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Immunocompetent in vitro urovaginal mucosa infection models for vaccine research

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Background

The lack of effective vaccines against gonococci and the rapid increase in antibiotic resistant strains worldwide presents a serious public health threat. The problem is further exacerbated by the 50-70% reported incidence of chlamydia and

gonococcus co-infections worldwide. New therapies are needed. However, the human specificity of the gonococcus limits the development of robust preclinical animal models that faithfully recapitulate the human infection. In vitro engineered models from human donor materials more accurately recapitulate the tissue architecture and microenvironment. Infections usually occur on the mucosal surfaces of the cervix and urethra.

Aim/Methods

We used 3D urovaginal mucosa models to assess the pathophysiology of gonococcus and chlamydia co-infections and the effect of immune intervention strategies. The models were established by co-culturing primary cervical fibroblasts and epithelial cells on collagen-based scaffolds under air lift conditions for 21-28 days. Primary neutrophils and macrophages were incorporated into the models to make them immunocompetent. Models were infected with gonococci and chlamydia to assess the host response and recruitment of immune cells to the site of infection.

Results

The models show stratified squamous epithelia typical of the ectocervix and columnar epithelia typical of the endocervix. The models also express typical markers such as cytokeratins and p63. They also express junctional complexes in typical honeycomb organization and exhibit high barrier function. Established single and co-infection of gonococci and chlamydia increase >100-fold in 24hpi although only approximately 5% of cells were infected. Infections induced expression of inflammatory cytokines such IL-6 and IL-8 as well as TNF-α. Initial gonococcal infection seemed to inhibit the formation of chlamydial inclusion, and co-infections significantly reduced cytotoxicity. Neutrophils migrated from the basal side to the site of infection and secreted high levels of IL-6, IL-1B, TNF-α and IL-17α into the supernatant.

Conclusions

The in vitro 3D cervical mucosa models show high in vivo – in vitro correlation, hence used to overcome host-specificity limitations associated with 2D cell cultures and animal models. The models can be used to reveal factors important for host-pathogen and pathogen-pathogen interaction under co-infection scenarios. The models can therefore be used in the development of effective intervention strategies for infections.