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Review

Speculations on the clinical significance of asymptomatic viral infections

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ABSTRACT

A detailed understanding of asymptomatic chronic viral infections is critical to analyse their pathogenesis, assess the severity and burden of disease and, where required, optimize public health control measures. Recent studies on herpesviruses showed that the host–virus interactions are modulated by co-infections, emphasizing the relevance of co-infections in determining the clinical expression (from asymptomatic to symptomatic infections) and the severity of herpesvirus-associated diseases (either neoplastic or infectious diseases). To demonstrate causality between viruses (virome) and diseases, Koch's postulates should be adapted adding new knowledge on host–microbe relationship and microbial interactions. In the present review we aim to provide an update on asymptomatic chronic infections and criteria for causality and on the virological, immunological and host–virus interactions in asymptomatic chronic infections in human hosts, focusing on herpetic infections. **G. Gentile, CMI 2016;22:585**

Introduction

Asymptomatic, chronic viral infections occur in a large portion of humanity. It has been estimated that on average every human being can be concurrently infected with 8–12 chronic viral infections, caused either by DNA or RNA viruses [1]. Viruses considered to be commensal and opportunistic pathogens are widespread, especially in adults, and include members of the herpesvirus, adenovirus, papillomavirus, anellovirus, polyomavirus and circovirus families [2,3]. Conversely, viruses associated with high morbidity and mortality such as hepatitis C virus, hepatitis B virus and human immunodeficiency virus (HIV) chronically infect millions of individuals [4].

Until a few years ago, the approaches applied to studying host immunity and viral virulence were mainly based on the analysis of symptomatic acute infections, and evaluated virus shedding and serological evidence of infection, together with the analysis of the immune responses of the host. Studies of acute infections have been relevant for analysing viral virulence and host immunity; however, the mechanisms that establish and perpetuate chronic viral infections are still not well known [1]. These mechanisms can be analysed taking into account the behaviour of a component of the microbiome, the virome. The microbiome, defined as all the microorganisms (viruses, bacteria, parasites and fungi) living within a human host, is a component of human physiology [5], while the virome is part of the microbiome of healthy humans, and includes the viruses (pathogenic and non-pathogenic) that infect the eukaryotic cells of the host, those that replicate in bacteria (bacteriophages or phages) and the endogenous viral elements [6]. A new and emerging concept includes the view that viruses may have deleterious or beneficial immunomodulatory effects other than affecting the adaptive and innate immune response [7,8]. For instance, recent studies on herpesviruses clearly evidenced that the host–virus interactions are modulated by co-infections (reviewed in refs [9–11]), emphasizing the relevance of co-infections in determining the clinical expression (from asymptomatic to symptomatic infections) and the severity of herpesvirus-associated diseases (either neoplastic or infectious diseases), such as those induced by Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV-8) [9,11].

For two centuries, Koch's postulates were the landmark for establishing causation in infectious diseases. In recent years, Koch's postulates have been modified to take into account new knowledge of the host–microbe relationship and microbial interactions by means of genome sequencing. Therefore, it has been proposed to

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dynamically adapt Koch's postulates taking into account the new advances in technology [12].

An understanding of asymptomatic chronic viral infections, defined as infections without any sign or symptom, is important for understanding the pathogenesis of viral infections, assessing their severity and the burden of disease and, where required, for optimizing public health control measures. It is important to recognize that the study of asymptomatic chronic viral infections is an emerging field, and part of our discussion will necessarily be speculative. Specifically, our goal is to provide an update on asymptomatic chronic infections and criteria for causality and about the virological, immunological and host–virus interactions in asymptomatic chronic infections in human hosts, focusing on herpetic infections. Due to space constraints, we will focus our review mainly on EBV and HHV-8 infections because, in our opinion, they represent the paradigm of chronic asymptomatic infections. They are well-known viruses, but recent studies showed that the host–virus interactions are modulated by some co-infections, greatly expanding our knowledge in the general field of chronic viral infections.

Asymptomatic chronic infections and criteria for causality

The criteria commonly used to assign causality in medical research, especially by infectious diseases physicians, are the Koch postulates [13]. The criteria were partially redefined by Jacob Henle in 1840 [14] and later expanded and referred to as the Henle–Koch postulates [15]. These postulates state that: (a) the organism is always present in every case of the disease in question and under circumstances that can account for the pathological changes and clinical course of the disease; (b) the organism is not found with any other disease or as a colonizer without disease; (c) after being isolated from the body and repeatedly grown in pure culture, the organism reproduces the disease again in an another susceptible host. The main problem concerning the application of the Henle–Koch postulates is linked to the impossibility of applying them to the majority of pathogens and in particular to viruses. As obligate cellular parasites, viruses cannot be formally evaluated in pure culture; for example cells that become cancer cells due to viral infections are non-permissive for viral replication, and therefore virions are not identifiable, and in these conditions Koch's postulates are not applicable.

The culture-dependent approaches could not demonstrate the role of the association between infectious agents, mainly viruses, and chronic or neoplastic diseases. Two significant examples show the long latency period between a primary viral infection (often asymptomatic or subclinical) and the occurrence of a disease: human T lymphotropic virus-1-associated myelopathy/tropical spastic paraparesis or T-cell leukaemia following T-lymphotropic virus type 1 decades after the primary infection (reviewed in ref. [16]) and Kaposi sarcoma (KS) following Kaposi's sarcoma-associated herpesvirus (KSHV, also called HHV-8) (reviewed in ref. [16]).

Hill's criteria (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, analogy) are now used to determine causality for infectious microorganisms in chronic or neoplastic diseases [17]. However, again the strict application of Hill's criteria or Henle–Koch postulates may not be able to identify the causal role of viruses in the aetiology of infectious diseases or tumours [18,19]. The high-throughput deep sequencing assays, together with bioinformatics systems, have revolutionized the studies on microbial communities, providing useful tools for assigning causality between microorganisms and infectious diseases. At present two main methods are applied: (a) the bacterial 16S ribosomal gene profile analysis, used to study bacterial phylogeny and taxonomy, which allows determination of the relative abundance of each species in a given sample; (b) the next-generation sequencing or 'shotgun' metagenomic sequencing, which uses a direct sequencing of total DNA and examines also viral sequences, allowing the detection of a broad range of both cultivable and non-cultivable DNA viruses [20,21]. Metagenomic studies applied to viruses provide a significant insight into identification and characterization of new viruses, on viruses associated with diseases of unknown aetiology, molecular epidemiology, molecular pathogenesis, genome characterization, gene discovery with genetic diversity, and on dynamics of microbial populations, focusing primarily on the interaction between viruses and host immune system [22,23]. However, a present limitation of the metagenomic studies applied to viruses is that the detection of DNA viral sequences in a given sample does not formally demonstrate that the viruses found are replicating. Therefore, future studies should be focused on active viral infections by assessing, for instance, cell-free virus particles and on analyses and sequencing of RNA viruses [6]. With the intention of avoiding a reductionist methodological approach it will be important to perform, in addition to the metagenomic studies, also metatranscriptomic (analyses of messenger viral RNA) together with metaproteomic (analyses of expressed proteins) studies [24], allowing a better comprehension of the pathways and community interactions of the viruses and their role in the asymptomatic and symptomatic infections.

Herpesviruses: paradigm of chronic asymptomatic infections

Herpesviruses are ubiquitous viruses, infect a high number of subjects with a variable worldwide distribution, and it is estimated that >90% of humans are infected with at least one herpesvirus [1]. For example, primary cytomegalovirus (CMV), human herpesvirus-6 and EBV infections usually occur more frequently during the first two decades of life as asymptomatic infections or symptomatic mononucleosis-like syndrome [25–27]. Herpesviruses may also cause several forms of diseases in humans, and in particular, HHV-8 and EBV are associated with several tumours: HHV-8 with KS and lymphoproliferative diseases [16], and EBV with lymphomas and nasopharyngeal carcinomas [16].

Reactivation of herpesviruses from latency is required for the viruses to persist and to spread among cells and host. Environmental conditions induce herpesviruses to switch from latency to lytic phases [28], but the mechanisms by which these stimuli function *in vivo* have not been elucidated. Short-chain and medium-chain fatty acids found in the diet or produced by human microbiota may modulate the balance between the latent and lytic phases of both EBV and HHV-8, showing that an interaction between bacteria and virome may affect herpesvirus activation [29]. Epigenetic alterations may stimulate lytic reactivation, productions of virions and spread of herpesviruses [30]. In particular, HHV-8 and EBV are probably regulated by epigenetic modifications induced by bacteria [31,32] and it is possible to speculate that bacterium–virus interactions might contribute to the pathogenesis of cancers such as KS and gastric cancers associated with *Helicobacter pylori* and EBV [30].

Chronic herpesviruses infections induce a modulation of the host immune defences, which in turn promote immune suppression and a greater susceptibility to infections. For example, asymptomatic chronic infections with CMV and human herpesvirus-6 are able to reduce or to alter the immune response through various mechanisms and in specific clinical settings, such as solid organ or haematopoietic stem cell transplants. These chronic infections may be associated with the development of secondary clinically relevant infections due to fungi, bacteria and/or other viruses other than allograft rejection and with decreased

patient survival [33–35]. On the other hand, experimental studies have shown that a chronic asymptomatic herpesvirus infection, being a physiological viroma constituent, may have a surprisingly protective effect on the host against viral and bacterial infections [36]. For example, latent murine γ-herpesvirus 68 infection might prevent the development of tumours [37], and might increase the resistance to *Listeria monocytogenes* and *Yersinia pestis* [36]; in addition, asymptomatic CMV infection may have a beneficial effect on the immune responses to influenza virus of younger human adults [38], showing that herpesvirus latency may be a symbiotic relationship with immune benefits for the host. In addition, an interplay between bacteria and CMV has been shown by studying the relationship between experimental inflammatory bowel disease in mice, murine CMV infection and commensal Gram-negative and anaerobic bacterial antigens; it was found that murine CMV infection might have increased colitis by altering the intestinal immune response to gut microbiome [39].

EBV co-infection with malaria

It remains unclear why some individuals infected with EBV develop infectious mononucleosis and others do not. Acute symptomatic infectious mononucleosis, is more frequently observed during adolescence or later in life in Western countries [40]. On the contrary, children in sub-Saharan Africa have the primary infection within the first years of life, mainly by 12 months of age and are typically asymptomatic [41].

Primary infection acquired at an early age or in addition with a co-infection can induce poor control of EBV replication and might be a risk factor for the development of subsequent chronic diseases, including cancer. For example, EBV and malaria co-infections have been associated with the development of endemic Burkitt lymphoma (eBL) [42], a common endemic childhood malignancy in Africa, rapidly fatal if not treated. On the contrary, the impact of acute EBV on the immunity to *Plasmodium falciparum* infections and on malarial disease severity have not been fully evaluated [43]. Malaria infects about 200 million people worldwide and approximately 700 000 individuals die every year, mainly children under 5 years of age [44]. In this regard, HIV-negative infants living in regions with high malaria exposure were infected with EBV earlier in life, and young age at the time of infection (before 6 months of age) led to frequent EBV detection and higher EBV loads [41], supporting de-The's hypothesis [45] that young age at the time of asymptomatic EBV infection might be a risk factor for the development of eBL [41]. A recent longitudinal study confirmed the impact of *Plasmodium falciparum* co-infection on EBV replication in Kenyan children [46]. BL is characterized by chromosome translocation between the c-*myc* oncogene and immunoglobulin gene loci, which deregulates c-*myc* but is not sufficient by itself to induce lymphoma [47]. *Plasmodium* infection alone does not induce cancer, and other transforming events such as an EBV infection or other unknown mechanisms are required. In this regard, the first evidence of a mechanism to explain the link between eBL and holo-endemic malaria have been recently provided [48,49]. In particular, it has been shown that chronic infection with *Plasmodium* parasites induces genomic instability and the expression of enzyme activation-induced cytidine deaminase promotes *Plasmodium*-associated B-cell lymphoma in mice [49]. If these observations are confirmed, reducing the exposure to *Plasmodium falciparum* or developing drugs able to block malaria parasites to induce the deregulated expression of the activation-induced cytidine deaminase should significantly decrease the incidence of eBL in young children in Africa. In addition, the interactions between EBV, malaria and HIV, and the effect of these interactions on the incidence of B-cell lymphoma in Africa will have to be further elucidated [10].

HHV-8 co-infection with *Plasmodium falciparum* and with helminth

HHV-8 (after a long period of asymptomatic chronic infection) causes KS, which manifests itself in four clinical forms: classic KS, a rare disease of the elderly; endemic KS which mainly affects children in sub-Saharan Africa and was well documented before the explosion of the HIV epidemic; AIDS-associated KS, and iatrogenic KS associated with immunodepression, such as that observed in solid organ transplant patients [50,51]. Furthermore, HHV-8 has been associated with primary effusion lymphoma and multicentric Castleman's disease, a lymphoproliferative disorder [50,51]. As other herpesviruses, HHV-8 escapes the host immune control during all the phases of the infection (primary infection, latency and reactivation). The host uses the innate and the adaptive immune systems to defend itself from the infection [51].

Chronic herpesvirus infection might have a protective effect against viral and bacterial infections [36]. In contrast, helminth co-infection stimulates the replication of γ-herpesviruses (murine γ-herpesvirus-68 and HHV-8) [52,53]. The study of Reese [52] and Osborn et al. [53] expands our perspectives on the complexity of infectious diseases, showing that members of the gut microbiome, such as helminthic worms, in addition to bacteria, have relevant effects on intestinal antiviral immunity and possibly on public health in tropical medicine [54]. The above-mentioned studies show that viruses (virome) interact with helminths, generating a trans-kingdom interaction [6,8], allowing speculation that chronic herpesvirus infection in humans evolved in the context of co-infections.

Several epidemiological studies have shown that seroprevalence to HHV-8 has been associated with hookworm and in particular with malaria in sub-Saharan African countries [55–58]. The latter finding might be explained by the fact that repeated malarial infections can induce HHV-8 reactivation and might modify the infectivity and/or transmission of HHV-8 [56,58]. Therefore, based on the detection of a high prevalence of HHV-8 infection in areas where malaria is endemic, malaria has been proposed as a co-factor for the transmission or reactivation of HHV-8 infection [55–59].

However, HHV-8 co-infection with HIV remains one of the most significant factors associated with the progression and development of KS (reviewed in ref. [9]).

Conclusions

The asymptomatic chronic viral infections are part of the virome, that includes diseases and physiological effects. In particular, chronic herpesvirus infections are multifactorial infections arising from complex interactions among the herpesviruses, host factors, co-infections and other unknown aspects. Given the fact that the combinations of host, microbe and environment can happen in any host–microbe interaction, it has been proposed to dynamically adapt Koch's postulates adding the new findings on host–microbe relationship and microbial interactions [12,60].

Nowadays, the approach to understanding the pathogenesis of viral infections studying a single virus that interacts with a single host is too limited to explain the complexity of the relationships between host and viruses [61]. For example, while evaluating the virome composition in the blood of solid organ transplant recipients, it was found that the decline and control of anellovirus replication might be considered as an indicator of immunocompetence [62]. The reasons why some individuals will develop symptomatic viral infections are not fully acknowledged at present. Future studies should combine metagenomic, metatranscriptomic and metaproteomic analyses, allowing a better comprehension of the

pathways and interactions of the viruses and their role on the effects of chronic asymptomatic infections on human health and diseases.

Transparency declaration

The authors declare that they have no conflicts of interest.

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