

Public Abstract

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Title:Hormonal Regulation of Innate Immune Responses and Toll-Like Receptors in the Human Endometrium

The human immune system can be divided into two major systems: the adaptive and the innate immune systems. Adaptive immune responses are highly specific and are essential for control and elimination of pathogens following infection. However, the response requires several days to occur. The innate immune system functions to prevent the establishment of infection prior to the initiation of adaptive immune responses. This response is immediate, directed against broad classes of pathogens rather than a specific organism, and is usually sufficient to prevent establishment of infection. In addition, the innate immune system is able to direct and shape adaptive immune responses against invading pathogens. Mucosal tissues lining the body cavities, such as the respiratory tract, the gastrointestinal tract, or the reproductive tract, are primary contact sites for invading pathogens. These surfaces are composed of epithelial cells that act as a barrier to pathogen entry into the body and alert the immune system to the presence of an invading pathogen by initiating innate immune responses to pathogen. The human reproductive tract is exposed to a variety of sexually transmitted pathogens including Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), and Human Papilloma Virus (HPV). These viruses are the cause of vast global human health and reproductive problems. Currently, there is a need to develop vaccines and treatment strategies to prevent transmission of these viruses. This study examines a cellular protein known as Toll-like receptor 3 (TLR3) that is involved in detecting viral pathogens and initiating innate antiviral immune responses to these viral pathogens. We have found that TLR3 is expressed by endometrial epithelial cells in the human uterus, and that expression levels fluctuate with progression through the menstrual cycle. TLR3 expression peaked during the secretory phase of the menstrual cycle, when the uterus is undergoing changes to prepare for embryo implantation, and was dramatically decreased during menstruation until ovulation, when TLR3 expression levels again begin to increase. Due to the cyclic nature of TLR3 expression, we postulated that TLR3 expression was controlled by the endometrial steroid hormones, estrogen (E2) and progesterone (P4). Our results demonstrate that although TLR3 expression is not directly controlled by E2 and P4, the immune responses initiated upon recognition of viral infection by TLR3 are controlled by E2 and P4. These data indicate that antiviral responses in the human uterus can be mediated by TLR3 and can be controlled by fluctuating levels of E2 and P4 throughout the menstrual cycle, indicating that susceptibility to viral infection may be altered at different stages of the menstrual cycle. These results suggest that TLR3 ligands may be utilized in development of treatment and vaccine strategies against viral pathogens of the reproductive tract.