Toll like receptors: Sensors for herpes simplex virus infection

Sir,

In recent times, significant developments have been made in understanding the mechanisms involved in initial host recognition to viral infections, and how this viral recognition leads to the immune response. The viral recognition is mediated by pattern recognition receptors (PRR), which are a primeval part of the immune system. PRR is the protein expressed by cells of the innate immune system to identify highly conserved structural motifs known as pathogen-associated molecular patterns (PAMP). PAMP are exclusively expressed by microorganisms which include viral double-stranded RNA and various bacterial cell wall components such as lipopolysaccharide, and bacterial DNA.

Toll like receptors (TLR) are the most eminent members of the PRR. TLR owe their names to a famous Drosophila gene, Toll (in German Toll, means super or fantastic).[1] Ten human TLRs (TLR1 to TLR10) have been characterized so far. TLR is a type I transmembrane protein characterized by an extracellular domain containing leucine-rich repeats and a cytoplasmic extension that contains a conserved region called the Toll/interleukin-1 receptor domain. TLR is located on the plasma membrane with the exception of TLR3, TLR7, and TLR9 which are localized in the endosomal compartment. TLR are mainly expressed in tissues involved in immune function, such as spleen and peripheral blood leukocytes. Their expression profiles vary between tissues and cell types.

Toll like receptors recognition with their corresponding PAMP triggers two distinct pathways: A MyD88-dependent pathway that leads to the production of inflammatory cytokines, and MyD88-independent pathway associated with the stimulation of interferons-β (IFN). 

Herpes simplex viral (HSV) double stranded RNA is recognized by the endosomal TLR. After binding to its cognate, TLR activates the adapter protein, toll/interleukin-1 receptor domain containing adapter protein (TRIF), in a MyD88-independent pathway. TRIF combines with a protein kinase TBK1 (TANK binding kinase 1) to produce interferon regulatory factors (IRF 3 and IRF 7) which subsequently produces IFN-β, resulting in antiviral activity [Figure 1].[2] There are yet other receptors in the cytoplasm called RLR (retinoic acid inducible gene, RIG like receptors) which also recognize the viral RNA and work together with TLR in the production of IFN-β.

However, HSV has a unique way to evade this anti-viral IFN-β response by producing serine protease NS3/4A (degrades the cellular adapter protein TRIF) and immediate early protein ICP0 (prevents the aggregation of activated IRF-3).[3]

Clinical and virological manifestations of genital HSV-2 infections vary widely due to the single-nucleotide polymorphisms in TLR. Studies proved that polymorphisms in TLR 2 had resulted in increased HSV-2 genital shedding. Svensson et al. in their study suggested that the absence of TLR3 functional activity predisposes children to HSV-1 encephalitis.[4] Apart from genetic variations in TLR which modify the course of HSV illness, Resiquimod, a TLR 7 and TLR 8 agonist also decreases HSV-2 genital shedding.[5]

Thus, the critical role played by TLR in innate immunity has been a tremendous advancement in the pathogenesis of HSV infection and more treatment options could be tried in this line.

Figure 1: Schema for toll like receptors recognition of herpes simplex viral - pathogen-associated molecular patterns and its signalling cascade.
Sir,
Pyoderma gangrenosum (PG) is defined as an inflammatory, reactive, noninfective, nonneoplastic skin disease. The four main clinical types of PG are ulcerative, pustular, bullous, and vegetative. A few atypical variants have also been described such as peristomal PG, genital PG, an oral variant that is pyostomatitis vegetans, and an extracutaneous neutrophilic disease. The diagnosis of PG is one of the exclusion. Classic PG usually occurs on the lower extremities, but may occur anywhere. A very few cases of vulvar PG are reported in the literature. We describe a young girl who presented with an ulcer over the genitalia who was diagnosed as a case of PG and treated successfully with systemic steroids.

A 21-year-old unmarried girl presented with the history of genital ulcer of 2 weeks duration that had developed from a small pus filled lesion. There was history of intermittent fever and painful oral aphthae. The ulcer was asymptomatic initially, later associated with severe pain and foul smelling discharge. Patient denied history of any genital trauma and had never been sexually active. There was no history of vaginal discharge, bleeding on touch, joint pain, or eye complaints. Her menstrual cycles were regular. Review of systems was noncontributory.

On local genital examination, there was a solitary well-defined ulcer with foul smelling discharge and slough over the lower aspect of the left labia majora extending to labia minora and the adjacent groin [Figure 1]. It was tender and nonindurated. The ulcer did not bleed on touch. There was no regional lymphadenopathy. Pathergy test was negative. Evaluation for sexually transmitted infections was negative. Blood investigations revealed anemia and elevated erythrocyte sedimentation rate. Liver and renal function tests, urinalysis, and stool examinations were within the normal limits. The skin biopsy specimen for histopathological examination revealed epidermis with a canthosis and granulation tissue along with diffuse infiltration of the dermis with neutrophils, occasionally lymphocytes and macrophages [Figure 2]. These findings were consistent with PG. Patient was then treated with

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