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Commentary

Trying to Understand NK Cell Function in vivo Points towards a Severity Score for CVID Patients

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Natural Killer (NK) cells were described 40 years ago as lymphoid cells exerting cytolytic activity against tumor cell lines in vitro (Herberman et al., 1975) and are accounted to the group of innate lymphoid cells. Functionally, they have been associated with anti-viral immunity (esp. herpesviridae) and tumor surveillance. However, NK cells have been less in the research focus compared to other components of the immune system (citations in Pubmed in 2015: ~2600 for NK cells compared to ~7100, ~14,600 and ~12,100 for B, T cells and macrophages, respectively). An isolated reduction of NK cells in humans has been suggested to be asymptomatic. Whether this notion somewhat reflects the inattentiveness towards NK cells or if NK cells in humans have only redundant functions in the immune system is still a matter of debate.

Eric Vivier and colleagues hypothesized that the function of NK cells in humans might be revealed in immunocompromised subjects and report on a large cohort of patients with common variable immunodeficiency (CVID) registered in the French Registry (DEFI) (Ebbo et al., 2016). They stratified 457 CVID patients according to their NK cell numbers at study inclusion: roughly half of the patients had normal NK cell counts (>100/μl), one quarter of the patients had slightly reduced NK cell counts (50–99/μl) and almost one quarter had severely reduced NK cell numbers (<50/μl). CVID patients with severe NK cell lymphopenia exhibited a statistically significant increased rate of invasive bacterial infections defined as septicemia, pneumonia or meningitis: the frequency of invasive infections was 68.7% in severe NK lymphopenia, 60.2% in mild NK lymphopenia and 48.8% in patients with normal NK cell counts. However, there was no correlation of NK cell number and viral infections or malignancies. These results rely on prospectively collected registry data that might be skewed by reporting bias and correlations do not necessarily prove causality. Nonetheless, this observation fits well into the increasingly recognized role of NK cells in adaptive immunity.

Apart from insights into NK cell biology the paper by Ebbo et al. reveals interesting aspects of NK cells in CVID. On a clinical basis CVID patients can be separated into patients who suffer from infectious complications as only complaint ("infection-only group") and those who additionally suffer from non-infectious complications/immune dysregulation with e.g. lymphoproliferation, lung disease, enteropathy and malignancies. Whilst the infection-only group has a close to normal life expectancy when treated with immunoglobulin replacement, patients with immune dysregulation have an elevated mortality (Resnick et al., 2012). It is therefore of crucial interest to identify these patients early in the course of the disease and multiple groups have attempted to identify biomarkers in CVID by different approaches targeting B and/or T cells in the majority of cases (Piqueras et al., 2003; Giovannetti et al., 2007; Moratto et al., 2006; Driessen et al., 2011; Kamae et al., 2013; Wehr et al., 2008; Chapel et al., 2012). Ebbo and co-workers now add NK cells as a potential biomarker to the list as they showed that CVID patients with non-infectious complications are overrepresented amongst the patients with severe NK lymphopenia. This was significant for patients with granulomatous complications (NK cells severely reduced vs mildly reduced vs normal: 25.3% vs 13.6% vs 8.8%, $p < 0.001$) but there was also a trend towards higher frequencies of lymphoid hyperplasia (35.4% vs 24.6% and 19.2%), enteropathies (41.4% vs 28% vs 24.2%) and autoimmune cytopenia (25.3% vs 12.7% vs 14.6%). The authors also report that severely reduced NK cell counts in CVID are associated with lymphopenia i.e. CD4+ lymphopenia (median 415/μl vs 568 and 691/μl, $p = 0.003$), reduction of naïve CD4+ cells (median 63/μl vs 135 and 183/μl, $p = 0.003$), CD8 lymphopenia (310/μl vs 431/μl vs 479/μl, $p = 0.003$) and B lymphopenia (median: 59/μl vs 99/μl and 122/μl, $p = 0.003$). CVID patients with severe NK lymphopenia also had lower levels of IgG, A and M at initial diagnosis compared to the two other groups. Mortality was higher in CVID with low T cell numbers (T cells <200/μl) but not in patients with isolated low NK lymphopenia. Whilst other groups have associated low naïve CD4 cell counts and expansion of CD21low B cells with a more severe CVID phenotype, Ebbo et al. show a weak, positive correlation between NK cell counts and CD21low B cells ($r = 0.13$, $p = 0.05$).

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Considering the large CVID cohort investigated by Ebbo et al., NK cells will have to be considered in future attempts to stratify CVID patients. Ideally the topic will be approached by a multinational team to unify the multiple attempts and dissect predictive biomarkers in CVID helping to early identify patients at risk from severe manifestations.

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