Cigarette smoking suppress T cell immunity in MR1 dependent mechanism

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Cigarette smoking is a worldwide epidemic and is linked to numerous diseases. While cigarette smoke (CS) compromises the immune system, relatively little is known about its effect on T cell functions. CS is a complex mixture of products resulting from the combustion of tobacco and other components of the cigarettes. The MHC I-related molecule MR1 presents small molecule metabolites [1] to a diverse population of αβ and γδ MR1-restricted T cells including Mucosal-Associated Invariant T (MAIT) cells [2, 3]. MAIT cells are an innate-like T cell population that are highly abundant in a number of tissues, including the lung and is emerging as a major player in antimicrobial immunity, autoimmunity and cancers [4].

Using cellular, biochemical, and structural approaches, we identified components of cigarette smoke that could bind MR1, impact MR1 cell surface expression, and modulate T cell mediated immunity. These included nicotinaldehyde, phenylpropanoid, and benzaldehyde-related scaffolds. The high-resolution crystal structures of four ternary MAIT T cell receptor (TCR)-MR1-CS complexes showed that these MR1-binding CS based ligands reside within the A` pocket of MR1. Furthermore, we found that cigarette smoke extract (CSE) modulated T cell activation and effector functions ex-vivo in MR1 dependent manner. CS exposure increases lung MAIT cells in uninfected mice but dysregulates their responses to influenza A virus infection. Thus, cigarette smoking may impair the function of T cells in humans via interactions between cigarette smoke components and MR1, with potential implications in their response to respiratory infection or disease.