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Single-cell RNA sequencing of PBMCs treated with ADP-heptose reveals a type-II interferon driven immune response

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Background

Neisseria gonorrhoeae (Ngo) elicits a potent immunopathogenic inflammatory response in infected tissues. Neisseria are unique among bacteria in that they shed heptose phosphates, which are metabolic intermediates of lipopolysaccharide synthesis. These were recently-discovered to be recognized by mammalian cells as a microbe associated molecular pattern (MAMP) that elicits an innate inflammatory response through the ALPK1/TIFA/NF-κB signalling axis. While this effect was originally identified using the immortalized Jurkat CD4+ T-cells, their effect on primary human innate and adaptive immune cells remains unclear.

Aim/Methods

Here, human peripheral blood mononuclear cells (PBMCs) were exposed to the ADP-heptose and their transcriptional response was then characterized by single-cell RNA sequence analysis.

Results

While ADP-heptose did not activate naïve T cells, it does activate memory CD4 T-cell subsets, presumably through direct NF-κB engagement. Beyond this, exposure to ADP-heptose drives a predominant type-II interferon (interferon-gamma, IFNγ) response within this heterogenous population. Rather than being a T cell-driven effect, the IFNγ is primarily produced by a subset of NK-cells. This appears to drive a secondary defence response in monocytes, which displayed the greatest transcriptional response among cells in the heterogenous population, highlighted by interferon-stimulated gene upregulation. Of these, IL-15 is especially interesting as this interferon-stimulated cytokine has been shown to promote and stimulate the activation and proliferation of NK cells. However, our subsequent in vitro analyses revealed that isolated NK cells do not respond directly to ADP-heptose, suggesting that the monocyte-derived IL-15 supports the ADP-heptose-dependent NK cell activation and IFNγ expression.

Conclusions

Together, this study suggests that heptose phosphates broadly stimulate memory T cells in an antigen-independent manner, and initiate an immunological cross-talk between NK cells and monocytes that stimulates an IFNγ-dependent inflammatory response and upregulation of anti-bacterial effector functions.