Sexual Dimorphism in Immunity to Oral Bacterial Diseases: Intersection of Neutrophil and Osteoclast Pathobiology

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Appendix

Sex Differences in Other Inflammatory Mediators During Oral Infections

In addition to chemokines, many other soluble factors play a critical role in the inflammatory response following infection. Moreover, many of these molecules are influenced by sex. IL-1β is a critical inflammatory cytokine activated by caspase-1 in the inflammasome that promotes innate immune responses in leukocytes and induces release of antimicrobials and other agents including proteases and enzymes to degrade bacteria (Eldridge and Shenoy, 2015). Interestingly, IL-1 blockage induced dentoaveolar abscess formation in male mice only in response to infection. Mechanistically, estrogens directly stimulated the induction of IL-1 following infection which was confirmed using ovariectomized females treated with anti-IL-1 antibodies which developed similar extent of abscess formation following infection to males (Youssef and Stashenko, 2017).

During oral infections, a number of inflammatory and anti-microbial mechanisms are elicited. Besides the cytokines and chemokines, the immune response to oral infectious diseases comprises many other immune systems including the complement system (Hajishengallis et al., 2015), lipid mediators of inflammation (e.g. eicosanoids) (Bennett and Gilroy, 2016; Van Dyke, 2008), and other specific anti-microbial factors, including defensins (Bissell et al., 2004). Regarding sex differences in the complement system, males elicited a stronger complement

response than females, thus propagating more inflammation. With regard to eicosanoids, a recent review effectively captures the differences in the eicosanoid production between males and females in the innate immune response (Pace et al., 2017). Interestingly, while there is an established link between sex-dependent differences in eicosanoid production and eicosanoids role in periodontal disease, there are no studies that have directly addressed sex-differences and role of eicosanoids in periodontal disease. Finally, defensins are part of a group of anti-microbial peptides released by salivary glands, epithelial cells and neutrophils in response to periodontal infection and estrogens can strengthen endothelial barrier function by increasing gene expression of β-defensins (Gorr, 2012; Luthje et al., 2013). Together, these few examples highlight the dynamic responses of the immune system and the impact of sex differences. Clearly, there are additional avenues of research needed in many of these areas to provide clearer fundamental comprehension of the intersection of immunity and impact of sex differences in oral diseases.

Another interesting explanation for sex differences in the immune system may be epigenetic factors and genomic imprinting as a contributing factor to phenotypic expression. Conceptually, this phenomenon was captured by Saeed et al, who showed that monocytes can be imprinted with factors that can tolerize/paralyze the immune response or enhance it. Moreover, prolonged exposure to stimuli induced histone modifications and other epigenetic changes in regions related to transcriptional regulation, thereby modifying terminal differentiation and ability of these macrophages to secrete cytokines in response to pathogens (Saeed et al., 2014). Under the same paradigm, it was reported on faulty genomic imprinting on the immune system and how that many influence the innate immune response for indefinitely (Csaba, 2014). Specifically, faulty imprinting was shown to directly impact cytokine and chemokine production, infiltration of immune cells and other various innate immune defenses. Interestingly, hypermethylation of CpG

regions was noted in aggressive periodontal disease by contributing to a heightened innate immune signaling response (Shaddox et al., 2017). Interestingly, other inflammatory-based diseases show that sex-dependent hypermethylation is a major contributing factor in susceptibility to disease. (McCormick et al., 2017). Together, imprinting may be an additional aspect to sex dependent differences that affects the overall immune response to pathogens and must be explored with regard to periodontal disease. Conversely, sex-dependent differences in development of the immune system and imprinting may be an interesting factor contributing to inborn sex differences not directly influenced by sex hormones at the time of infection. In all, the concept of imprinting on the immune system is noteworthy and requires further research to understand the contribution in the context of oral infectious diseases.

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