Journal club

NK CELL ALLORECOGNITION

My interest in uterine natural killer (NK) cells began in the early 1990s, when I and others described the striking accumulation of NK cells in the uterine mucosa during the establishment of the placenta. Whilst working as a reproductive pathologist, I had become intrigued by pre-eclampsia, a mysterious syndrome that only occurs in pregnant women. It was the discovery of the killer cell immunoglobulin receptor (KIR) gene family by several groups, and in particular the study by Colonna and Samaridis in 1995, that provided the stimulus to understanding the link between NK cells and pre-eclampsia.

The primary defect of pre-eclampsia was known to be failure of placental trophoblast cells to adequately transform the spiral arteries so that the placenta becomes 'starved' as fetal demand increases. Pre-eclampsia occurs most often in

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first pregnancies, and paternal genes have been implicated in the pathology owing to the increased risk of pre-eclampsia in a second pregnancy after changing partners following a normal first pregnancy. These features of pre-eclampsia — memory and specificity for the partner — suggested involvement of the immune system. The accumulation of uterine NK cells around the fetal trophoblast cells made it likely that these were the maternal immune cells involved in regulating placentation, but it was a mystery how they might do so. Emboldened by the phenomenon of hybrid resistance in mice — in which NK cells from F1 hybrids reject parental cells — we sought to understand how human uterine NK cells could mediate allorecognition of trophoblast cells.

Following findings that NK cell clones were heterogeneous and could distinguish between groups of HLA class I molecules (reviewed by Moretta *et al.*, 1992), monoclonal antibodies raised to these NK cells were used by Colonna and Samaridis to define the highly polymorphic family of KIRs.

Together with our finding that HLA-C is the only polymorphic HLA class I molecule expressed by invasive trophoblast, this discovery showed how recognition between maternal KIRs and fetal HLA-C could operate differently in each pregnancy. Our subsequent work identified genetic variants of maternal KIRs and fetal HLA-C, combinations of which are associated with pregnancy disorders such as pre-eclampsia. Thus, the evolutionary selective pressures for NK cell-mediated allorecognition make sense in the context of reproductive success (reviewed by Moffett and Colucci, 2015).

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ORIGINAL ARTICLE Colonna, M. & Samaridis, J. Cloning of immunoglobulin-superfamily members associated with HLA-C and HLA-B recognition by human natural killer cells. *Science* **268**, 405–408 (1995)
FURTHER READING Moretta, L. *et al.* Allorecognition by NK cells: nonself or no self? *Immunol. Today* **13**, 300–306 (1992) | Moffett, A. & Colucci, F. Co-evolution of NK receptors and HLA ligands in humans is driven by reproduction. *Immunol. Rev.* **267**, 283–297 (2015)