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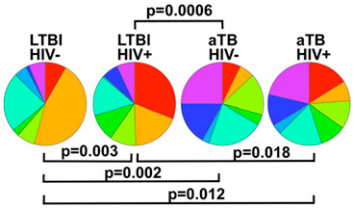
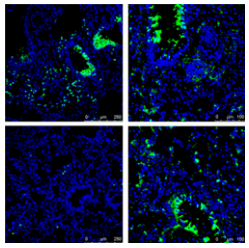
$CD4^+$ T Cell Phenotype Changes during HIV and *Mycobacterium tuberculosis* Coinfection



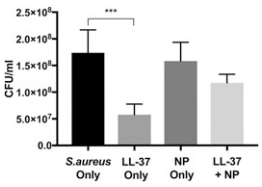
Coinfection with HIV and *Mycobacterium tuberculosis* is associated with accelerated tuberculosis (TB) disease progression, likely due to qualitative defects in *M. tuberculosis*–specific $CD4^+$ T cell responses. To provide insight into protective immunity to TB in the context of an HIV infection, Strickland et al. (p. 2440) examined HIV-induced alterations in circulating *M. tuberculosis*–specific $CD4^+$ T cells that lead to failed host resistance. Using MHC class II tetramers recognizing CFP-10 or ESAT-6 epitopes from *M. tuberculosis*, the authors observed that, despite general $CD4^+$ T cell depletion, circulating *M. tuberculosis*–specific $CD4^+$ T cell populations were maintained in HIV^+ individuals with active TB (aTB), as they were present at levels similar to those observed in HIV^- individuals with aTB. Phenotypic analysis of *M. tuberculosis*–specific $CD4^+$ T cells ex vivo revealed that, regardless of HIV status, $CD4^+$ T cells from individuals with aTB were highly activated and exhibited a mature memory phenotype, whereas cells from those with latent TB infection (LTBI) exhibited an early memory phenotype. Circulating *M. tuberculosis*–specific $CD4^+$ T cells from individuals with LTBI were primarily $CCR4^-CCR6^+CXCR3^+$ cells, which were classified as a nonconventional Th1∗ subset that produces IFN-γ and low levels of IL-17. HIV infection did not result in significant changes in maturation or activation status of *M. tuberculosis*–specific $CD4^+$ T cells; rather, HIV infection induced alterations in their chemokine receptor expression profile and resulted in a reduction in the frequency of the Th1∗ subset and an enrichment of both the $CCR4^+CCR6^+CXCR3^-$ (Th17) and $CCR4^+CCR6^+CXCR3^+$ subsets. Furthermore, whereas both aTB and HIV were shown to impact the phenotype of *M. tuberculosis*–specific $CD4^+$ T cells, neither promoted *M. tuberculosis*–specific $CD4^+$ T cell exhaustion, as *M. tuberculosis*–specific $CD4^+$ T cells stimulated ex vivo with *M. tuberculosis* peptides produced levels of IFN-γ, IL-2, and TNF-α similar to those from HIV^- individuals with LTBI. Overall, this study describes the profiles of *M. tuberculosis*–specific Th cells and the phenotypic changes induced by aTB and/or HIV infection. Additionally, it suggests that increased susceptibility of HIV-infected individuals to TB could be related to a loss of circulating Th1∗ $CD4^+$ T cells rather than major changes in the total number of circulating $CD4^+$ T cells.

Natural dsRNA Drives Antiviral Immunity



The components of innate antiviral immunity have been elucidated mainly through the use of synthetic RNA, such as polyinosinic-polycytidylic acid (poly I:C), but innate immune responses to more physiological dsRNA species have not been well characterized. Kasumba et al. (p. 2460) have now isolated a naturally occurring dsRNA extracted from rice bran (rb-dsRNA) that appears to come from the viral genus *Endornavirus* and can activate innate immune responses both in vitro and in vivo. Intranasal administration of rb-dsRNA induced rapid upregulation of type I IFNs, chemokines, and proinflammatory cytokines; alveolar macrophages were identified as the main source of IFN production. These antiviral and proinflammatory activities appeared to be induced by recognition of rb-dsRNA by both TLR3 and MDA5, but not RIG-I, followed by signaling through TRIF and IPS-1 pathways. Mice given rb-dsRNA both before and after intranasal viral challenge showed increased survival and early reductions in lung viral titers following infection with influenza A virus or parainfluenza type I virus. Antiviral protection mediated by rb-dsRNA was completely abrogated in mice doubly deficient in TRIF and MDA5, but was only partially reduced in mice lacking the IFNAR1, suggesting that type I IFN was not the only mechanism by which rb-dsRNA protected against viral infection. Indeed, rb-dsRNA treatment induced release of lactate dehydrogenase from macrophage cultures that was dependent on caspase-1 activation, suggesting the induction of pyroptosis. TLR3/TRIF signaling, but not MDA5/IPS-1 signaling, was necessary for rb-dsRNA–induced caspase-1 activation and induction of IL-1β secretion, and caspase-1 activation was confirmed to play a role in antiviral protection. In addition to these antiviral activities, rb-dsRNA could also modulate the numbers of alveolar macrophages, neutrophils, and monocytes in the lung following viral infection. Taken together, these data suggest that this naturally occurring dsRNA species promotes antiviral immunity through multiple mechanisms, differing somewhat from those mediated by poly I:C, and may be useful both for future studies of basic immune mechanisms and for potential therapeutic applications.

Carbon Nanoparticles Gum Up Antimicrobial Peptides



In developed countries with high levels of particulate air pollution, individuals are routinely exposed to nanoparticles, via inhalation or skin contact. Although it has been well documented that proteins can undergo significant structural alterations following interaction with nanoparticles, it remains poorly understood whether they impact host antimicrobial defense peptides such as cathelicidin (LL-37), which is upregulated during inflammation and has immunomodulatory functions within the innate immune system. Following exposure of LL-37 to carbon black nanoparticles, which model combustion-derived particulate air pollution nanomaterials, Findlay et al. (p. 2483) demonstrated that nanoparticles adsorbed to the surface of LL-37 and potentially altered its structure, as evidenced by a significant decrease in the amount of LL-37 detectable by ELISA. MALDI-TOF analysis revealed that LL-37 was neither cleaved nor degraded into smaller fragments in the presence of carbon nanoparticles. When compared with untreated controls, pre-exposure to carbon nanoparticles partially inhibited the ability of LL-37 to cross-link primary amine sites located at the N terminus of the peptide with amine groups on the side chains of lysine residues, possibly indicating alterations in the secondary structure of LL-37. Likely related to possible structural alterations, carbon nanoparticles interfered with the antibacterial and antiviral activities of LL-37. When compared with untreated controls, LL-37 exposed to nanoparticles prior to incubation with either a minor-group rhinovirus strain, *Staphylococcus aureus,* or *Escherichia coli* failed to reduce viral titers or bacterial load. Furthermore, nanoparticles inhibited the ability of LL-37 to suppress epithelial cell production of TNF-α following LPS stimulation. Therefore, the data presented in this study suggest that carbon nanoparticles are capable of inhibiting the activity of antimicrobial peptides, such as LL-37, which may have significant consequences for the health of individuals living in areas with high levels of particulate air pollution.

CD154 Reveals Antimycobacterial T Cells

Limitations to common approaches for identifying Ag-specific $CD4^+$ T cells include failure to keep cells alive for downstream RNA isolation and functional analysis. CD154 is transiently upregulated on $CD4^+$ T cells upon activation, suggesting its expression could be used to identify live Ag-specific cells. Treatment of stimulated T cells with monensin and labeled anti-CD154 Abs can enhance detection of this molecule after it undergoes endocytosis, and Kunnath-Velayudhan et al. (p. 2596) have now demonstrated that measurement of CD154 expression by this method can be used for analysis of Ag-specific cells in mycobacterial infection. With this technique, the authors detected OVA-specific OT-II T cells that had been expanded in vivo by OVA vaccination and restimulated in vitro with OVA peptide; in addition, CD154 expression identified a polyclonal population of activated $CD4^+$ T cells that had been expanded by bacillus Calmette-Guérin (BCG) vaccination and restimulated in vitro with either a mycobacterial Ag or lysate of *M. tuberculosis.* In both cases, cytokine production triggered by cellular activation correlated with CD154 expression, and CD154 was upregulated only on Ag-experienced ($CD44^+$) T cells. To better characterize the $CD154^+$ cell population, $CD44^+$ $CD4^+$ T cells were isolated from *M. tuberculosis* lysate–stimulated splenocytes of BCG-immunized mice, sorted into $CD154^+$ and $CD154^-$ populations, and then subjected to microarray analysis. $CD154^+$ cells were found to have a transcriptome distinct from that of $CD154^-$ cells, and pathway analysis revealed that $CD154^+$ cells upregulated components of pathways involved in metabolic changes associated with T cell activation. Transcription of cytokine genes was also upregulated in these cells, including not just the expected Th1 cytokines but also those associated with Th2, Th17, and Tfh cells; in contrast, IL-10 and regulatory T cell-associated genes were upregulated in $CD154^-$ cells. Interestingly, IL-3, which is not generally associated with antimycobacterial immunity, was upregulated in a small subset of the $CD154^+$ $CD44^+$ $CD4^+$ T cells that also expressed IFN-γ and T-bet, suggesting a relationship to Th1 cells. IL-3–expressing $CD4^+$ T cells were also observed following infection of mice with *M. smegmatis* or *M. tuberculosis*, suggesting that IL-3 production could be a common feature of antimycobacterial immune responses. This study indicates that detection of CD154 expression can be used to identify Ag-experienced $CD4^+$ T cells during mycobacterial infection and to elucidate novel characteristics of a population of T cells responding to infection or vaccination.