnancy.

Granulysin belongs to a family of proteins that efficiently permeabilize cholesterol-poor mammalian membranes but not cholesterol-rich mammalian membranes (Fig. 1). In classical NK action, granulysin and another cytotoxic molecule, granzyme, are delivered to cells through the action of perforin, which damages mammalian membranes. However, granulysin itself is a potent, multipronged weapon: it induces microptosis — microbial programmed cell death — by blocking microbial antioxidant defenses and biosynthetic and metabolic pathways required for bacterial survival. The mechanism by which granulysin selectively cleaves the enzymes that are essential for microbial survival is unclear, but this ability may be evolutionarily conserved: granulysin causes substantial mitochondrial damage, probably because mitochondrial membranes resemble bacterial membranes. Granulysin can also attack the membranes of other organelles with low cholesterol content (e.g., endoplasmic reticulum) (Fig. 1).

Crespo and colleagues have elucidated a new mechanism by which decidual NK cells protect the developing fetus from infection without damaging the placenta. Further work to delineate the extent to which this mechanism is at play in protecting human pregnancies could lead to new strategies to treat infections during pregnancy. Moreover, because peripheral NK cells and some cytotoxic T cells appear to share with decidual NK cells the ability to secrete granulysin, it will be exciting to see whether this nanotube-mediated mechanism functions in other tissues to kill pathogens while limiting tissue damage.

Disclosure forms provided by the author are available at NEJM.org.

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