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YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"The Role of type I and type III Interferons in Bacterial Superinfecion"

by
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Molecular Biology, Genetics and Cancer Track

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Wednesday, December 18st, 2019
1:00 P.M.
Cancer Center G1196

ABSTRACT

Much of the mortality and morbidity associated with influenza infection is due to subsequent bacterial superinfection, usually involving either *Streptococcus peumoniae* (*Spn*) or *Staphylococcus aureus*. This correlation suggests that the robust antiviral responses induced by influenza virus infection may be interfering with the innate antibacterial responses. While several mechanisms have been proposed to explain the susceptibility to bacterial pneumonia after influenza virus, its cause remains unclear. Influenza infections, particularly with highly pathogenic strains, induce high levels of type I and type III IFNs, important mediators of anti-viral defense. Recently it was shown that influenza-infected IFN-α/β-receptor knock out (IFNARKO) mice challenged with *Spn* controlled bacterial infection better than wild type (WT) mice, raising the possibility that type I IFNs specifically interfere with clearance of secondary *Spn* after influenza infection.

Given that type III, as well as type I IFNs are strongly induced by influenza infection, we wished to characterize the contributions of both IFN types to the clearance of secondary bacterial infection. To do this we used mice deficient in type I IFN, type III IFN, and type I and III IFN receptors to develop a superinfection model.

Our studies corroborated published work showing enhanced bacterial clearance after influenza infection in IFNARKO mice. Furthermore, we observed type I and type III IFNs working together have a profound inhibitory effect on secondary bacterial clearance. We observed that, in mice lacking both IFNAR and the IFN-λ-receptor (IFNLR) (IFNALRKO), the control of secondary bacterial infections was restored.

In our hands, only minor differences in Immune cell trafficking into lung during superinfection were observed between WT and IFNALRKO mice, suggesting that immune cell function, not numbers, were inhibited by the IFN responses. *In vitro* analysis of bone-marrow derived macrophages (BMDM) from WT and IFNALRKO showed no differences in bacterial killing, nor did treatment of WT BMDMs with type I and/or type III IFNs. Despite this inability to recapitulate inhibition of bacterial control *ex vivo*, immune cells from bronchoalveolar lavage (BAL) samples consistently demonstrate significant differences in bacterial killing. Cells harvested from the airways of influenza-infected WT mice are defective in bacterial killing when compared with BAL cells from IFNALRKO animals. Taken together, our findings demonstrate that phagocytes recruited by influenza infection in the presence of type I and III IFNs are defective in response to a bacterial challenge. While the mechanism underlying this defect has yet to be elucidated, our data show that IFN induction by influenza antagonizes host antibacterial defenses.