Investigating the Female Reproductive Tract Mucosa as a Sex Specific Site for Anti-Citrullinated Protein Antibody Formation

Ari O. Sequoia[1], Rachael Horne[1], Kali Franckowiak[1], Heather M. Rothfuss[1]; M. Kristen Demoruelle[2]; Brian D. Cherrington[1]

1. Department of Zoology and Physiology, University of Wyoming, Laramie, United States
2. Division of Rheumatology, University of Colorado School of Medicine, Aurora, United States

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by the inflammation and subsequent degradation of synovial joints. While both men and women develop this disease, there is a three-fold higher rate of women suffering from RA. Women often develop the disease earlier and experience worse clinical outcomes compared to men. Years of research has been unable to explain the clear sex disparity seen in RA, despite several known reproductive factors that affect risk in women, including age of menarche, parity, and the post-partum period. Previous studies show that RA autoimmunity develops when citrullinated (cit) proteins are generated at a mucosal surface by peptidylarginine deiminase (PAD) enzymes, which post-translationally covert arginine to a non-coded citrulline residue in target proteins. Auto-antibodies to cit-proteins termed anti-citrullinated protein antibodies (ACPAs) are produced in the mucosa, but can become systemic and lead to joint inflammation. Shared mucosal sites (ie. lung, gingiva, and gastrointestinal tract) have yet to explain the sex disparity, leading us to hypothesize that the female reproductive tract (FRT) mucosa is a female specific site of ACPA formation. Specifically, we are investigating whether PAD enzymes and cit-proteins are present in FRT fluid (FRT-F) and serum across the menstrual cycle in women and estrous cycle in mice. Our results demonstrate that PAD enzymes and cit proteins fluctuate in women's FRT-F across the menstrual cycle and in wild type mouse FRT-F during the estrous cycle. Interestingly, PAD enzymes are not detectable in wild type mouse serum, but are abundant in FRT-F across the estrous cycle. The FRT has a unique immune system, prompting us to next examine if total immunoglobulin G (IgG), ACPAs, and the cytokines IL-6, IL-8, and TNFα are also present in FRT-F and serum in wild type mice. Our results show that they not only fluctuate across the estrous cycle, but their respective levels differ between FRT-F and serum. Our current studies are using mass spectrometry to identify the mouse FRT citrullinome across the estrous cycle. Ultimately, our objective is to identify possible targets for sex-specific diagnostic tests or treatments to improve clinical outcomes for women suffering from RA.