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Editorial overview – Cell dysfunction and exhaustion in HIV infection

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Since the initial descriptions of CD4 T cell depletion as a critical factor associated with progression to AIDS, our understanding of immune dysfunction in HIV infection has dramatically evolved. Over the past decade in particular, technical progress and conceptual advances have allowed the exploration of a wide array of qualitative and functional changes that occur in multiple cell types and several compartments of the body. The realization that chronic immune activation is a major driving force in disease progression and associated with clinical complications even in patients on antiretroviral therapy has fostered progress in clarifying the complex interplay between the virus and the infected host. Unfortunately, whereas improvement in antiretroviral therapy has been dramatic since the mid 90s, the better understanding of immune impairment has yet to result in therapeutic interventions that efficiently complement ART or improve the efficacy of HIV vaccine candidates. However, recent progress in other fields of medicine gives reasons for optimism. In particular, new immunotherapies have shown dramatic results in treatment of several autoimmune diseases and previously refractory types of cancer, with in many cases very good tolerance by the patients. The efficacy of these clinical interventions suggests that in the field of chronic infectious diseases – in particular HIV – the knowledge gained in animal models and human studies will translate into better patient care and preventive strategies.

In this issue, a series of reviews cover new progress in the understanding of immune cell dysfunction in HIV infection. Several themes are also addressed in the perspective of studies of other chronic viral infections in humans, non-human primates or mice. The importance of both cell-extrinsic factors provided by the altered microenvironment of HIV infection and cell-intrinsic factors, including genetic exhaustion programs, is addressed. These articles

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provide an overview of mechanisms that affect function of both the innate and adaptive immunity.

The critical importance of inhibitory co-receptors in the functional impairment of T cells in chronic infection has been well demonstrated over recent years. Kuchroo et al (this issue) review recent findings on their role in CD8 T cell exhaustion and discuss their interplay. However, recent data show that CD4 T cell dysfunction is not a copycat of T cell impairment and is in part governed by distinct mechanisms. Morou et al (this issue) underline the importance of CD4 T cell plasticity in infectious diseases, and the contributing roles of both skewing of CD4 T cell differentiation and exhaustion mechanisms. Seddiki and Draenert (this issue) describe recent advances on suppressor cells and the availability of new markers and functional assays to investigate regulatory T cells, regulatory B cells and myeloid-derived suppressor cells.

A critical component of T cell dysfunction resides in a complex network of transcription factors, discussed by Collins and Henderson (this issue). Major progress has been made recently in the understanding of the role of non-coding microRNA in regulating cell function in both physiologic and pathological conditions. Swaminathan and Kelleher (this issue) discuss miRNAs as potential new important players in the T cell dysfunction observed with HIV-1 infection and their potential as therapeutic targets.

The B cell compartment is affected in HIV infection as well. Moir and Fauci (this issue) review the role played by immune activation in B cell exhaustion, and compare it to T cell exhaustion and B cell alterations in other diseases. Antigen-presenting cells are profoundly altered in HIV infection, and Piguet et al (this issue) review the adverse effects of chronic hyperactivation of this critical population. It is only in the early 2000s that T follicular helper cells have been identified as a critical population for B cell help. Tremendous progress has been made in this area since. Cubas and Perreau (this issue) report on recent findings addressing the role of Tfh cells in HIV infection as well as the impact HIV infection has on germinal center Tfh and circulating memory Tfh (cTfh) cell frequency and function. The precise links between these populations still need to be fully defined, and studies in animal models are particularly informative in this regard. In line with this, McGary et al (this issue) describe the most recent advances in the use of animal models for the study of cell exhaustion following HIV/SIV infection, and their critical role on the path to possible new immunotherapeutic approaches. Finally, Mudd and Lederman (this issue) describe the adverse effects of the expansion of the CD8 compartment in HIV infection that is associated with adverse clinical events, even in ART-treated individuals.

Our understanding of the complexity of immune cell dysfunction – here defined as exhaustion in a broad sense – has expanded dramatically in recent years. There are reasons to be optimistic and to hope that the time is near when this knowledge will be translated into new therapeutic approaches to complement ART and into better patient care.