Medical Microbiology and Immunology (2019) 208:259–261
https://doi.org/10.1007/s00430-019-00618-5

EDITORIAL

‘Checks and balances’ in cytomegalovirus-host cohabitation

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Received: 26 April 2019 / Accepted: 5 May 2019 / Published online: 25 May 2019

Species-specific cytomegaloviruses (CMVs) and their corresponding hosts have co-speciated during eons of co-evolution adapting to each other by establishing ‘checks and balances’. Accordingly, CMVs of different host species have acquired different sets of private genes dedicated to moderate intrinsic, innate, and adaptive defense mechanisms of their respective host, and those, in turn, have found counterstrategies to keep their lodger in check. The popular term ‘immune evasion’ of CMVs is clearly an unfortunate misnomer, as immune surveillance of CMV infections prevents viral pathogenesis so that CMV disease is restricted to the immunocompromised or immunologically immature host. The immune response resolves acute infection with no overt symptoms of CMV disease, neither symptoms of viral pathogenesis nor of immunopathogenesis. Lifelong immune surveillance keeps the virus in a non-replicative state referred to as latency. Latency is defined as absence of infectious virus but durable retention of reactivation-competent viral genomes. Productive recurrent infection can be re-initiated by not yet fully defined signals resulting in virus spread and histopathology under conditions of compromised immune control.

It is becoming increasingly clear that latency is not a transcriptionally silent state but is noisy in that silenced viral genes can transiently be desilenced in a stochastic off–on–off fashion [1, 2]. If a transiently desilenced viral gene happens to encode an antigen for T cells, antigen presentation can (re)stimulate cognate T cells. At a given time, latent viral genomes are desilenced at an antigen-expressing gene locus only in a small proportion of latently infected cells. Nonetheless, if the number of latently infected cells is high enough, steady antigen presentation can occur on the whole organ level. The probability for such a gene expression thus increases with increasing numbers of latently infected cells and viral genomes, that is with increasing latent viral genome load. Continuous antigen presentation and consequent permanent (re)stimulation of T cells leads to a steady expansion of the CMV-antigen-specific T cell pool eventually usurping the specificity repertoire, a phenomenon known as ‘memory inflation’ (MI). This subject is covered by a number of reports on the mouse CMV model in this special issue of *MMIM*. As, at least in the mouse model, latently infected cells are non-hematopoietic lineage tissue cells [3] that do not constitutively express MHC class-II molecules, MI in the mouse model is primarily a phenomenon of $CD8^+$ T cells that recognize antigenic peptides presented by the constitutively expressed MHC class-I molecules. It has been proposed previously that an extensive allocation of the immune response to CMV, a single and, moreover, a not very harmful pathogen, can weaken the host’s capacity to respond to more harmful pathogens. This may also explain vaccination failures, in particularly in the elderly in whom thymic involution limits the refreshment of the specificity repertoire with newly generated naïve T cells. This phenomenon is referred to as CMV-associated ‘immunosenescence’ in an indirect sense, not to be mixed up with cellular senescence, as inflationary CMV-specific T cells continue to divide on the population level and are not exhausted but are functional T effector cells.

This special issue of *MMIM* covers many aspects of how CMVs imprint the host’s immune system during lifelong CMV-host cohabitation. What I have learned by editing the contributions is that CMV science appears to be a science of misnomers: (1) ‘immune evasion’ is a misnomer, because CMVs do not evade an intact immune system; (2) ‘memory inflation’ is a misnomer, because the expanding T cell pool consists of functional effector cells, and (3) ‘immunosenescence’ is a misnomer, because the typical characteristics of cellular senescence do not apply.

I cannot highlight here all the outstanding contributions, but, in editor’s view, most challenging for all ‘mouse

This editorial is part of the Special Issue on Immunological Imprinting during Chronic Viral Infection.

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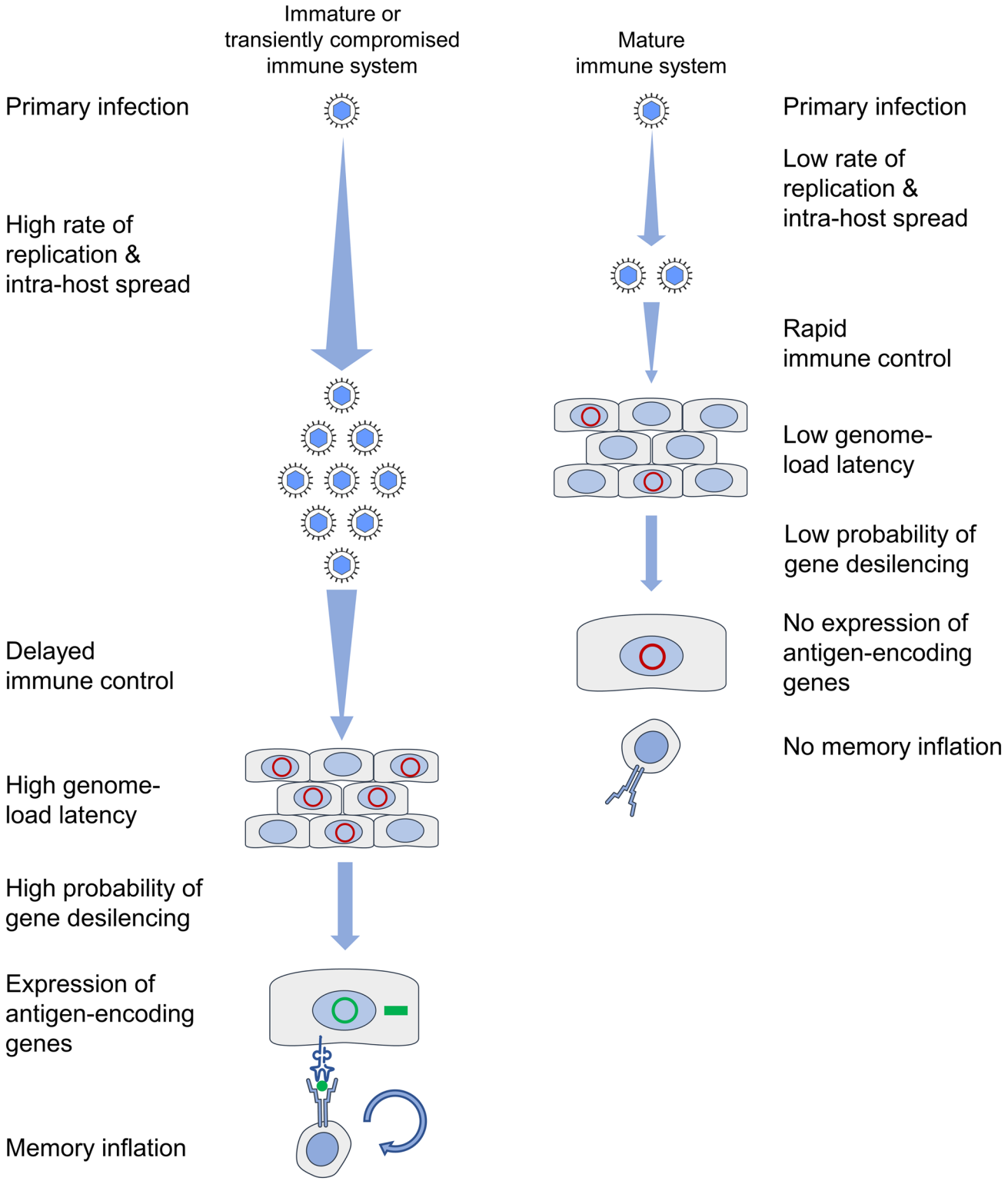

Fig. 1 Model relating the extent of virus replication and spread during primary infection to latent viral genome load and MI-driving antigen presentation during latent infection. Red circles: latent viral genomes silenced at an antigen-encoding gene. Green circle: latent viral genome desilenced at an antigen-encoding gene. Green bar: antigen-encoding transcript expressed in latency

modelers' is the contribution by Jackson and colleagues [4] who conclude "that there is only limited evidence supportive of memory inflation occurring in humans", a conclusion that contradicts the generalized statement found in almost all papers on MI in animal models, namely that "MI is a hallmark of CMV infections". In accordance with missing MI in most human CMV-seropositive but otherwise healthy volunteers, previous protagonists of CMV-associated immunosenescence appear to back away from a relevance in humans [5] and a systematic review and meta-analysis in influenza vaccinees by van den Berg and colleagues [6] arrives at the conclusion "that there is no unequivocal evidence that latent CMV infection affects the influenza antibody response to vaccination".

This brings me to the decades-lasting conflict between clinical CMV research and CMV research in animal models. Co-authored by Lemmermann [7], I have recently discussed the importance of appropriate mouse model design for matching a clinical correlate and have reviewed examples where the 'test of time' showed that 'lies of mice' eventually turned out to have correctly predicted much later results of clinical science and, so, became 'truths of mice'. Animal models of MI choose experimental conditions of infection that elicit MI, whereas such conditions are not necessarily met, and actually appear to be rarely met, in natural infection of humans, for whom time, dose, and route of infection are unknown parameters. The paper by Adler and Reddehase [8], proposing a pediatric root of virus recurrence incidences as well as of MI, offers an explanation harmonizing mouse and human findings. Perinatal primary infection, or even more so congenital infection, will allow for extensive and prolonged virus replication and intra-host spread to all target organs of CMV infection, which eventually result in a high number of latently infected tissue cells, and, accordingly, in a high overall load of latent virus genomes. A high copy number of latent virus genomes entails a high probability that at least some of them are desilenced at genes that code for antigenic peptides that can drive MI. In contrast, primary infection later in life, when the immune system is more mature, is rapidly controlled, resulting in a low overall load of latent virus genomes entailing a lower incidence of antigen-encoding viral gene expression, insufficient for driving MI (Fig. 1).

So, not knowing the time of primary infection in CMV-seropositive volunteers enrolled for clinical studies, immunological data would have to be stratified by latent viral genome load to verify MI in humans, and consequences of MI-associated immunosenescence, such as vaccination failures, can logically be expected only for those vaccinees who actually undergo MI at the time of vaccination. Obviously, this applies only to a minority of vaccinees, as otherwise, based on the high population prevalence of human CMV, billions of people worldwide would show MI.

It is the editor's view that the concepts on CMV-associated MI and immunosenescence, developed in the mouse model, are not yet buried for humans but likely apply only to the group of individuals infected very early in life when the immune system was still immature as well as of individuals who were immunocompromised at the time of primary infection.

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