



Conference report

Mechanisms behind TB, HBV, and HIV chronic infections

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ABSTRACT

Immune evasion is critical for pathogens to maintain their presence within hosts, giving rise to chronic infections. Here, we examine the immune evasion strategies employed by three pathogens with high medical burden, namely, tuberculosis, HIV and HBV. Establishment of chronic infection by these pathogens is a multi-step process that involves an interplay between restriction factor, innate immunity and adaptive immunity. Engagement of these host defences is intimately linked with specific steps within the pathogen replication cycles. Critical host factors are increasingly recognized to regulate immune evasion and susceptibility to disease. Fuelled by innovative technology development, the understanding of these mechanisms provides critical knowledge for rational design of vaccines and therapeutic immune strategies.

1. Introduction

When a pathogenic microorganism infects the human body, a dramatic activation of the innate and adaptive immune response occurs. In most cases, the interaction between the immune system and the pathogen results in clearance of the infection. However, some pathogens are capable of maintaining their presence, giving rise to persistent infection.

To survive in its host, pathogens have evolved a range of elaborate immune-evasion strategies, which may involve (1) passive hiding from the immune system (Favoreel et al., 2000; Agosto et al., 2015), (2) active interfering with the function of the immune system (Gilden et al., 2011; Natali et al., 1984) and/or (3) exploiting the immune system for their own benefits (Imran et al., 2016; Rensing et al., 2015; Hmama et al., 2015a, 2015b, 2015c; Wu et al., 2000).

To examine immune-evasion strategies employed by three pathogens with a very high medical burden, namely, tuberculosis, HIV and HBV, the Fondation Mérieux organized a conference from May 2–4, 2016 (“Les Pensières” Conference Centre, Annecy-France). The purpose of this workshop was to discuss how these pathogens employ evasion mechanisms, and how to translate this knowledge to the development and rational design of new medicines and therapeutic vaccines.

2. Hepatitis B virus

Despite the existence of a vaccine and the demonstration of its long-term efficacy (Poovorawan et al., 2009), 250 million people are chronically infected with HBV (Schweitzer et al., 2015). Overall, 5–10% of immune competent adults exposed to the virus will develop a chronic infection and subsequent type-B hepatitis (Ott et al., 2012). The current treatment of HBV infection, based on interferon alpha (IFN- α) and nucleotides analogues (NUC), suppress HBV replication, but are not curative (Zhang et al., 2016; Wong et al., 2013; Dandri and Locarnini, 2012; Werle-Lapostolle et al., 2004).

The natural history of chronic HBV infection is a complex, dynamic and continuum process during which the interplay between infected liver and immune responses change from apparent tolerance to very active immune-inflammatory phases (Boni et al., 2012). Mirroring this is the release of hepatocyte-death-associated liver enzymes (ALT/ASAT), which can vary from normal to very high levels in the blood of the patients. If both a strong and wide HBV-specific CD8 (+) T cell response (Bertoletti and Ferrari, 2016), together with the action of NK/NKT cells (Hoh et al., 2015) play an important role in the clearance of the virus during an acute event, a non-specific response of the killer cells in the context of chronic infections is responsible for immune driven pathogenesis (Shin et al., 2016). HBV actively impairs the immune response in chronically infected patients, resulting either in “a pathogen-specific and liver-located immune tolerance” or inadequate virus-specific T cell response (Shin et al., 2016; Han et al., 2013; Bertoletti and Ferrari, 2012). Therefore a profound understanding of the interplay between HBV and immune responses is compulsory to develop immune-therapeutic strategies aiming at a better long-term control of the virus, thus defining a *functional cure*.

HBV infection establishment is a multistep process (Dandri and Locarnini, 2012; Yan et al., 2012; Schulze et al., 2007; Macovei et al., 2010; Blondot et al., 2016; Urban et al., 2014) that depends on complex interactions with specific host factors (Blondot et al., 2016). The recent discovery of this bona fide HBV entry receptor has opened new avenues for the development of in vitro and in vivo model to better study viral persistence related to intrinsic HBV biology and immune evasion.

Covalently closed circular DNA (cccDNA) is the key molecule of the HBV lifecycle, which serves as the template for the transcription of viral RNAs and permits the persistence of infection (Levrero et al., 2009). Its activity is regulated by various liver-enriched transcription factors and by the histone acetylation status (Zhang et al., 2013).

cccDNA formation is a black box and new knowledge is required to uncover mechanisms of its formation (Cui et al., 2015; Königer et al., 2014). Targeting cccDNA requires the development of small molecules or immune stimulators that could either block its formation, transcription or lead to its chemically-driven destruction (Nassal, 2015; Cai et al., 2012; Xia et al., 2016; Kennedy et al., 2015a; Kennedy et al., 2015b; Seeger and Sohn, 2014; Shlomai and Rice, 2014; Lutgehetmann et al., 2010; Allweiss et al., 2014; Lucifora et al., 2014; Belloni et al., 2012). In this respect, immune stimulators such as lymphotoxin beta (Lucifora et al., 2014), IL-1b and IL-6 (Palumbo et al., 2015) have been shown to induce the silencing or degradation of cccDNA in vitro, and a strategy aiming at restoring the local expression of those cytokines could lead to a repressive effect on HBV replication in vivo.

Viral HBx is a regulatory protein required for full cccDNA transcriptional and viral replication (Lucifora et al., 2011; Belloni et al., 2009). HBx prevents recruitment of negative regulators on cccDNA (Decorsière et al., 2016; Rivière et al., 2015) and contributes to hepato-carcinogenesis (Levrero and Zucman-Rossi, 2016). In the absence of HBx, HBV transcription was repressed and cccDNA was silenced through the establishment of repressed chromatin (Rivière et al., 2015). Conversely, HBx expression is able to relieve this repression (Rivière et al., 2015). HBx could therefore be an attractive target for HBV cure but the difficult task is that HBx has no enzymatic activity.

HBV core protein (HBc), is also a main component of the HBV cccDNA proteome. HBc binds to cccDNA early post infection and would promote an epigenetic permissive state (Guo et al., 2011). The removal of HBc from cccDNA by the use of specific HBc inhibitors is expected to impact on the biology of cccDNA, although this remains to be fully demonstrated. NVR 3-778 is the first potential HBV core inhibitor being tested in a phase 1b clinical trial (NVR3-778-101 Protocol, Clinicaltrials.org # NCT02112799).

Beside innate and adaptive immune response, a line of antiviral resistance can be exerted by pre-existing host cellular factors present in the cell. Spindlin1, a cellular Tudor-domain protein, has been recently identified as a new HBx interacting protein that is recruited on the cccDNA and represses its transcription in the setting of HBV infection (Ducroux et al., 2014). Spindlin1 represses more severely HBx deficient virus than wild type virus, suggesting that HBx encounters Spindlin1 activity on HBV. The “structural maintenance of chromosomes” (Smc) complex Smc5/6 has also been recently identified as a new HBV restriction (Decorsière et al., 2016). HBx counteracts the repressive activity of Smc5/6 complex and relieves the inhibition to allow productive HBV gene expression (Decorsière et al., 2016). These results suggest that HBV cccDNA transcription is silenced by cellular antiviral responses that can be counteracted by HBx. In this respect, molecules targeting HBx itself leading to degradation or HBx functions are expected to impact on HBV replication by enabling restoration of intrinsic host restriction factors.

Besides persisting in hepatocytes, HBV has also evolved strategies to evade both innate and adaptive immunities (Wieland et al., 2005; Wieland et al., 2004). HBV uses its viral proteins, included into virions (HBc protein) or trapped inside infected cells (Luangsay et al., 2015; Gruffaz et al., 2013; Lang et al., 2011; Jiang and Tang, 2010). HBV polymerase would be able to both block DNA sensing by targeting STING adaptor (Liu et al., 2015) and IRF3 mediated response through targeting DDX3 (Wang and Ryu, 2010). HBc would be capable to block dsRNA-mediated IFN response by acting as a negative epiregulator protein on IFN genes and some ISGs (Gruffaz et al., 2013). Secreted antigens HBsAg would be able to inhibit some innate cell functions (Zannetti et al., 2016; Martinet et al., 2012; Shi et al., 2012; Xu et al., 2012; Woltman et al., 2011).

Human myeloid-derived suppressor cells (MDSC) have been postulated as suppressors of T cell-mediated immunopathology (Pallett et al., 2015). In persistent infection, granulocytes MDSC (gMDSCs) expand in patients replicating HBV without immunopathology and decline before the onset of hepatic flares (Pallett et al., 2015).

Also, the NK cell function appears to be impaired during chronic infection and most of the available studies indicate depressed cytokine production (IFN- γ and TNF- α) with preserved cytotoxic activity (Boni et al., 2015; Peppia et al., 2010). Whether NK-cell response can participate in regulating T-cell response by killing effector T-cell has not been defined, even though recent results suggest the existence of an interplay between NK and T cells and a reciprocal behaviour of these cell responses in nucleotides analogues (NUC)-treated patients (Boni et al., 2015).

The adaptive response is also thought to be deficient during chronic HBV infection (Tang et al., 2016; Guidotti et al., 2015). The main mechanisms explaining persistent viral escape are related to quantitative and functional impairment of HBV-specific T-cell functions (Bertoletti and Ferrari, 2016). A better understanding of the hierarchical importance of each component responsible for inhibitory phenotype is compulsory to develop immunotherapeutic strategies to restore immune control of HBV replication. Following the blooming of use of checkpoint inhibitors (e.g. antibodies targeting PD1, PDL1, CTLA4, etc.) in oncology, the repositioning of these strategies to persistent viral infection could be envisaged. Moreover the development of therapeutic vaccine and immune stimulators (e.g. TLR7 agonist), should also complement the strategy consisting in removal of immune checkpoints.

3. Human immunodeficiency virus 1

HIV-1 infection is established from a single HIV-1 variant termed “the founder virus” (Joseph et al., 2015).

The HIV-1 replication cycle presents multiple target points for antiviral therapy but none of the approved therapies target the integrated provirus and HIV-1 reservoirs (Mouquet, 2014). Furthermore, there is an extensive inter-individual variability in response to HIV and escape mutants are observed very quickly after infection (Henn et al., 2012). Insufficient control of infection leads to exhaustion of the immune response and damage of lymphoid structures (Kök et al., 2015; Freeman et al., 2006; Estes et al., 2008).

The main HIV-1 reservoirs include productively infected CD4 + T lymphocytes, and latently infected resting CD4 + T cells. Long-lived macrophages and myeloid cells, dendritic cells (DCs) and follicular dendritic cells may also be part of the reservoir (Kandathil et al., 2016). Persistence of viral reservoirs to cART could be explained by the inability of the therapy to completely block viral replication (Shen and Siliciano, 2008). The ability for the virus to replicate in several organs even in the presence of ART plays also a role in maintaining HIV reservoirs (Santangelo et al., 2015). Germinal centers also represent a niche for HIV to hide in HIV controllers i.e. individuals who spontaneously control HIV in the absence of ART.

Formation of HIV-1 reservoir is a multifaceted process that takes place only few days after infection (Whitney et al., 2014; Haase, 2010) and is a function of the balance between restriction and dependency host factors (Brass et al., 2008). Establishment of viral reservoirs is concomitant to the development of immune response during the acute phase of HIV-1 infection (McMichael et al., 2010a, 2010b).

HIV-1 infected macrophages are also involved from the onset of the infection to pathogenesis. They retain infectious pathogens in their endosomal compartment and represent a crucial viral reservoir upon arrest of cART (Gaudin et al., 2013a; Jouve et al., 2007). Upon HIV-1 infection, the group specific antigen Gag is synthesized and recruited to preexisting CD36 + compartments in macrophages where it replicates (Gaudin et al., 2013b). It was recently demonstrated that macrophage sensing of HIV-1 entry triggers an early induction of IFN-stimulated genes (ISG) observable from 8 h post-infection that is independent of the retrotranscriptase (RT) activity (Decalf et al., 2017), which is in agreement with other experimental models of HIV sensing in macrophages (Lahaye and Manel, 2015a, 2015b). These results shed light on a new step of HIV-1 sensing by macrophages

that may confer an early protection through type-I IFN signaling.

Viral rebound can occur after cART secession (Davey et al., 1999) due to silent HIV-1 proviruses residing in a subset of memory resting CD4 + T cells (Siliciano and Greene, 2011), making this reservoir of silent HIV-1 proviruses a major barrier to HIV-1 infection cure. A forward genetic screen in haploid cells was performed in order to identify novel regulators required for gene silencing (Tchasovnikarova et al., 2015). The screen identified four genes, three of which together constitute a novel human epigenetic repressor complex named HUSH (Human Silencing Hub). Loss of HUSH components resulted in decreased H3K9me3 at endogenous genomic loci and altered transcription, as well as de-repression of retroviruses integrated into heterochromatin. Therefore HUSH mediates epigenetic repression through the recruitment of the SETDB1 histone methyltransferase which deposits the repressive methylation mark.

Innate immunity, i.e. antiviral activity of NK cells and production of type I IFN by dendritic cells (DCs), constitutes the first barrier of defence against HIV-1 infection (Altfeld et al., 2011; McMichael et al., 2010a, 2010b). CD8 + T cells response contributes also to partial control of HIV infection (Haase, 2010). The infection is also influenced by adaptive immune responses (Ivashkiv and Donlin, 2014). They are 2 main directions in which innate immunity could be involved in HIV-1 infection. Unchecked induction of innate immune response participates in pathogenesis while avoidance of innate sensing pathways contributes to immune evasion (Silvin and Manel, 2015). DCs play a critical role in antiviral immunity through innate sensing pathways and the induction of adaptive immune responses (Silvin and Manel, 2015). HIV-1 fails to activate cytosolic innate immune sensors in DCs while HIV-2, a virus with reduced pathogenicity, efficiently infects DCs and activates a cytosolic innate immune response in DCs (Manel and Littman, 2011). This could be explained by the absence of Vpx protein in HIV-1 as the cytosolic innate sensing of HIV-1 by DCs can be rescued by complementing the virus with this protein (Manel et al., 2010). Stimulation of DCs by HIV-2 or HIV-1 plus Vpx leads to the degradation of SAM domain and HD domain-containing protein 1 (SAMHD1) (Manel and Littman, 2011). The latter is a highly conserved protein that functions as a restriction factor for HIV-1 infection by inhibiting HIV-1 replication (Hrecka et al., 2011; Laguette et al., 2011). However, the antiviral activity of SAMHD1 affects the immune response by limiting IFN induction and antigen presentation by DCs, and innate immune sensing of HIV-1 is limited by SAMHD1 (Manel et al., 2010; Ayinde et al., 2015). This indicates that there is competition between the antiviral activity of SAMHD1 to reduce viral replication (in dendritic cells, in resting T cells) with the necessity to sense viral replication to activate innate and adaptive immunity. SAMHD1 deficiency in mice have increased susceptibility to HIV-1 infection (Rehwinkel et al., 2013; Behrendt et al., 2013), but the induction of antiviral innate and adaptive immunity is strongly impaired (Gao et al., 2013).

In the absence of SAMHD1, HIV activates the enzyme cyclic GMP-AMP (cGAMP) synthase (cGAS)-mediated cytosolic innate sensing that triggers the production of low doses of IFN response and DC maturation (Manel et al., 2010; Gao et al., 2013; Lahaye et al., 2013) and leads to protection of CD4 + T cells from subsequent HIV infection (Manel et al., 2010). When cGAS is active, new viral particles package and transmit cGAMP to target cells, which is a form of Trojan Horse immune defence (Gentili et al., 2015; Bridgeman et al., 2015). cGAMP-containing HIV virus like particles (VLP) might potentially be used to develop effective vaccines against HIV-1 and other pathogens.

Interaction between viral and host proteins play a critical role to escape immune recognition and ensure viral replication. Cyclophilin A (CypA) is a host protein that binds the HIV capsid that plays multiple regulatory activities (uncoating, nuclear entry, etc.) on the virus (Luban et al., 1993) and is required for the early step of infection. In DCs, an increasing capsid affinity for CypA leads to HIV sensing. HIV affinity capsid (HIVac) mutant are blocked at nuclear import and increase cGAS sensing, leading to increased stimulation of T cells from HIV-1 infected patients (Lahaye et al., 2013). Restriction of HIVac capsid is mediated by CypA and can be rescued indicating the participation of additional host proteins (Lahaye et al., 2016). In macrophages, CypA appears instead to limit innate sensing and CypA inhibitors were shown to increase antiviral activity (Rasaiyaah et al., 2013). The role of Cyclophilin A in HIV sensing is complex and insufficiently understood (Lahaye and Manel, 2015a, 2015b), but it could lead to new strategies for immunomodulation and vaccines.

SUN2, a nuclear envelope protein, was recently found to be an essential host factor for HIV infection in CD4 + T cells and mediates CypA activities (Lahaye et al., 2016). HIV dependency on SUN2 constitutes a new target for therapeutic strategies.

HIV-1 encodes four “accessory proteins” (Vif, Vpr, Vpu, and Nef) that are essential for its pathogenesis (Matheson et al., 2015). It has recently been shown that Nef induces the relocation of the multipass transmembrane proteins SERINC3 and SERINC5 from the plasma membrane of infected cells into endosomal compartments, and thereby prevents their incorporation into progeny HIV-1 virions (Rosa et al., 2015; Usami et al., 2015). Ectopically expressed SERINC5 dramatically reduced the specific infectivity of HIV-1, and this effect was counteracted by Nef. Knockdown experiments indicated that endogenous SERINC3 and SERINC5 synergistically inhibit the infectivity of HIV-1 lacking Nef. Remarkably, Nef-deficient virions produced in double-knockout CD4 + T cells lacking SERINC3 and SERINC5 were more than 100-fold more infectious than virions produced in the parental cells, and reconstitution experiments confirmed that SERINC5 accounted for this difference.

Inhibiting the Nef-induced down-regulation of SERINC5 is thus a potential strategy to combat HIV.

HIV-1 envelope protein gp120 is heavily glycosylated and the glycans can interact with some lectin receptors such as DC-SIGN. DC-SIGN expression is restricted to a fraction of DCs, in particular in mucosal tissues (Jameson et al., 2002). Initially considered to be the main receptor for capture and transmission of HIV-1 by DCs, DC-SIGN is now recognized to play a minor role in this process (Ménager and Littman, 2016; Izquierdo-Useros et al., 2014). The interaction of gp120 with DC-SIGN was also reported to act either positively or negatively on immune activation (Hodges et al., 2007; Moris et al., 2004). The relative contribution of these possible mechanisms to the overall immune response against HIV is not understood.

4. Tuberculosis

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (Mtb). Infection can remain latent for many decades but reactivates in 3–10% of latently infected persons during their life time (Nunes-Alves et al., 2014). Multi-drug resistance (MDR) and extensively-drug resistance (XDR) TB is an emerging threat that complicates TB treatment.

Mycobacterium bovis Bacille Calmette Guérin (BCG) is the only currently used vaccine against TB. BCG protects fairly well against severe TB in childhood, but has limited impact on the TB pandemic because it fails to protect adults consistently against pulmonary TB; TB reactivation and it does not induce immunity against all relevant antigens of Mtb (Lin et al., 2007). The primary T cell response induced by BCG vaccination was investigated in healthy BCG-naïve adults from a non-endemic region and showed surprisingly divergent responses (Boer et al., 2015). Moreover, BCG vaccination resulted in the induction of the T-cell exhaustion marker, i.e. killer cell lectin-like receptor subfamily-G1 (KLRG1) on CD8 + T-cells (Boer et al., 2016). This was in contrast with the expression of KLRG1 and PD1 (programmed cell death protein-1) on CD4 + T-cells during TB disease and following successful TB treatment, suggesting heterogeneity in the T-cell response following infection and vaccination that deserves further

investigation.

Mtb is recognized by T cells following presentation by HLA molecules which involve not only classical HLA molecules, but also non-classical HLA molecules such as HLA-E (van Meijgaarden et al., 2015; Joosten et al., 2010). HLA-E is enriched within Mtb phagosomes and thus may preferentially present phagosomal antigens (Grotzke et al., 2009). HLA-E is considered as a potential candidate antigen presentation molecule for new TB vaccine antigens, given its essentially monomorphic nature, which distinguishes it from the classical, highly polymorphic HLA class Ia and class II molecules. In further contrast to classical HLA restricted Mtb specific T cells which are typically Th1 like, Mtb specific HLA-E restricted T clones produced Th2 cytokines (IL-4, IL-5, IL-13) that were able to inhibit intracellular growth of Mtb (van Meijgaarden et al., 2015). A similar T cell phenotype was seen in the blood of TB patients (Caccamo et al., 2015).

The human immune response to Mtb not only involves T-cells but also other parts of the immune system. TB patients had decreased B-cell frequencies, and, more importantly, the remaining B-cells from TB patients as well as those latently infected with Mtb were functionally much impaired in terms of proliferation, cytokine production and Ig production (Joosten et al., 2016). Also antigen presentation to T-cells was hampered, indicating an until now underappreciated but important role for B-cells during Mtb infection and disease (Joosten et al., 2016).

Initial host-pathogen interactions dictate TB pathogenesis leading to either active or latent TB (Cadena et al., 2016; O'Garra et al., 2013; Ottenhoff et al., 2012). There is growing evidence that “latent infection” is not a single entity, but rather a spectrum of infection outcomes. Granuloma is a site of replication and persistence of Mtb with equal variability (type, response to drug, composition, etc.) within individual hosts (Lin et al., 2014). Granulomas are formed in the lung parenchyma and composed of mononuclear phagocytes (MPs), neutrophils (PMNs), T and B lymphocytes (Ramakrishnan, 2012). In Macaques infected with low doses of Mtb, early formation and dissemination of new granulomas was associated with active TB outcome (Coleman et al., 2014). Early after infection, bacterial number by granuloma was high and decreased progressively after 4 weeks even in monkeys who were developing active TB (Lin et al., 2014). Members of C-type lectins receptors, expressed by DCs, were involved in immunity to TB (MacMicking, 2014; Sancho and Reis e Sousa, 2012; Geijtenbeek and Gringhuis, 2009). In particular, DC-SIGN is an essential receptor of Mtb on DCs (Tailleux et al., 2003). Strong evolutionary constraints on DC-SIGN suggest that it could be a critical role in the susceptibility to and pathogenesis of Mtb (Neyrolles et al., 2006).

Investigations focusing on cellular immunology in TB have recently unveiled that the myeloid compartment controlling inflammation in TB is diverse (Dorhoi and Kaufmann, 2015). Specialization of myeloid subsets for particular immune processes has tailored their roles in protection and pathology. Moreover, myeloid subsets' activation modes also significantly influence the outcome of inflammation during TB. Recently, myeloid-derived suppressor cells (MDSCs), also known as regulatory myeloid cells have been identified in TB patients at sites of pathology and have also been reported in experimental models of TB (Dorhoi and Kaufmann, 2015). Accumulation of MDSCs and PMNs within infected lung causes exuberant pathology, whereas their enrichment in the periphery represents an indicator of disease severity and serves as a disease prognostic marker (Knaul et al., 2014). Deciphering the manifold nature of myeloid cells in TB will contribute to a better understanding of disease pathogenesis. Such information will pave the way for development of future immune therapies aiming to fine-tune inflammation in TB for the host's advantage.

The biology of TB infection involves extensive immune modulation and inflammation, both compromising host immunity. A prospective transcriptomic TB signature was found that was predictive of TB progression with a sensitivity of 66.1% (95% CI 63.2–68.9) and a specificity of 80.6% (79.2–82.0) (Zak et al., 2016). The predictive signature was similar to the ones described in active TB, in which transcriptomic signatures dominated by a neutrophil-driven type 1 and type 2 interferon-inducible gene profile have been reported (e.g. Ottenhoff et al., 2012; Berry et al., 2010). This transcriptomic signature related to disease extent and normalized during successful treatment (Ottenhoff et al., 2012; Berry et al., 2010; Bloom et al., 2012). Furthermore, the differentiation of active from latent tuberculosis and other conditions is aided by the discovery of yet other diagnostic transcriptomic signatures (e.g. Anderson et al., 2014; Kaforou et al., 2013).

Currently, several TB vaccines are in different phases of development but so far no one outperforms BCG. MVA85A, a recombinant strain of modified Vaccinia Ankara virus expressing antigen 85A (MVA85A) did not confer significant efficacy against TB or Mtb infection in a double-blind randomized placebo-controlled study of children previously vaccinated with BCG (Tameris et al., 2013). The authors concluded that the protective effect of MVA85A against severe TB could have been masked as the endpoint was mild TB. However, based on a fundamental understanding of host pathogen interactions in TB, it should be possible to identify candidate vaccine antigens that can improve BCG (Coppola et al., 2015; Black et al., 2009). Mtb antigens targeted by vaccination must be expressed during infection in the lungs of susceptible individuals (Coppola et al., 2016; Commandeur et al., 2013). New antigen discovery approaches yield novel classes of Mtb antigens, with promising vaccine potential. Among these, latency as well as in vivo expressed (IVE)-TB antigens are promising as they can induce protection in humanized mice and guinea pigs (Commandeur et al., 2013). No response to latency antigens induced by BCG in both mice and human could partially explain BCG's inefficiency (Lin et al., 2007). Recognition of Mtb dormancy regulon (DosR) antigens are thought to be associated with latency and were potentially recognized by human T-cells across different TB exposed populations (Black et al., 2009). The most commonly DosR-encoded antigen recognized by participants in South Africa and Uganda was Rv1733c (Black et al., 2009). Rv1733c protein has been shown to elicit significant reduction in the bacterial load in the Mtb challenged mice and to boost the protective effect of BCG (Coppola et al., 2015; Reece et al., 2011).

Better understanding of the human host response to Mtb, and particularly factors that determine protective immunity and disease susceptibility are among the major goals to be reached for the design of effective new vaccines and vaccination strategies.

5. Conclusions

New scientific discoveries allow paving the way to a better understanding of pathogenesis, the mechanisms on how pathogens interact with their host as well as with the immune system. This knowledge can be used in the design for new vaccines and drug development.

The newly identified HBV restriction factors, SMC5/6 are degraded by HBx interaction with DDB1 directing SMC5/6 to degradation with Cullin4-ligase3 complex. Therefore, strategies aiming at blocking HBx function or interaction with DDB1 are expected to be beneficial for the restriction of HBV infections. Subsets of MDSC cells are important for HBV and TB infection/latency. They are important for immunological read-outs in pre-clinical, clinical endpoints, and treatment with a strategy aiming at either depleting these cells or re-differentiating them into pro-inflammatory ones. HBV proteins interact with innate immune system through activation of STING and IRF3 pathways. More generally, PRR agonists could be important adjuvant of a more complex immune-based therapy. Furthermore, following recognition of the importance of co-inhibitory molecules expressed on T cells and APCs/infected cells to explain T-cells exhaustion, the repositioning check-point inhibitors (ex. anti-PD1, anti-PDL1, Anti-CTLA4, ...) to persistent viral infection could be imagined in the future. The use of new technologies, such as siRNA technology, should allow to specifically destroy HBV viral transcripts in infected hepatocytes, leading to inhibition of all viral protein synthesis, including secreted viral antigens, which play a role in

immune subversion. Clinical evaluations of this strategy are ongoing and could lead to the first medical use of siRNA. Finally, the CRISPR/Cas9 technology could be very useful to induce the functional degradation of cccDNA, and therefore lead to a *complete cure* of HBV.

HIV is hiding in CD4 T cells in germinal centers or in macrophages. Identification of specific markers of infected reservoir cells can be the target of new small molecules that could completely block viral replication. Inhibition of SAMHD1 by interaction with VPX of HIV-2 may “tip the balance” towards induction of more potent innate immune activation. SUN2 has been found to be an essential host factor for HIV infection can be used as a new target for modulation of HIV infection and immune response. Interaction of the multipass transmembrane proteins, SERINC3 and SERINC 5, with Nef allows identification of epitope that is important for the interaction – small molecule identification. The ability of enveloped viruses, including HIV, to package the critical immune second messenger cGAMP (ligand of STING) bypasses the need for viral replication to induce immunity. This opens the way to develop a new class of vaccines, combining desired viral particles with cGAMP to stimulate immunity.

In the field of TB, B-cell responses are important during TB infection/latency and could provide novel immunological read-outs as preclinical and clinical biomarkers of disease. In addition, the role of antibodies in TB suggests a potential for new TB vaccines to optimal protection by also inducing protective antibodies (Lu et al., 2016). HLA-E provides a novel candidate antigen presentation molecule for new TB vaccine antigens, given its essentially monomorphic nature, which distinguishes it from the classical, highly polymorphic HLA class Ia and class II molecules. Investigating transcriptomic signatures help in the identification of immune signatures of protective host responses, and/or clearing immune responses. Diagnostic as well as prognostic applications are foreseen (Petruccioli et al., 2016).

Identification of protective or clearing immune responses could be used for the identification of appropriate antigens or to be used as clinical endpoints.

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Conflict of interest

IK is employee of Sanofi Pasteur. Other authors declare that they have no conflicts of interest to report.

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