

Infectomic Insights into the Roles of Exosymbiosis-Endosymbiosis Imbalance (EESI) in HIV-1 and SIV Infections

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Abstract

The vast majority of microbes form a healthy symbiotic 'superorganism' with the hosts. There are two types of symbiosis (Sym), exosymbiosis (e.g. microbiota) and endosymbiosis (e.g. mitochondria). It has been suggested that the exo-endo Sym balance (EESB) highly contribute to maintain the host homeostasis. However, alterations to the EESB caused by microbial (e.g. bacterial and viral pathogens) and non-microbial factors (e.g. substance abuse, diet and/or lifestyle) can disturb this symbiotic relationship and promote disease, such as inflammatory bowel diseases and acquired immune deficiency syndrome (AIDS). Progressive AIDS caused by human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) is characterized by systemic inflammation, opportunistic infection and malignant disorders resulting from generalized immune activation-mediated destruction of the healthy symbiotic super organism. Two extreme phenotypes are present in both HIV and SIV infections, including slow or rapid progression to AIDS (Pat: pathogenesis) in a majority of the infected human subjects and the non-natural primate host (i.e. rhesus macaques, RMs), and nonprogression to AIDS (Sym) in a minority of the infected people and the natural primate hosts (i.e. sooty mangabeys, SMs). Recently, it has been demonstrated that both exosymbiotic and endosymbiotic disorders contribute to the development of AIDS through infectomic studies of the extreme phenotypes of HIV/SIV infections. The involvement of the EESB in the pathogenesis and therapeutics of HIV infections is becoming increasingly clear. Indeed, many changes in the microbial diversity, abundance and composition of the gut microbiota and mitochondrial functions have been reported in HIV/AIDS, suggesting that there exist EESB problems in this disease. HIV virotoxins have been implicated in exploiting mitochondria to promote the targeted progressive and inexorable depletion of key immune cells (e.g. CD4 T cells), a hallmark of HIV/SIV infections. These findings support the notion that the exo-endo Sym imbalance (EESI) may play a central role in epidemiology, pathogenesis and management of infectious diseases, including AIDS caused by HIV-1 and SIV. Correction of the EESI problems in HIV/SIV infections may lead to a rational control of AIDS.

Keywords: Exosymbiosis; Symbiosis; Endosymbiosis; Exo-Endo symbalance; Exo-Endo symimbalance; HIV; AIDS

Introduction

Infectious diseases, including HIV-1/AIDS, continue to be the leading cause of morbidity and mortality worldwide despite the availability of effective antimicrobial agents and vaccines over the last several decades [1].

The continual emergence of new pathogens, re-emergence of old pathogens, and the rising crisis of antibiotics resistance will certainly heighten the global impact of microbial threats to human health today. HIV/AIDS is the most salient emerging disease in modern medicine [2]. Progressive AIDS caused by HIV and SIV is characterized by systemic inflammation, opportunistic infection and malignant disorders resulting from generalized immune activation-mediated destruction of the host defence system [3]. Pathogenesis, prevention, treatment and cure of HIV-1 infection remain one of the greatest challenges in modern medicine since the discovery of this disease 1981 [4,5]. There are usually two basic phenotypes [pathogenesis (Pat) and symbiosis (Sym)] of microbial infection including human HIV/AIDS [6,7]. However, the conventional wisdom places emphasis on the

pathogenic process-namely antagonism-rather than mutualism [1]. Two extreme phenotypes are present in both HIV-1 and SIV infections, including slow or rapid progression to AIDS (Pat) in a majority of the infected human subjects and the non-natural primate host (i.e., rhesus macaques, RMs), and nonprogression to AIDS (Sym) in a minority of the infected people and the natural primate hosts (i.e., sooty mangabeys, SMs) [7]. Infectomic insight into the differences in phenotypes of HIV-1/SIV infections has been essential for uncovering this relationship and conquering AIDS. The most fundamental issue in infectomics is how to dissect the dynamic Sym-Pat duality in microbial infections [1,8]. There are two types of symbiosis, exosymbiosis (e.g. microbiota) and endosymbiosis (e.g. mitochondria). It has been proposed that the Exo-Endo Sym (EES) balance is essential for health and that the EES imbalance (EESI) plays a central role in the pathogenesis of infectious diseases, including AIDS caused by HIV-1 and SIV [8]. This notion is further supported by our infectomic analysis of the two extreme phenotypes of SIV infection [7].

Exo-Endo Sym Balance (EESB) and health

There are two types of symbiotic relationships, including those associations in which one organism lives on another (exosymbiosis,

e.g. microbiota living on the body surface of the host), and where one partner lives inside the cells or tissues of the other (endosymbiosis, such as mitochondria in eukaryotic cells) [8]. The vast majority of microbes form a healthy symbiotic 'superorganism' with the hosts. The ecology and evolution of the exosymbiotic relationships between microbes and their hosts are essential and fundamental for health. Most of our microbial commensals reside in our gastrointestinal (GI) tract packed with up to 100 trillion (10^{14}) microbes, with up to 1000 or so different bacterial species [8,9]. The GI tract microbiota constitutes a natural defensive barrier to infection. They may provide a number of positive health benefits for their hosts. These include stimulating the immune system, protecting the host from microbial invasion, aiding digestion, maintaining host homeostasis and modulating energy balance. The GI tract is a complex ecosystem formed by the symbiotic alliance of GI epithelium, immune cells, and microbiota. Just as most exosymbiotic microbes form a healthy symbiotic superorganism with the hosts, an elegant balance of this symbiotic relationship is essential to the development and function of immune system. A few recent studies showed that mitochondria, an endosymbiotic organelle, could play an important role in the cross-talk between microbiota and host [10-12]. There are many common features shared by both microbiota and mitochondria due to the prokaryotic origin of mitochondria. These include similar structures/functions, protein degradation pathways, sensitive to antibiotics and the presence of their DNAs in the nuclear genome [10]. Reactive oxygen species (ROS) produced by mitochondria may be important for the innate immune response and inflammation induced by microbial pathogens. Mitochondria may affect ROS signaling induced by the microbiota to regulate the gut epithelial barrier. It has been reported that health problems such as obesity, diabetes mellitus, Crohn's disease or even autism and depression are associated with specific microbiota diversity and quality that may be regulated by mitochondria [10,11]. These findings suggest that the exo-endo sym balance is essential for health.

Exo-Endo Sym Imbalance (EESI) and AIDS caused by HIV-1 and SIV

It is well known that both microbial translocation across the gut barrier (disturbing exosymbiosis) and mitochondria mediated disorders (dysregulation of endosymbiosis) are involved in the pathogenesis of AIDS [8]. HIV and SIV infections can contribute to increased bacterial translocation and chronic immune activation through altering the intestinal immune system and microbiota interplay [13-15]. Increased abundances of Proteobacteria and decreased abundances of Firmicutes are observed in colon biopsies of HIV-1-infected subjects compared with that in uninfected donors. There is a significant increase in *Prevotella* and decrease in *Bacteroides* in HIV-1-infected subjects. The increase in *Prevotella* abundance was correlated with increased numbers of activated colonic T cells and myeloid dendritic cells during HIV-1 infection. These findings suggest that an important relationship exists between altered exosymbiotic microbial communities and the mucosal immune system during chronic HIV-1 infection. Meanwhile, endosymbiotic (mitochondrial) disorders also contribute to the pathogenesis of HIV infection and HIV-associated neurocognitive disorders (HAND) [16-18]. Mitochondria can directly influence the progression of AIDS, including the viral infectivity, the course of HIV-1 infection, and the prevalence of side effects from the primary HIV-1 therapy, highly active antiretroviral therapy (HAART). Point mutations and deletion of mitochondrial DNA can lead to decreasing HIV-1 infection [16]. Mitochondria play a key role in the production of energy and the induction of cellular apoptosis, which can be dysregulated by HIV viral

genes [18]. We have demonstrated recently that both exosymbiotic and endosymbiotic disorders contribute to the pathogenesis of AIDS through infectomic studies of the Sym/Pat phenotypes of HIV and SIV infections [6-8,19]. The Pat+ phenotype in SIV-infected RMs is specifically associated with disorders in the protein ubiquitin proteasome system, p53, granzyme A, granzyme B, polo-like kinase, Glucocorticoid receptor, oxidative phosphorylation and mitochondrial signaling. Mitochondrial (endosymbiotic) dysfunction is solely present in RMs. Sym+ pattern changes identified in SIV-infected SMs are the pathways contributing to the host defense against viral infection, including interferon signaling, BRCA1/DNA damage response, PKR/INF induction and LGALS8. The genes LGALS8 and IL-17RA, which positively regulate the barrier function of the gut mucosa and the immune homeostasis with the gut microbiota (exosymbiosis), were significantly differentially expressed in RMs and SMs. These findings suggest that the exo- and endo-sym imbalance (EESI) may play a central role in the pathogenesis of HIV/SIV infections.

Suspected involved mechanisms

The underlying mechanisms contributing to the EESI in HIV/SIV infections remain unclear. Recently, the concept of ecoimmunity has been proposed to explore the interplay between the immune system and its ecology [8]. The immune system and microbial communities are viewed as two interrelated and dynamically co-evolving components of a predator-prey ecosystem. These efforts emphasize the interchange between the organism and its ecological environments with more holistic consideration of immune regulation through chemical and genetic communications. HIV/SIV infections can induce significant changes in the diversity, abundances and components of microbiota, which disturb ecological environments. HIV virotoxins have been implicated in exploiting mitochondria to promote the targeted progressive and inexorable depletion of key immune cells (e.g. CD4 T cells), a hallmark of HIV/SIV infections. It disturbs the ecoimmunity and directly contributes to disease progression and immunodeficiency [18]. Correction of the ecoimmunity problems and EESI in HIV/SIV infections may lead to a rational control of AIDS.

Conclusion

The advent of microbiome sequencing and infectomic technologies has greatly improved the characterization of virotoxins and host factors that contribute to the pathogenesis and therapeutics of HIV/AIDS. However, a better understanding of the EESI in health subjects and EESI in patients with HIV-1 infections requires further structural and functional studies of both the exo and endo sym systems and the connectivity between the two systems. Most of the studies published in this regard have been carried out without characterizing the EESI/EESI and their connection. Investigations should also consider the use of the ecoimmunity approaches to study the ecoimmunity system that is modulated both by external and internal factors in relation to molecular and cellular pathways involved in EESI associated with HIV infections. In summary, the role of EESI in HIV/SIV infections is increasingly evident and perhaps represents a new central approach towards the development of rational therapeutic interventions in AIDS.

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