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Integrative Immunobiology and Inflammation

Prespective

An Integrative Immunobiology and Inflammation Study on Cytomegalovirus

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Abstract

The human immune system plays a cardinal role in host defense against the assault of foreign agents, particularly that from microbes, such as bacteria, fungi, or viruses of which human cytomegalovirus serves as an example. Immune reactions consist of inflammation, however, either hyper or hypo inflammatory reaction results in diseases. Additionally, host immunity operates a dynamic balance of symbiosis among host and microbes, at both intracellular and extracellular levels. We aim to harness the knowledge and technology in studying this ubiquitous opportunistic virus, its interplay with the host immune system, evading immune response, exacerbating inflammation, and causing damage in host whereas in symbiosis with the host DNA genome. We will address how we define the tipping point of immunity and inflammation, via studying the mechanism of the immune reconstitution inflammatory syndrome, as well as the mechanism of this diminutive mega creature causing cardiovascular injury in immune competent individuals, to develop and comply an immunomodulation, to reprogram patient immunity against the viral infections, including immunity against human immunodeficiency virus, towards a cure of AIDS.

Keywords: Cytomegalovirus; Immune reconstitution inflammatory syndrome; Human immunodeficiency virus; Highly active anti-retroviral therapy/Combination anti-retroviral therapy; Cardiovascular injury

Abbreviations: CMV: Cytomegalovirus; IRIS: Immune Reconstitution Inflammatory Syndrome; HIV: Human Immunodeficiency Virus; HAART/cART: Highly Active Anti-retroviral Therapy/Combination Anti-retroviral Therapy

Human cytomegalovirus (HCMV) is a DNA virus, a member of the Herpesviridae family. Similar to its cousins such as herpes simplex virus 1, 2, and varicella-zoster virus, HCMV lives in the human cells by establishing latent infection that follows the primary infection, and causes human diseases whenever the host immunity weakens in different conditions at different states, ranging from fetus, neonate, infant, adolescent, adult, to the elderly.

Scientifically, the study of HCMV has a long history, from unraveling that HCMV causes diseases in newborns, in organ transplant recipients, to the recent findings in patients with AIDS (acquired immunodeficiency syndrome). All, however, show

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a commonality – whenever host immunity weakens, HCMV thrives. Whenever host immunity functions well, HCMV survives and being dormant.

Immunity, aka the immune response, consists of inflammation. The latter manifests an immune reaction with a localized physical condition in which the part of body becomes red, hot, swollen, and often painful, responding to an injury or infection. Inflammation is the phenomenon, however, the underpinning mechanism is that the immune cells assembling into the site, on call, to manage the damaged tissues, specifically to get rid of the invading agents, through an arsenal of immune components, including but not limited to neutrophils, eosinophils, macrophages, complement, cytokines, antibodies, lymphocytes, and more modernly defined, anti-microbial nucleic acids, host genomic methylation, acetylation, and re-modeling. In other words, inflammation flags an underpinning mechanism of immune response, starting a healing process, gaining immune control, and returning the body into a condition of dynamic immune balance as immune surveillance. Too much of inflammation causes immune damage termed as hypersensitivity, whereas too little of inflammation called hyposensitivity, leading to immune deficiency.

The recent studies on host immunity against HCMV have made important progress in the immunobiology field, specifically on the role of nature killer cells (NK) as well as the inflated CMV-specific T-cells, which compromise up to 10% of the entire T-cell repertoire, despite being not clear whether the inflated T-cells belong to the CD4 or CD8 T-cell [1,2].

In this perspective article, we briefly state our point of view on how we harness the knowledge obtained from studying of HCMV to reconstitute patient anti-HIV immunity, to explore the interfaces of virus, immunobiology, and inflammation in the pathogenesis of disease and reconstitution of host anti-viral immunity, in an angle of integrative immunobiology and inflammation, following an induced immunomodulation strategy and ushering our studies towards a control of viral latent and active infection, to contribute to a cure of immune maladies that includes not only AIDS but also cancer.

First, we discuss HCMV infection in immune compromised individuals, epitomizing HCMV infection in patients with AIDS after treatment with HAART/cART (highly active anti-retroviral therapy/combination anti-retroviral therapy). Next, we summarize the studies of HCMV infection induced diseased conditions in immune competent subjects, focusing on HCMV infection that results in injuries of the cardiovascular system. Taken together, we hope to lay down a blue print, to advance further studies on HCMV, to harness and maneuver the host immunity in balance of immune response vs. inflammatory reaction, to reinstitute patient immunity, to steer viral infection in both active and latent states, achieving a dynamic immune balance among host immunity and inflammation against the invasion of pathogenic nucleotides, and to study and control the tipping point that governs the symbiosis of host, virus, immunobiology, and inflammation.

HCMV IRIS and Reconstitution of Immunity

It is not a surprise that HCMV, a ubiquitous, opportunistic virus living in host cells, becomes a major cause of mortality in AIDS patients before the development of HAART/cART. Here we discuss the immune reconstitution inflammatory syndrome (IRIS), which occurs after the initiation of HAART.

HIV (human immunodeficiency virus) is the pathogen of AIDS, and HIV infection causes AIDS. It is well known that HIV infection severely damages the host immunity. After HHART, studies have shown that anti-HCMV immunity is the first to be restored, serving as a signal of patient restored immunity [3-6], and the continuation of HAART might lead to a reconstitution of patient immunity against HIV. Later on, however, this has proven to be not the case. HAART has not reconstituted patient's immunity, specifically the patient's immunity against the infection of HIV. Meanwhile, the immune reconstitution inflammatory syndrome (IRIS) has been reported, which correlates to HAART restored immune response against opportunistic infections, flagged by inflammatory reaction, resulted in clinical worsening of existing opportunistic infections after commencing HAART (paradoxical IRIS), or an initiation of a new

and previously unrecognized opportunistic infections soon after HAART (unmasking IRIS). Both show an inflammation syndrome lacking of immune efficiency to get rid of the pathogen and to start a healing process [7-13].

Based on clinical data and from the etiologic point of view, it is clear that HCMV causes IRIS. In distinction from other microbes, HCMV caused IRIS is termed and treated as HCMV-IRIS. It is also clear that HAART treats the HIV infection, not the HCMV infection. Finally, it is quite clear that HAART does not restore patient immunity against HIV [1-13]. The immunobiological mechanism and microbial pathogenesis of IRIS, nonetheless, remain unclear. We believe, therefore, further investigations should aim to resolve an enigma of anti-HIV therapy – whether HCMV-IRIS represents a restored immunity against HCMV or an inflated T-cell inflammation reaction against a mega-diminutive creature on its opportunistic, ubiquitous but catching infectivity. Most importantly, can an inflammatory response such as IRIS be tuned and ushered into reconstituting patient immunity or the anti-HIV immunity? Is it not true that the underpinning mechanism of inflammation is an immune response, launched by the same immune cells, humoral elements, and the components against the infections of foreign, pathogenic nucleic acids, meaning the viruses?

We urge that this should be studied via a multidisciplinary collaborative investigation, at the interface of immune dynamic balance between anti-HCMV immunity and HCMV-IRIS, aka a balance of immunity vs. inflammation, elucidated at the clonal expansion level of memory CD4 T-cell, specifically of memory CD4 T-cell renewal and differentiation into effector cells in a systemic manner, to match the progress built upon the principles of personalized/ precision medicine.

It is worth to note that the mechanism of IRIS cannot be elucidated by the magnitude of data, i.e., how many patients have IRIS, since immune reaction is not going to be explained by a model of linear reaction. In the field of immunobiology, similar to many biological reactions showing a non-linear pattern, such as the effect of T-cell tetramers is larger than that of “quintetmers”, and the function of one CD8 T-cell plus one CD8 T-cell is not equal to the sum function of two CD8 T-cells, which heavily depends on another factor, the CD4 T-cells. In the field of viral pathogenesis, e.g., in HCMV infection of host cells, even on the cell culture, the ratio of virus vs. cell is not represented by a linear relationship, meaning the more virus used does not result in more cells infected. It, however, depends on us being armed with modern molecular techniques and with an overarching systemic mind (Figure 1), to objectively identify why IRIS occurs only in some patients but not in others, similar to why some HIV patients are elite controllers, others are post-treatment controllers, and furthermore, some others are AIDS patients.

Thus, we believe that the morbidity of IRIS should be elucidated at the mechanism level of immunobiology, to decipher the mechanism of viral specific immunity based on CD4 T-cell clonal response, defining the interconnection of anti-HCMV immunity and HCMV-IRIS, and finally, delineating the interface of anti-HCMV immunity, anti-HIV immunity, and reconstitution of host immunity. The further study of IRIS can elucidate the mechanism of immunity against opportunist infection vs. primary pathogenic infection, and why IRIS occurs in some patients but not in others, interpreted via the relationship of immunity and inflammation, at a perspective of integrative immunobiology and inflammation.

HCMV Infection and Cardiovascular Injury

Host immunity plays a cardinal role in human-microbe symbiosis. Seminal studies have been done and continued to focus on the interplay of host immunity in symbiosis of microbes at the human skin and digestive system. In the past, we have studied what a role of HCMV infection plays in the immune competent individuals, and studied the relationship among immunity, inflammation and organ function via utilizing the human cell cultures and experimental mouse models. We have defined that a persistent cytomegalovirus (CMV) infection is a risk factor for hypertension (increased arterial blood pressure), and a cofactor in aortic atherosclerosis. By animal model

Figure 1: Butterfly effect in immunomodulation.

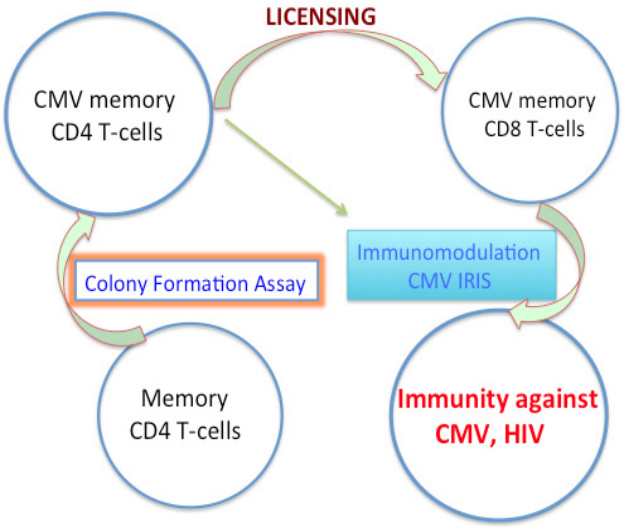

Figure 1: Complying CD4 T-cell colony formation assay in immunomodulation of CMV-IRIS leads to reinstitute CMV specific memory CD4 T-cells, usher IRIS into an anti-CMV specific immunity, paving a road to reprogram patient anti-HIV immunity, embodying the butterfly effect towards a cure of immune maladies including not only AIDS but also cancer, in line with the principles of personalized/precision medicine.

experiments, we have found that the significantly increased expression of pro-inflammatory cytokines IL-6, TNF-alpha, MCP-1, renin and angiotensin-II (Ang II) caused by CMV infection underpins the mechanism to above cardiovascular disorders [14].

Other investigators have further reported that a persistent presence of mouse cytomegalovirus (mCMV) has an proinflammatory influence on the microvasculature, and suggest that mCMV infection enhances microvasculature susceptibility to both inflammatory and thrombogenic responses caused by hypercholesterolemia, promoting an inflammatory phenotype in the microvasculature long before clinical disease is evident. Survey of patients on infectious burden and carotid plaque thickness supports that past or chronic exposure to common infections, including HCMV infection, possibly by exacerbating inflammation, contributes to atherosclerosis [15-23]. Furthermore, clinical trial and epidemiological studies have shown that in the elderly populations, high tiers of antibodies to HCMV are associated with the greater incidence of cardiovascular events, such as stroke, atherosclerosis, and a higher mortality than that of the control groups [24,25].

In line with the progress in the studies of HCMV infection in immune competent individuals, our further research specifically answers the question why HCMV can live in a host cell, and reveal a tipping point that turns HCMV from latent, chronic, to active infection, in relation with the viral infection to immunobiology and inflammation, to focus on unraveling elements with tipping point effect, epitomized a phase transition in non-linear pattern among virus, immunobiology and inflammation.

To conclude, we believe there is a commonality underlying the mechanisms of HIV specific immunity, HCMV-IRIS and HCMV related cardiovascular injury, although the former two occur in immune compromised individuals, and the latter, in immune competent subjects. In a context of host immunity vs. a mega, opportunistic, diminutive creature, it is the host immunity that plays a cardinal role in control of CMV infection, although the relationship does not show in a linear manner, which, however, epitomizes immune response vs. inflammatory reaction in CMV latent, persistent and

active infection, by which HCMV juggles with host, even "modifying" immune reaction into an inflammatory response, evading immunity, causing damage while surviving in site (in situ) in the cell ("i.t.c."). Further study on HCMV-IRIS complemented by the investigations of inflammation in immune competent subjects is no doubt to pave the road to unravel the interfaces of CMV specific immunity with CMV inflammatory response, to achieve the goal of reconstituting, or more accurately, reprogramming patient immunity specifically against HIV, towards AIDS cure.

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