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NK CELLS

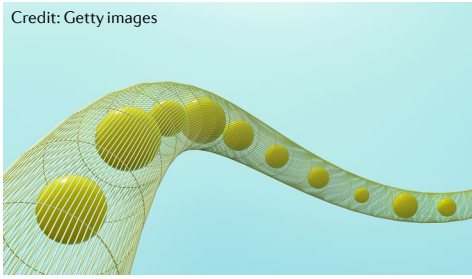
Killing via nanotubes

> decidual NK cells reduced bacterial loads while sparing the infected cells

During pregnancy, maternal immune cells must balance the contradictory demands of tolerating the fetus and providing protection against placental infection. A new study in *Cell* shows that natural killer (NK) cells in the placenta decidual tissue have an elegant way of achieving this balance. Instead of killing infected placental trophoblasts, decidual NK cells transfer the antimicrobial peptide granulysin through nanotubes to trophoblasts to kill intracellular bacteria, sparing the trophoblast.

Decidual NK cells are inferior killers compared with NK cells from the periphery, yet they express high levels of the cytotoxic effectors perforin, granzymes and granulysin. To better understand this conundrum and its impact on infection, Judy Lieberman and colleagues studied placental infection with *Listeria monocytogenes*, which can cause miscarriage, stillbirth and neonatal sepsis. Co-culture of human decidual or peripheral NK cells with a trophoblast-like cell line JEG-3 infected with *L. monocytogenes* significantly reduced intracellular bacteria levels but did not result in JEG-3 cell death. Bacterial killing could be inhibited by granulysin-blocking antibodies, but not by inhibitors of degranulation or perforin pore formation, and required NK cell–JEG-3 cell contact. Similar results were observed using primary extravillous trophoblasts, 3D placental villous explants as well as decidual macrophages and dendritic cells, in which decidual NK cells reduced bacterial loads while sparing the infected cells.

To investigate the cell contact dependency of the bacterial killing, the authors tracked cytotoxic mediators in co-culture assays. Granulysin, but not granzyme B, was transferred to infected and non-infected trophoblasts after 3 hours of co-culture with decidual NK cells or activated peripheral NK cells, which have upregulated granulysin expression. By also labelling for actin and lymphocyte function-associated antigen 1 (LFA1), which is expressed by NK cells not trophoblasts, confocal microscopy revealed that NK cells did not form classical immune synapses with JEG-3 cells and instead cytoplasmic extensions resembling nanotubes connected the cells, occurring more frequently from decidual NK cells than from peripheral NK cells. Moreover, granulysin was observed within the nanotubes connecting decidual NK cells and trophoblast cells. Granulysin transfer and bacterial killing was reduced by inhibition of actin polymerization but not by inhibition of endocytosis or microtubule formation, confirming the role for nanotubes.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Lastly, the in vivo relevance was evaluated using mice expressing human granulysin. Uterine NK cells from these mice selectively reduced intracellular bacteria while sparing the infected trophoblasts in vitro, in a granulysin-dependent, perforin-independent manner. Compared with wild-type mice, pregnant granulysin-transgenic mice had much lower bacterial loads in the placenta and fetus and no evidence of systematic spread following infection with *L. monocytogenes*. Most importantly, granulysin-transgenic mice were protected from infection-induced pregnancy loss.

So, delivering cytotoxic molecules via nanotubes ensures that decidual NK cells protect against infection and preserve maternal–fetal tolerance.

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ORIGINAL ARTICLE Crespo, Â. C. et al. Decidual NK cells transfer granulysin to selectively kill bacteria in trophoblasts. *Cell* https://doi.org/10.1016/j.cell.2020.07.019 (2020)