The Female Cervicovaginal Mucosa Is a Unique Site for the Production of Autoantibodies Associated with Rheumatoid Arthritis

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Abstract

Purpose/Background: Women have a 3-fold higher incidence of rheumatoid arthritis (RA) and a lower likelihood of remission compared to men suggesting a gender disparity in the etiology of RA. In order to devise female specific prevention and treatment strategies, it is critical to understand the mechanism initiating the production of RA autoantibodies termed anti-citrullinated protein antibodies (ACPA). ACPA target proteins that are posttranslationally modified by a family of enzymes termed peptidylarginine deiminases (PADs), which convert arginine into citrulline. Research suggests that ACPA are generated at a mucosal site years before becoming systemic and causing clinical joint disease. Mucosal sites such as the lung, gut, and gingiva have been explored as sites of ACPA production, yet none of these account for the higher incidence of RA in women. We hypothesize that the cervicovaginal mucosa is a novel, sex-specific site for APCA production in women.

Materials & Methods: To begin to test this hypothesis, healthy control (HC) women, women at risk for RA (AR), and those with clinical RA self-collected cervicovaginal fluid (CVF) at three time points during the menstrual cycle. CVF samples were examined for PAD activity, total citrulline concentration, and cyclic citrullinated peptides (CCP) as a marker for ACAP levels.

Results: In naturally cycling HC women, CCP peak in early follicular phase (d5), dropped substantially by ovulation (d14), and remained low at the end of the luteal phase (d26). PAD enzymatic activity and total citrulline concentration also peak in CVF at d5 of the menstrual cycle, suggesting that changes in citrullinated proteins may drive local ACPA production. We next examined if CCP, PAD activity, and total citrulline concentration are increased in CVF from women at-risk (AR) for developing RA and women with RA. Although PAD activity and total citrulline concentration does not increase in these groups compared to health controls, CCP levels are significantly increased between the HC and RA CVF samples at d25.

At issue is the identity of the citrullinated proteins in HC, AR and RA CVF, and if their abundance changes across the cycle and with disease progression. To address this, we performed mass spectrometry on CVF samples which identified a number of citrullinated proteins present in HC, AR, and RA women.

Discussion/Conclusion: Our work suggests that citrullinated proteins and ACPA are produced in the cervicovaginal mucosa and may help explain why women have increased risk of developing RA.

Keywords

Rheumatoid Arthritis; Autoantibodies; Female Cervicovaginal Mucosa

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