HORMONAL REGULATION OF THE INNATE IMMUNE RESPONSE AND TOLL-LIKE RECEPTORS IN THE HUMAN ENDOMETRIUM

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ABSTRACT

This study examines the role of the steroid hormones, estrogen (E_2) and progesterone (P_4) in the regulation of TLR3-mediated mucosal immune responses in the human reproductive tract. TLR3 expression in endometrial epithelium could be significant, as the reproductive tract is a major site for viral pathogen infection. Additionally, stimulation of TLR3 could alter cytokine production and lead to endometrial dysfunction, since the cytokine milieu is essential for normal endometrial functions. We demonstrated uterine cycle-dependent expression of several TLRs and associated molecules in the endometrial epithelium. We found that TLR3 expression was specifically up-regulated during the window of implantation, a time at which all other TLRs and associated molecules examined were expressed at baseline levels. We established that cyclic expression of TLR3 is not due to a direct action of E_2 and P_4 on TLR3 mRNA or protein expression, but that E_2 and P_4 are able to significantly alter TLR3-mediated proinflammatory and anti-viral response upon ligation of TLR3 with dsRNA. These results suggest that TLR3 function can be regulated by E_2 and P_4, and that TLR3 can mediate innate antiviral immune responses in the endometrial epithelium, with the potential of producing alterations in the cytokine milieu that may influence the outcomes and consequences of viral infection, as well as influence normal endometrial functions such as establishment and maintenance of pregnancy. This research suggests that TLR3 ligands may be utilized in developing treatments and vaccines against viral pathogens of the reproductive tract and identifies possible targets for treatment of endometrial dysfunctions such as endometriosis, infertility, and spontaneous abortion.