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A role for NK cell-derived granzyme B in host defenses against gonorrhea

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Background

Neisseria gonorrhoeae (Ng) is an exclusively human pathogen. Host defenses responsible for clearance of gonorrhea remain to be fully elucidated. The mouse vaginal colonization model has proven useful to study immune defenses against gonorrhea. We interrogated the roles of innate and adaptive immunity in host defense against experimental gonococcal infection.

Aim/Methods

The following mouse models were used for vaginal colonization experiments: T cell-depleted (anti-CD3 treatment), B cell-deficient (JhD), B and T cell-deficient (Rag1-/-), Rag1-/- mice that lacked perforin (Prf; Rag1-/-/Prf1-/-), granzyme B (GzmB; Rag1-/-/GzmB-/-), or IFN-γ receptor (Rag1-/-/Ifngr-/-), Rag1-/- that were NK cell-depleted (anti-asialo-GM1 or anti-NK1.1 treatment), complement-depleted (cobra-venom factor treatment) or PMN-depleted (anti-Gr1 treatment). Three parameters of gonococcal colonization were evaluated: time to clearance, log10 CFU vs time, and Area Under Curve. The ability of primary human NK (pNK) cells isolated from peripheral blood or human NK cell lines to kill Ng in vitro in the presence or absence of the GzmB inhibitor 3,4-dichloroisocoumarin (DCI) was measured.

Results

The role of adaptive immunity was first examined. Gonococci colonized mice that lacked either T cells or B cells to the same extent as wild-type controls. Rather unexpectedly, we observed significantly decreased

duration and burden of infection in Rag1-/- mice compared to control wild-type mice. Depleting complement and PMNs simultaneously in Rag1-/- mice did not affect colonization. However, NK cell depletion restored gonococcal colonization to wild-type levels. Interestingly, NK cell activity in vivo required GzmB (colonization was restored in Rag1-/-/GzmB-/- mice), but not Prf or IFN-γ activity (accelerated clearance persisted in Rag1-/-/Prf1-/- and Rag1-/-/Ifngr-/- mice). pNK cells from eight donors and human NK cell lines killed Ng in vitro (>50% reduction in CFU relative to controls with media alone) at effector:bacteria ratios of 10. Killing was contact-dependent and required GzmB activity (killing was abolished by DCI). pNK cells associated with gonococci expressed higher levels of GzmB compared to NKs not associated with bacteria.

Conclusions
These data suggest a novel role for NK cell-derived GzmB in killing Ng in vivo and in vitro. Targeting gonococci for elimination by NK cells (or granzyme B) may provide a therapeutic modality against multidrug-resistant gonorrhea.