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Comment on: “Evidence of innate lymphoid cell redundancy in humans”

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A recent study from Vély et al suggested a dispensability for innate lymphocytes, including ILC and NK cells, in the control of human disease¹. These conclusions are based on cohort studies of patients with severe combined immune deficiency (SCID) due to *JAK3* and *IL2RG* mutations who have extremely low or undetectable ILC and NK cells after non-myeloablative allogeneic hematopoietic cell transplantation (HCT)¹. These findings are important additions to the literature, and investigation of such rare patient populations with long-term follow-up (up to 39 years) is to be commended. As noted in the accompanying News and Views from Weinkove et al², limitations of the study included the small sample size, a limited number of tissue samples to investigate resident ILCs, and the suggestion of infectious susceptibility with a lack of innate lymphocytes with almost half of patients having human papilloma virus (HPV) infection.

Based on the findings from this single study, we have become aware of an emerging viewpoint in the field that NK cells are not required for human health in an otherwise immunocompetent patient. Here, we respectfully offer evidence that human NK cells are an essential, non-redundant component of the human immune system.

While there are over 50 primary immunodeficiencies that impact NK cells, the most informative are NK cell deficiency (NKD) in which NK cells are the main affected immune defense³. A common feature of NKD is severe viral infection and malignancy, and many affected NKD patients die in young adulthood of severe herpesviral infections despite intact T and B cell function. To date, there are 7 reported genetic causes of NKD: *FCGR3A*, *GATA2*, *GIN1*, *IRF8*, *MCM4*, and *RTEL1* (reviewed in³) and *MCM10*⁴. Other immune compartments may be involved to varying degrees, but particularly in patients with *FCGR3A*, *GIN1*, *MCM4* and *IRF8* mutations, there are minimal or no immunological phenotypes outside of NKD. Late onset cutaneous HPV has been reported in common γ

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chain deficient SCID patients, frequently accompanied by reduced NK cell function and number^{5,6}. This suggests that NK cells (and potentially other ILCs) function in controlling viral infection post-transplant. While many patients with NKD do not survive until adulthood, the prevalence of virally-driven lymphomas and solid tumors in patients with *FCGR3A* and *GATA2* mutations, suggests that innate immunity is also required to prevent these particular cancers.

While patients with NKDs uniquely highlight the importance of NK cells in human health and disease, there is also evidence for a non-redundant role of NK cells in host defense against viruses and tumors in immunocompetent individuals^{7,8}. HCMV infection induces the differentiation of ‘adaptive’ NK cells with enhanced functionality and distinct epigenetic profiles⁹. Expansion of CMV-adapted NK cells in humans in response to other infections provides indirect evidence that these cells play a role in early host defense. Epidemiologic links between NK cell killer immunoglobulin receptor (KIR) and MHC haplotype and risk of infection with or severity of hepatitis C virus and HIV provide further evidence for the importance of an NK cell response to viral infection^{10,11}. NK cell tumor immunosurveillance has been well-documented in the mouse, and in humans is highlighted by a prospective study correlating decreased NK cell cytotoxic capacity with an increased incidence of cancer¹². Direct evidence for NK anti-tumor effects in humans comes from a multitude of studies demonstrating NK cell anti-leukemia effects in the context of mismatched hematopoietic cell transplantation and allogeneic adoptive immunotherapy⁷.

Finally, for most aspects of experimental immunology context matters. The study provided evidence of innate lymphocyte redundancy with adaptive immunity in humans within a very specific context – that of genetically immunodeficient children who underwent treatment with non-myeloablative allogeneic HCT resulting in a donor or chimeric immune system. These patients received intensive post-HCT medical surveillance that included broad antimicrobial prophylaxis for 6–12 months, life-long immunoglobulin replacement in many (half in this cohort), and enhanced surveillance for and evaluation of infection/fever compared to the general population. Thus, this unique patient population is challenging to clinically generalize to the average human being living in natural conditions, even in developed countries. The clinical results reported selected infections, but were not benign, with 8 of 18 (44%) having common warts, while more clinically significant events included severe HPV (11%), ear-nose-throat (ENT) infection (17%), diarrhea (11%), and respiratory sequelae (11%). While these problems were not considered a disease susceptibility, 7 of the 18 (39%) γ_c /Jak3-SCID patients experienced at least one of these clinically significant events, compared to 0 of 8 in the control HCT patients.

In summary, while the findings of Vely and colleagues are provocative, we contend they should be used to generate new hypotheses that will require extensive further study, as opposed to arriving at a definitive conclusion.

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