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**Title:** The impact of long-term tobacco smoking on circulating IL-16<sup>+</sup> NK cells

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**Body:** Natural killer (NK) cells constitute a first line of anti-viral host defence and tobacco smoke may cause reduced cytotoxicity. Among the cytokines expressed in NK cells, interleukin-16 (IL-16) is of interest since it is known that the extracellular concentrations of this CD4 cell chemoattractant are increased in the airways of long-term smokers. Here, we investigated whether long-term smoking alters the number and IL-16 content of circulating NK cells. Never-smokers (NS) and asymptomatic smokers (AS) with a normal ventilatory capacity plus a normal diffusion capacity for carbon monoxide (DLCO) were included. We also examined smokers with COPD (GOLD stages 2 & 3) with reduced DLCO (>2SD from the predicted mean). In each subject, a peripheral, venous blood sample was taken during clinically stable conditions for flow cytometry analysis of intracellular IL-16 in NK cells (IL-16<sup>+</sup> NK cells; IL-16<sup>+</sup>CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup>). The relative and absolute number of NK cells (CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup>) was determined. Smokers (AS and COPD) exhibited a lower relative number of IL-16<sup>+</sup> NK cells compared to NS (Mann-Whitney U test, p<0.05). In line with this, the absolute number of IL-16<sup>+</sup> NK cells tended to be lower in smokers as well, although this trend was not statistically significant. Among smokers, there was a negative and statistically significant correlation for both the absolute and relative numbers of NK cells, on the one hand, and tobacco load (ie. pack-years; Spearman Rank Corr. test; p<0.05; rho=-0.056 for both correlations) on the other. Our study indicates that long-term smoking exerts a negative impact on circulating NK cells, in terms of number and IL-16 content. Hypothetically, this impact may impair anti-viral host-defence.