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Modeling and Remodeling the Cell: How Digital Twins and HCMV Can Elucidate the Complex Interactions of Viral Latency, Epigenetic Regulation, and Immune Responses

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Abstract

Purpose of Review—Human cytomegalovirus (HCMV), while asymptomatic in most, causes significant complications during fetal development, following transplant or in immunosuppressed individuals. The host-virus interactions regulating viral latency and reactivation and viral control of the cellular environment (immune regulation, differentiation, epigenetics) are highly complex. Understanding these processes is essential to controlling infection and can be leveraged as a novel approach for understanding basic cell biology.

Recent Findings—Immune digital twins (IDTs) are digital simulations integrating knowledge of human immunology, physiology, and patient-specific clinical data to predict individualized immune responses and targeted treatments. Recent studies used IDTs to elucidate mechanisms of T cells, dendritic cells, and epigenetic control—all key to HCMV biology.

Summary—Here, we discuss how leveraging the unique biology of HCMV and IDTs will clarify immune response dynamics, host-virus interactions, and viral latency and reactivation and serve as a powerful IDT-validation platform for individualized and holistic health management.

Keywords

Human cytomegalovirus; Digital twin; Immune response; Latency; Epigenetics; Personalized medicine

Introduction

Human cytomegalovirus (HCMV) is a prototypical betaherpesvirus infecting up to 90% of the world's population [1, 2]. While asymptomatic in healthy individuals, the virus is the

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leading cause of congenital abnormalities following fetal infection [3, 4] and is a significant cause of morbidity and mortality during hematopoietic stem cell [4–6] and solid organ [4, 7] transplants. Like other herpesviruses, HCMV can establish lifelong persistence in the host, leading to distinct cellular regulation and disease states. Disease occurs following three distinct viral life cycle stages: initial infection, or after the establishment of viral latency from viral latency-induced myelosuppression, and/or acute CMV disease following reactivation. The complex interplay between the virus and host control viral latency and reactivation [8•, 9], cellular signaling (including differentiation, cell fate regulation, and hematopoietic processes) [10, 11], and the host immune responses to the virus (including specific T and B cell-driven immune responses) [12–14].

Hematopoiesis, including stem cell maintenance and the development of functional immune cells and appropriate immune responses, is an essential process for life and is intertwined with HCMV biology. Much of what we know about hematopoiesis comes from model organisms such as mice, which have been invaluable for elucidating basic functions and the natural responses to viral infection. Yet, significant differences between mice and humans demonstrate that not all functions are comparable between species, between disease states and/or infection, and “normal” hematopoiesis, demonstrating the complexity of these processes. Furthermore, biological differences at the individual level highlight a need to embrace this complexity by implementing personalized medicine. Development of medical digital twins or patient-specific computer models that integrate human physiology, immunology, and real-time data may support new understanding of disease mechanisms and prediction of disease course and outcome and identify the most appropriate treatment [15, 16•, 17, 18]. Digital twins also have the potential to elucidate the complex nature of biological processes including immune system responses to viral infections and the complexity of normal hematopoiesis.

One classic example of the differences between mice and humans is that while we now know the identity of specific stem cell subsets that are required for reconstitution in mice, the basic definition of a human hematopoietic stem cell (HSC) vs hematopoietic progenitor cell (HPC) remains only broadly defined (reviewed in [19]). This is illustrated in the success rate of serial transplants in mice where various HS/HPC subsets can be transplanted from wild-type to immunodeficient mice with full reconstitution ability. However, despite numerous advances since the early transplantation studies of human stem cells into mice (humanized mouse models) in the late 1980s [20–22], human cells still lack full lineage reconstitution. Additionally, a refined population for reconstitution has yet to be defined. Second, species-specific viruses highlight hematopoietic differences. HCMV is a classic example of this, as parallel evolution with the host immune system has made these viruses highly species-specific [23], to the degree that different primate CMVs have distinct mechanisms of viral behavior and cannot cross-infect [24]. Additionally, even differences within a single species, including sex [25], age [26], and environment (i.e., inflammation [27]), can significantly impact stem cells, differentiation, and risk for related malignancies. This demonstrates that while the basic principles of hematopoiesis are conserved, specific differences influence cell fate and function. Finally, immune responses to viral infections are highly specific due to external (e.g., environmental and species) and internal (e.g., age, coinfection, comorbidity) factors. This suggests that HCMV is an ideal case study that when

combined with a method for integrated data analysis (e.g., digital twins) could elucidate the complexities of human hematopoiesis and immune responses.

Medical Digital Twins

The concept of digital twins (DTs) was first described by Michael Grieves in 2002 as a virtual or real space containing an object, with data flowing between the two spaces [28]. This technology involves creating a computer-based simulation of real-world systems, allowing for testing and analysis across various industries, including manufacturing, automotive, and medical devices [29]. In recent years, there has been a growing interest in applying digital twin technology to human health and biology [30, 31]. For instance, in the context of HCMV infection, the physical space would include the host's immune cells, HCMV, and the interactions between them. Data about these interactions are collected through laboratory tests (e.g., viral load, seroconversion), clinical observations (e.g., myelosuppression), patient histories (e.g., comorbidities), and other empirical means (including laboratory-identified mechanisms). The virtual space is a digital model that replicates the human immune response as closely as possible. This model would integrate the data collected from the physical space to create a dynamic and predictive simulation of the immune response to something like HCMV infection. For example, it might simulate how the virus interacts with immune cells, how the immune system responds, how the disease progresses, and how different treatments might affect the outcome. The potential of digital twins lies in their ability to predict immune responses and provide tailored treatments. This concept acknowledges the heterogeneity in disease progression and treatment, thereby improving patient care and healthcare system resilience.

Advancements in digital twins for human organs, diseases, and immune digital twins (IDTs) have led to new drug predictions, methods for clinical analyses and health screening, and personalized treatments. Recent examples of IDTs include a digital twin of the human airway system, which combines fluid dynamics of drugs in aerosols (the delivery platform via an inhaler) with data from cell absorption of the same drugs to enhance drug delivery accuracy [32, 33], and Dassault Systèmes' Living Heart project that utilizes individualized measurements of blood flow, mechanics, and electrical impulses to create a personalized model of each individual's condition to assist in complex heart-related decisions, such as the need for a pacemaker [32, 34]. Similarly, Roy et al. propose a cardiovascular digital twin platform that simulates the effects of exercise on cardiac parameters, providing personalized guidance for patients with cardiac comorbidities [35]. In addition, the artificial pancreas is an exemplary medical digital twin that leverages continuous, real-time data feedback to assist type I diabetic patients in managing their insulin [36]. Combining these examples demonstrates the ability of DT technology to inform targeted treatment interventions.

The Immune System and Digital Twins

IDTs are digital representations or simulations of an individual's immune system. Ongoing efforts for IDT development include outlining opportunities, challenges, and roadmaps [15]. By integrating knowledge of human immunology, physiology, and patient-specific clinical data, IDTs can predict individualized immune responses, enabling targeted treatments. This

approach holds significant promise for improving patient outcomes [15, 16•, 18]. New comprehensive computational models of the immune system at the cellular level can serve as an “IDT blueprint” [37]. IDTs may allow us to understand complex systems, including hematopoiesis and viral regulation of immune responses, especially when complex intra- and inter-cellular interactions govern cell fate, interactions, and disease progression.

The immune system is activated in response to exogenous (infection, injury, or other harmful stimuli) and endogenous (chronic autoimmune and autoinflammatory) insults. HCMV, for example, delivers a series of twin controls of the immune response. During initial or acute infection, active viral replication simultaneously stimulates and suppresses different “arms” of the immune response (reviewed in [12–14, 38]). Latent viral infection modulates the immune response evasion by infection of the “immune-privileged” HPCs [39, 40], regulating immunomodulatory cytokines, including master cellular regulator TGF-β [41], and directly regulating stem cell maintenance and differentiation (reviewed in (9)).

Proper representation of the baseline state when developing a general-purpose IDT is critical. Accurate representation of the resting or surveillance state of the immune system in a digital twin is essential for understanding how the immune system transitions from this baseline state to an active state in response to insults. To do this, the balance between activation and suppression signals and the complex regulatory mechanisms that maintain immune homeostasis must be captured. Due to its complex interactions with the immune system and the diverse immune responses it elicits, HCMV can serve as a valuable perturbation system for IDTs to address some of the challenges associated with modeling immune system dynamics. This controlled perturbation, with an evolutionarily specific virus, could accurately capture the delicate interplay between activation and suppression signals and sophisticated regulatory mechanisms that ensure immune homeostasis to provide a more comprehensive understanding of the immune system’s functioning.

Viral Latency and the Immune System

HCMV latency is characterized by a distinct viral and cellular control, including the lack of virus particle production, a not yet fully defined replication program, and unique cellular responses [1]. Latent virus is commonly accepted to be maintained in $CD34^+$ HPCs, while $CD14^+$ monocytes support persistence and dissemination, and mature monocytic lineage cells (macrophages and dendritic cells (DCs)) support reactivation [1, 8•, 9]. Latency establishment in HPCs provides a unique and immune-privileged location for avoiding the host immune response. Yet, despite direct avoidance by the virus, the immune system is still highly involved in viral regulation.

Following vaccination or acute viral infection [42], including initial infection from other chronic latency-establishing infections (e.g., HIV or EBV [43]), naïve $CD8^+$ T cells can be activated and exhibit rapid expansion and differentiation into effector T cells. These effector T cells can target infected cells and eliminate the virus [43, 44], although these responses can vary between initial and persistent infection and/or asymptomatic, latent, or reactivated conditions (reviewed in [45–47]). After clearance of the initial viral infection, a subset of T cells further differentiate into long-lasting effector memory cells ($CD8^+$ T_{em}), which provide

long-term protection from subsequent infections or adaptive immunity [48, 49]. Continuous exposure to antigens can result in decreased number and functionality of T cells, also known as exhausted T cells (43). The pattern of T cell differentiation is controlled by a host of metabolic, epigenetic, and transcription factors which can lead to diverse immunological responses.

HCMV is unique in these responses as well. Similar to other viral infections, early studies demonstrated that the transfer of HCMV-specific $CD4^+$ and $CD8^+$ T cells to transplant patients are key to controlling the HCMV infection [50, 51]. Sylwester et al. found that HCMV-specific T cells dominate both the CD4 and CD8 T cell memory compartments [52••]. These responses included recognition of a wide range of HCMV antigens and were more common than any other pathogen response tested to date, including up to 10% of the total memory T cell compartment as an individual ages [52••]. However, these broadly reactive T cells can vary with donor, age, and clinical codependences. In HCMV seropositive donors, Jackson et al. observed that some donors had a more diverse $CD4^+$ T cell repertoire response to HCMV, while others had a more focused response [53••]. In contrast to exhaustion and decline over time with most viruses, HCMV-specific T cells in healthy individuals undergo a significant expansion of $CD4^+$ and $CD8^+$ T cells as an individual ages [52••]. Although HCMV, like other chronic infections, specifically manipulates subsets of T cells in distinct ways including controlled differentiation and/or expansion [54–56], HCMV has unique immune manipulation properties that make it an ideal case study for understanding the complexity of these processes.

In HCMV, this diversity in T cell responses could be, in part, due to periodic episodes of subclinical reactivation, perhaps stimulated by the interplay between infected myeloid lineage cells and other cells in the immune system. For $CD8^+$ T_{em} cells to continue expanding, the occasional presentation of antigen must occur which implicates the delicate balance between reactivation and latency [57]. Furthermore, the ability of $CD8^+$ T_{em} to resist exhaustion suggests the regulation of gene expression patterns by CMV. Hertoghs et al. performed a longitudinal transcriptome profiling study in which they identified that $CD8^+$ effector T cells exhibited different gene expression patterns in acute and chronic phases of HCMV [58]. These differences, in conjunction with the maintenance of an exhaustion-resistant $CD8^+$ T_{em} cell pool, hint at the epigenetic modifications involved in T cell differentiation and exhaustion [59]. Optimizing our understanding and control of this expansion either through the use of humanized mice that can model HCMV immune responses [60] or support CD8 engraftment and model this specific expansion [61] combined with digital twin predictions can focus and clarify complex biological outcomes prior to human studies (Fig. 1).

Epigenetics in Immune Regulation and HCMV Latency

Epigenetic regulation refers to the modification of a phenotype without changing the DNA. These dynamic, inheritable modifications (e.g., methylation, acetylation, chromatin remodeling) regulate gene expression and thus can impact viral replication [62], nutrition status [63], and cancer progression [64]. Because epigenetic modifications can be influenced by a variety of factors, everyone may have their own unique epigenetic “signature”

which further complicates diagnosis and disease management strategies. The contribution of epigenetic signatures is shown in breast and lung cancers, where chromosomal rearrangements or mutations can impact patient response to anti-cancer drugs [65]. Despite the importance of the epigenome, relatively few attempts have been made to integrate this data into digital twins. In addition to the transcriptomic, cellular, and organ layers, Barbiero et al. propose the addition of an exposomic layer to capture the totality of an individual's environmental exposure, serving as a proxy for epigenetic information [66]. This layer includes four types of exposure, namely dietary habits, physical activity, therapeutic treatment, and viral infections. Incorporating environmental exposures into the exposomic layer can increase the accuracy and comprehensiveness of DT predictions and thus improve patient health. As DT technology moves forward, the integration of epigenetic information must be prioritized to improve personalized treatments and diagnoses, especially in the context of HCMV and immunoregulation. Despite the robust immune response and memory inflation, the persistence of HCMV may be, in part, attributed to epigenetic regulation. Epigenetic information has the potential to be predictive for disease risk [67] and combining this information with data on HCMV regulation of these cellular pathways could predict which individuals are susceptible to reactivation following transplant or those at risk of immune dysregulation due to HCMV infection, for example, leading to preventative treatment or risk management.

During infection, viral genomes are often associated with histones where epigenetic modifications play a key role in regulating latency and reactivation [62]. Recent studies have shown that the epigenome plays a crucial role in development of hematopoietic cells and regulation of the viral life cycle of HCMV (reviewed by (9)). Specifically, the maintenance of viral latency may suggest an exploitation of the hosts' epigenetic regulation to control viral gene expression, including activation of genes that prevent detection by the immune system and suppression of viral replication genes to establish latency. A proteomics study of HCMV-infected cells observed increased levels of histone proteins using a glioblastoma fibroblast model of latency [68]. Furthermore, models of murine CMV infection have demonstrated decreased RNA polymerase activity but increased histone abundance and repressive methylation during latency [69]. The viral genome is also heavily methylated, likely contributing to viral gene suppression during latency. Recent work by Groves et al. demonstrates that treatment of latently infected cells with inhibitors to acetylation and histone control proteins results in reactivation of HCMV and induction of T cell-mediated killing of infected cells [70]. Additionally, suppression of histone demethylases in a myeloid cell model suppresses viral replication [71]. Importantly, while epigenetic changes and histone modification can control immune responses [72, 73], especially in the context of viral infection [74, 75], changes in these responses can also be modified by immune responses [76, 77]. For example, HCMV-specific $CD8^+$ T cells induce changes in the histone [58] which can control viral reactivation or latency.

While T cell responses to viral infections exhibit a common pattern following classic principles of adaptive immunology, the type, strength, and effectiveness of this response can vary due to the epigenetic regulation and extent to which the virus hijacks epigenetic processes. The impact of epigenetic modifications on the immune response has only begun to be appreciated. In innate immunity, epigenetic regulation has been demonstrated to

tailor the transcriptional program of progenitor, naïve immune cells (to establish cellular phenotype), and damage-associated molecular patterns to the appropriate immune response required for different pathogens [73]. Prediction of immune regulation in response to stimuli (whether pathogens, including HCMV, or drugs, or environmental conditions) in conjunction with genetic background differences and overlaying known modulators of cellular regulation would streamline drug development and allow prediction of responses to novel treatments.

During T cell development, epigenetic modifications contribute to lineage-specific gene expression programs, including differentiation of T cell subsets (e.g., Th1 vs Th2 [78], Th17, and $CD8^+$ T cells [79]). Changes in DNA methylation also influence T cell activation and differentiation through control of transcription factor and cytokine expression and in response to antigenic stimulation (recently reviewed by [80–82]). Additionally, changes in DNA methylation and histone modification can, in turn, lead to cytokine and chemokine expression changes and functional outcomes, including the establishment of T cell memory and exhausted phenotypes [83]. Understanding the interplay between these factors, particularly the relationship between stemness and exhaustion in T cells [84] and immunosenescence [85], is key to understanding HCMV biology [56] and how HCMV manipulates the global immune environment.

Modeling Cell−Specific Responses

Using mathematical and computational techniques to simulate T cell behavior, the researchers can elucidate the molecular mechanisms that govern T cell function, predict the outcome of T cell activation, and optimize the design of immunotherapies [86••, 87–89]. The cross talk between T cells and dendritic cells (DCs) plays a pivotal role in the immune system responses since DCs act as surveillance cells that can be influenced by invading pathogens like HCMV [90]. Computational models of human DC-T cell communication enable researchers to perform in silico experiments for DC-derived signals and T cell responses [86••, 91, 92]. For example, Aghamiri et al. developed a model of human DCs that cover molecular interactions and cell-to-cell communication [86••]. This multicellular mechanistic logical model [93] accounts for interactions between DCs and their environment, signals transduction leading to cytokines/chemokines, and growth factor and integrates DC communication with other immune cells including T cells through direct and indirect interactions. It can be applied to study various aspects of DCs, including maturation, differentiation, and function as APCs and their interactions with other immune cells, aiding the study of diseases and the basic mechanisms of DC function. Specifically, myeloid lineage DCs are sites of HCMV reactivation. Virus in these cells is critically linked to differentiation-dependent chromatic remodeling [94], and combining this biological data with an IDT such as developed for DCs [86••] would represent a platform of understanding HCMV reactivation in a specific cell type. Future studies combining the complexity of HCMV reactivation in multiple cell types with a complete IDT is one example of how modeling these interactions in multiple ways would elucidate key biological functions.

In another example, Puniya et al. created a computational model of the signal transduction pathway that controls $CD4^+$ T cell differentiation [88]. The authors analyzed the model under 511 different environmental conditions and found that it can predict classical and

novel mixed T cell phenotypes. These analyses suggest that the extracellular environment's composition and dosage of signals determine the lineage decision. This study identified the specific patterns of extracellular environments that result in novel T cell phenotypes, predicted the inputs that can regulate the transition between canonical and complex T cell phenotypes, and identified the optimal input levels that can maximize the activity of multiple lineage-specifying transcription factors. The authors offer insights into the plasticity of $CD4^+$ T cell differentiation and provide a tool to test hypotheses about generating complex T cell phenotypes using various input combinations and dosages. Puniya et al. also developed genome-scale models [95] for different subtypes of $CD4^+$ T cells, including naïve, Th1, Th2, and Th17 cells to investigate metabolic changes in autoimmune disease such as rheumatoid arthritis, multiple sclerosis, and primary biliary cholangitis [96]. Through in silico simulations, the authors analyzed the responses of these models to FDA-approved drugs and compounds, identifying 68 potential drug targets. By integrating disease-specific gene expression and metabolic perturbations, this study validated the efficacy of 50% of these targets in suppressing $CD4^+$ T cells suggesting their potential as therapeutic interventions. This approach can be applied to other diseases and these metabolic models offer further insights into $CD4^+$ T cell metabolism.

To understand CD4 + T cell responses to infection, Wertheim et al. developed a multiscale-approach framework [97], which integrated the modeling processes at three different spatial scales in various tissues using four modeling approaches [87]. This model is beneficial because it leverages four different computational properties (utilizing a logical model to describe signal transduction and gene regulation within each cell, constraint-based models to describe metabolism, an agent-based model to capture cell population dynamics, and ordinary differential equations are used to describe systemic cytokine concentrations), with three different spatial scales (to control of changes in, for example, cytokine concentration over time) and data from multiple tissues (infection site, lymphoid tissue, and circulatory system). This multifactorial approach was a significant improvement over individual small-scale models, was validated against known experimental results (including T cell differentiation data), and can be a powerful predictor of the dynamics of T cell function.

Overall, the application of mathematical and computational models has significantly advanced our understanding of cellular interactions, T cell function, and immune system behavior, offering valuable insights into the molecular mechanisms, predictive capabilities, drug target design, and optimization of immunotherapies for complex diseases. This approach provides a powerful means of gaining insights into the complex behavior of HCMV infection, particularly the immune responses governing disease protection, the control of latency and reactivation, and how inter- and intra-cellular communication influence and are influenced by both the host and viral factors.

Using CMV–Specific Immune Responses as a Digital Twin "Stress Test"

The models described above have great potential to be expanded to model the immune response and evasion mechanisms during HCMV infection. A few examples/scenarios are described below:

1. Diverse immune responses: HCMV infection triggers a wide range of immune responses involving both the innate and adaptive immune systems. By studying the immune system's response to HCMV, researchers can gain insights into the complex interplay between various immune cell types, cytokines, and signaling pathways, helping to improve the accuracy and predictive power of immune digital twins.
2. Immune evasion strategies: HCMV has evolved numerous strategies to evade and manipulate the host immune system, including modulating the expression of major histocompatibility complex (MHC) molecules, interfering with cytokine signaling, and impairing immune cell function. Investigating these immune evasion mechanisms in the context of an immune digital twin can provide valuable insights into the regulatory mechanisms that govern immune system function and help to identify potential therapeutic targets for enhancing immune responses.
3. Immune system perturbation: As an insult to the immune system, HCMV infection can help researchers understand how the immune system transitions from a resting or surveillance state to an active state. Studying the immune response to HCMV can provide information on the dynamic changes in immune cell activation, recruitment, and function during infection, which can be used to improve the representation of immune system dynamics in digital twins.

In short, HCMV with its highly human-specific responses can serve as a model calibration approach, providing highly tuned biologic control of differentiation, immune perturbation, and regulation of key cellular pathways including epigenetic regulation.

Digital Twins for Precise Control of Latency and Prediction of Latent Outcomes

HCMV's ability to establish a latent infection and reactivate provides a unique opportunity to study the immune system's response to chronic and recurring insults. Modeling the immune response to HCMV reactivation in a digital twin can help researchers understand the dynamics of immune memory and tolerance, as well as the factors that influence the transition between latent and active infections.

DT technology also has the potential to improve our understanding of HCMV infection and facilitate the development of novel treatments. The diverse function of HCMV-target cells (e.g., hematopoietic stem cells vs mature DCs) even in their native state, combined with the distinct properties of HCMV (replication, latency establishment, ability to reactivate as seen in different cell types and model systems [98, 99]) at different timepoints are a few of the reasons why, despite its relevance, many aspects of HCMV biology are still unexplored. To create an HCMV DT, we propose repurposing and building upon existing models that incorporate both HCMV and relevant components of the immune system. Joslyn et al. developed a whole-host model for the immune response to *Mycobacterium tuberculosis*, called HostSim, which can track events at different physiological and time scales [100••]. Similarly, Masisona et al. presented a modular design for medical DTs and

applied this approach by creating a model of the innate immune response to the respiratory fungal pathogen *Aspergillus fumigatus* [101]. Although neither study addresses HCMV infection, they demonstrate the potential of DT technology to improve diagnosis, prognosis, and personalized treatment for a variety of medical conditions. An HCMV-specific IDT would combine known biological properties (transcription, translation, metabolism, cell–cell signaling, etc.) of the relevant cell types (including those infected by HCMV during lytic and latent infection and responder immune cells) with what is known about HCMV-mediated cellular changes in these cell types. By integrating this data, gaps in knowledge can be visualized and new hypotheses developed. These studies offer a well-documented approach that can be used as an example for the development of an HCMV DT.

Conclusion: Future Uses for Digital Twins and the Interplay Between Epigenetics, Latency, and Immune Control

Despite highly regulated control of HCMV by the immune system and HCMV's tight regulation of immune responses, the advances in understanding the complex host-virus interactions, and broadly reactive, highly specific, and long-lasting immune responses, more progress has yet to be made to develop an HCMV vaccine either for congenital disease or for transplant conditions. Recent efforts to develop an HCMV vaccine have studied new technologies and utilized live and inactivated approaches, and yet no licensed vaccine is yet available (recently reviewed by [102–104]). Developing a vaccine has been challenging for several reasons, including the unique properties of HCMV itself and the immune responses it induces. For example, targeting a latency-establishing virus or clearing an already-established latent virus [105•] is challenging due to a lack of overt viral protein targets for clearance and the virus encodes multiple immune evasion strategies (discussed above). The location of HCMV infection including establishment of latency in the immune-privileged bone marrow and the unique aspects of fetal infection including the interaction between the maternal–fetal interface [106, 107] also complicate vaccine delivery. In addition, safety concerns of different vaccine platforms (including using live viruses that could establish latency and later reactivate) and the abundance of robust immune responses following natural infection do not result in protection from superinfection, infection with other HCMV strains nor from disease in immunosuppressed individuals. Digital twins are a groundbreaking new area that show promise for elucidating complex mechanisms in an integrated manner by combining data from diverse studies in one cohesive platform. When combined with in vivo models [60, 108, 109], DTs have demonstrated the power of unique CD8 + T cell responses [110] or antibody responses (111, 112) and show promise for development of new vaccines. The accuracy of DT predictions though is highly dependent on the quality and relevance of the data used to create them. HCMV, as an intricate cellular modulator of all major components of biological control, including epigenetics and immune responses, can serve as both a "stress test" for digital twin accuracy and a testing ground for hypothesis generation and clinical application.

The potential of IDT technology is vast and far-reaching. Its applications have the potential to improve current health inefficiencies that create daily impacts for many individuals, increase the effectiveness of interventions, develop new therapeutics in underexplored areas,

and ultimately save lives and reduce the adverse effects of chronic conditions. For chronic viral infections, including HCMV, DT technology has the potential to clarify the dynamics of immune memory and tolerance, as well as the factors influencing the transitions between latency and reactivation. More generally, the intentional integration of this technology into society shows great promise in revolutionizing our approach to individualized and holistic management of health.

Data Availability

All data and information are included in the manuscript.

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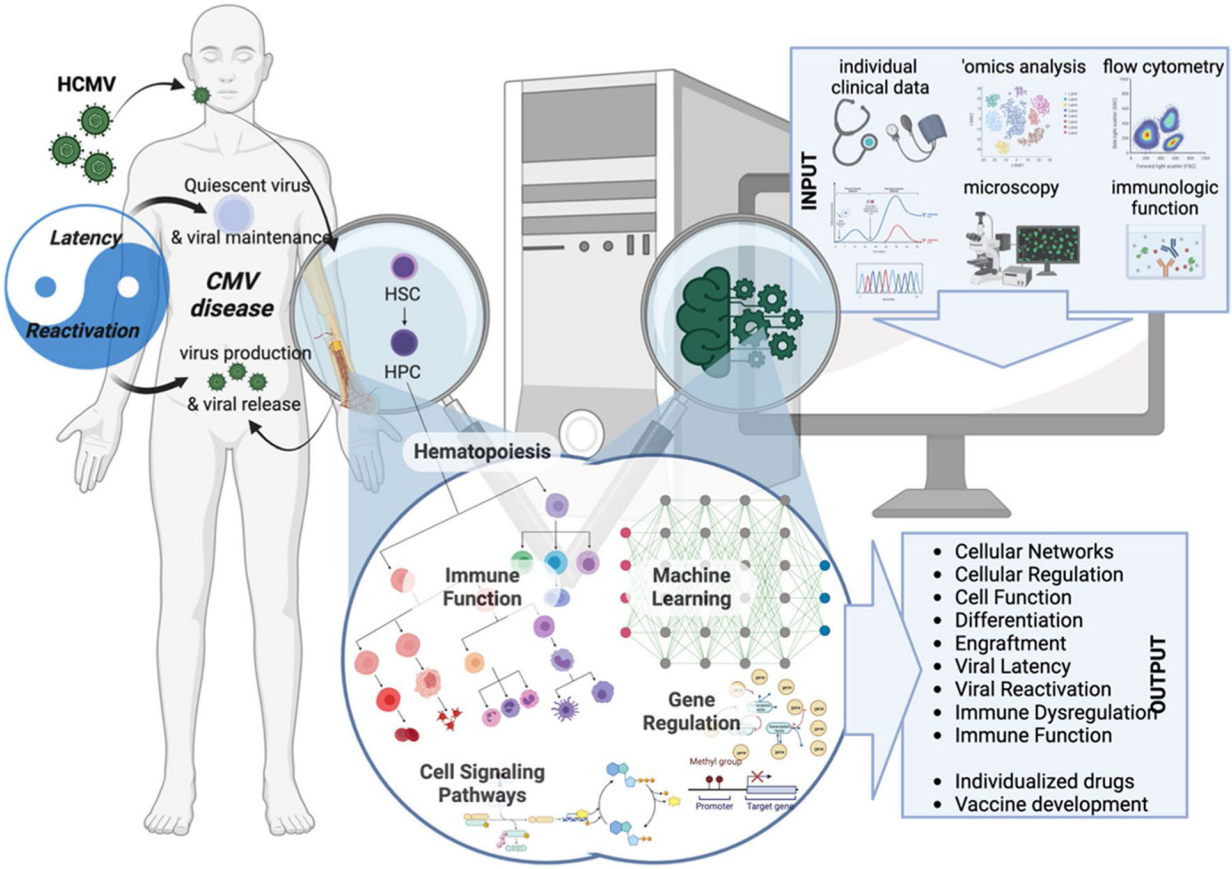

Fig. 1.

HCMV and IDTs. (Left to right) Following primary HCMV infection, the virus establishes latency in hematopoietic stem (HSC) and progenitor (HPC) cells. Latency is lifelong and is interrupted by periodic episodes of reactivation throughout an individual's lifetime. CMV disease occurs simultaneously with immunosuppression and can result from both latent virus and reactivating virus. The regulators of the balance between latency and reactivation and the mechanisms by which disease occurs are still understudied; however, the interplay between the virus and the host (specifically the hematopoietic system, including mature immune cells of the myeloid lineage (key cells for latency and reactivation) and lymphoid lineage (T and B cell-specific immune responses)) is key to understanding these processes. HCMV, like other CMVs, is also highly species-specific and this long-term evolution in parallel with the human hematopoietic systems and immune functions provides a novel platform to study immunology. Immune digital twins (IDTs) are new digital simulations that can incorporate data from numerous sources, including individualized measures of health, disease, immune profiling, and genetics, and can be integrated with laboratory studies using multi-omic (transcriptomic, proteomic, metabolomic, etc.) profiling. IDTs then allow prediction of individualized responses to pathogens, potential treatments and vaccines, and integration of this data in the complex environment of a human immune system. Leveraging the combined power of HCMV's fine-tuned control of these cellular pathways as a model of test and validate IDTs and the new technology of IDTs to predict complex biological

mechanisms to develop new treatments for HCMV has significant potential to change individual treatment of chronic conditions. The figure was created using BioRender