

Public Abstract

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The Innate Immune Response and Toll-Like Receptors in the Human Endometrium

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There are two major divisions of the human immune system: the adaptive and the innate immune systems. The adaptive immune responses are directed against specific pathogens and are essential for control and elimination of pathogens following infection. However, the response requires several days to occur. The innate immune system serves to prevent establishment of infection and protect an individual prior to development 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. Additionally, the nature of the innate immune response will direct and shape adaptive immune responses against invading pathogens. Contact with pathogenic organisms frequently occurs in mucosal tissues lining the body cavities such as the respiratory tract, the gastrointestinal tract, or the reproductive tract. These surfaces are composed of epithelial cells that act as a barrier to pathogen entry into the body and act as sentinel cells, alerting 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 are altered with progression through the menstrual cycle. TLR3 expression peaked during the secretory phase of the menstrual cycle, when the uterus is prepared for embryo implantation, and was dramatically decreased during menstruation until ovulation, when TLR3 expression levels again begin to increase. Stimulation of TLR3 with its cognitive ligand initiates antiviral responses by endometrial epithelial cells and epithelial cell secretion of natural antimicrobial peptides. These data indicate that antiviral responses in the human uterus can be mediated by TLR3 and may be regulated across 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.