THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER
ANNOUNCES THE FINAL EXAMINATION OF

Sapana Kadel

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

Department of Microbiology and Immunology

Tuesday, July 23, 2019 | 10 am
Biomedical Research Center, Room 109

Sex Differences In Group 2 Innate Lymphoid Cells in homeostasis and influenza virus infection

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ABSTRACT: Humans show significant sex differences in the severity of respiratory viral infection, with women often experiencing stronger immune responses and greater morbidity after influenza virus infection. Group 2 innate lymphoid cells (ILC2s) are potent lung-resident innate immune cells that are poised to produce type 2 cytokines and facilitate tissue repair in response to alarmins released during respiratory virus infection. While elegant studies have identified sex differences and the mechanistic role of sex hormone signaling in other innate immune cells, we lacked information about sex differences and role of sex hormone signaling in the regulation of lung ILC2s in homeostasis and respiratory virus infection. To test the hypothesis that females and males would show quantitatively or qualitatively different ILC2 responses in homeostasis and during influenza virus infection, we analyzed the numbers, phenotype and functional responses of lung ILCs of naïve and influenza virus infected wild-type female and male mice. We observed that female mice harbor significantly greater ILC2 numbers in homeostasis, in part due to a major subset of ILC2s lacking killer-cell lectin like receptor G1 (KLRG1), a population largely absent in male lungs. We further showed that male mice harbor a higher fraction of ILC precursors (ILCPs) in bone marrow, suggesting androgens might attenuate the progression from ILCPs to ILC2s. In a murine model of influenza virus infection, we observed that female mice retain their greater number of lung ILC2s as well as higher numbers of ILC1s compared to males. However, the female ILC2s are preferentially suppressed at the peak of infection, with a dampened type 2 program manifested as reduced proliferation, reduced propensity for type 2 cytokine production and reduced expression of characteristic ILC2 markers such as GATA-3 and IL-33R. Consistent with this, female ILC2s showed higher expression of IFN-γR and increased phospho-STAT1 levels following stimulation by IFN-γ. Gonadectomy experiments showed that androgens negatively regulated ILC2 numbers but protected males from influenza virus infection mediated suppression of ILC2s. Altogether, our data show that androgens play an important role in the regulation of lung-resident ILC2s, suggesting sex-specific intervention strategies might be useful in respiratory virus infection.