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Influence of host genetic and ecological factors in complex concomitant infections – relevance to sexually transmitted infections

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ABSTRACT

While there is evidence that host genetics plays a role in susceptibility and subsequent sequelae of sexually transmitted infections (STIs), association findings have been inconsistent in deciphering the causal genes or biological pathways involved in the different life cycle and pathogenesis of infectious microbes. The lack of replication and validation studies from genome-wide association studies in general and specifically with infectious diseases, including STIs, is a continuing problem that limits the utility of these studies. Cohort heterogeneity, sample size, and confounding by population stratification due to differences in genetic polymorphisms in different ethnic groups are the usual explanations. However, in the context of genetic epidemiology studies of infectious disease, apart from the involvement of at least two genomes (the host and the pathogen), local environmental factors in the host shared by concomitant infections are often not examined. Different infectious microbes contribute to the shared local microenvironment, and the immune response can be favorable or unfavorable to different microbes individually and concomitantly at various levels. The balance of each infection relative to the other concomitant infections is a major confounder that has been under-studied. Thus, host genetic studies examining only one pathogen can yield inconsistent associations. This warrants a new paradigm that uses an ecological network-based study design and analysis tools. Defining the role of genetics in concomitant infection is likely to provide insight into pathogenic and protective mechanisms and to identify interdependent molecular targets for prophylactic and therapeutic interventions to multiple co-infections.

1. Introduction

With growing evidence, modern science has embraced Louis Pasteur and Robert Koch's "germ theory of disease," suggesting microbe–host interactions in the pathogenesis of several diseases, but the relationships have not been successfully disentangled. Infectious disease, as defined by the pioneer epidemiologist and bacteriologist Theobald Smith, is "the result of the interplay between microbial virulence, dominance of the organism in terms of numbers, and the host defense" (Smith, 1934). Variation in the immune response to pathogenic infections is a function of exposure to microbes and the host biology which arguably, is regulated by its genetic makeup (Casanova and Abel, 2007). This simple model describes the disease pathogenesis for a single infection; however, concomitant infectious diseases, particularly sexually transmitted infections (STIs) have complex etiological factors. Genetic association findings have been inconsistent in pinpointing the causal genes or biological pathways involved in the different life cycles and pathogenesis of even a single infection. The lack of replication and validation of genetic association across studies is due largely to heterogeneity in ethnic background, cohort-specific risk factors,

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study designs, differential infection outcomes. However the ecological factors, for example the local environment, that are shared by concomitant infections often are not examined. Different infectious microbes often share the same environment and respond with similar or contradictory immunity in the host. These immune responses are biologically favorable or unfavorable to the pathogens, individually and concomitantly, at various levels. This cost-benefit balance of each infection relative to other infections may be a major confounder that has not been carefully examined. Here, using the female genital tract as a model, this concept is discussed in light of differential immune responses to concomitant infections and the significance of host genetic factors. The purpose of this review is to put forward the case that individuals often are infected with multiple sexually transmitted pathogens, and this necessitates a shift in the paradigm of how we examine and evaluate the role of host genetics in STI outcomes.

2. Female genital tract

The female genital tract, a major portal for several STI pathogens (virus, bacteria, fungus, and parasites), illustrates the complexity of concomitant infections (Fig. 1). An estimated 340 million cases of curable STIs occur worldwide each year (WHO, 2007) and disproportionately affect newly sexually active females. The mucosal surface of the reproductive tracts of women contain various immune response cells, including epithelial cells, lymphocytes, macrophages, and dendritic cells, which provide a barrier against these pathogens and also participate in both innate and acquired immune defense. It is essential that the mucosal surface has the capacity to recognize and respond to intruding foreign pathogens while simultaneously avoiding an imbalance of the steady-state mucosal environment. This mucosal lining adapts to a dynamic environment of endogenous vaginal pathogens along with non-pathogenic, commensal microflora. However, in response to the introduction of a new foreign pathogen, innate immunomodulatory molecules are secreted. These molecules act as messengers between cells to mediate and regulate immunity, inflammation, and hematopoiesis and also affect tissues outside the immune system. Any sequelae of chronic inflammation could break the epithelial lining, which might not only increase transmission of other STIs but also develop lesions that could lead to other complications, including cancer. While some pathogens such as HPV, gonorrhea, and chlamydia, predominantly infect the genital mucosa and rarely invade deeper into the body, others, such as syphilis, HBV, and HIV, are systemic infections that exploit the genitalia as their point of entry. The innate and adaptive immunity in the female genital tract has been extensively reviewed (Mestecky and Fultz, 1999; Russell et al., 2005; Wira et al., 2005), but the interplay between host genetics with outcomes of concomitant infections remains to be elucidated. Genetic variations are important in relation to how the immune-related molecules are produced and secreted.

3. Host immune adaptation and concomitant infections

Understanding how host factors contribute to the comprehensive defense is critical to ensuring overall protection or resistance to individual or concomitant infections. A mucosal surface such as the genital tract must have the capacity to recognize and respond to intruding foreign pathogens while simultaneously avoiding the disturbance of its “steady-state” internal ecology. Some immunomodulatory molecules are beneficial for some pathogens, but they may not be as beneficial to other pathogens present in the host. While many bacteria, viruses, parasites, or their products stimulate production of IL-10, this cytokine can be involved in inducing host susceptibility and persistence of several pathogens. On the other hand, IL-10 can be protective in some other infection outcomes; e.g., it prevents the development of immunopathological lesions and exaggerated inflammatory and immune reactions to acute or chronic infections (Mege et al., 2006). Thus, the protective and susceptibility effect might depend on the timing and sequence of infections.

Concomitant infection does not necessarily mean that the infections occurred simultaneously. Rather, the first infection might disturb the equilibrium enough physically (e.g., damage the epithelial lining) or biologically (e.g., secrete different cytokine and chemokines in response) to make the host more or less susceptible to subsequent infections by other pathogens. When one infection precedes the other, the immune response to the first infection will influence the adaptability of the second, favorably or unfavorably. For example, in mice, when *Toxoplasma gondii* precedes *Schistosoma mansoni* infection, murine hosts have milder schistosomiasis; conversely, when *S. mansoni* infects first, the host suffers severe inflammatory immunopathology (Graham, 2002). Additionally, various outcomes of infections, such as rapid recovery (e.g., clearance of acute infection), rapid progression of the disease (e.g., increase or decrease in biomarkers such as CD4 cell counts), rapid death of the host, superinfection (one pathogen dominating others), persistent infection (some infections such as HIV persist forever, whereas others such as low-risk HPV types are short term), and acute infection (either completely cleared from the system or just immunologically suppressed or in latency), are likely to be influenced by the sequence of concomitant infections, i.e., which infection precedes and how that influences subsequent infections. All of these outcomes are regulated in the host by the complex array of the immune system, triggered in response to various foreign stimuli. The residual cross-reactive immunity against various pathogens may play a role in overall mucosal immunity – for example, an intra-species cross-immunity, as with different HPV types (high-risk HPV type 16 and 18 versus other types) (Palmroth et al., 2010), or interspecies co-existence (HSV-2 versus bacterial vaginosis) (Kaul et al., 2007). Thus, it is naive to expect that a particular pathogen will elicit an identical response and have identical pathogenic sequelae in each infected individual without accounting for several factors, including concomitant infections and the