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Review

Chronic Bystander Infections and Immunity to Unrelated Antigens

Erietta Stelekati[1] and E. John Wherry[1,*]
[1]Department of Microbiology and Institute for Immunology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: wherry@mail.med.upenn.edu
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Chronic infections with persistent pathogens such as helminths, mycobacteria, *Plasmodium*, and hepatitis viruses affect more than a third of the human population and are associated with increased susceptibility to other pathogens as well as reduced vaccine efficacy. Although these observations suggest an impact of chronic infections in modulating immunity to unrelated antigens, little is known regarding the underlying mechanisms. Here, we summarize evidence of the most prevalent infections affecting immunity to unrelated pathogens and vaccines, and discuss potential mechanisms of how different bystander chronic infections might impact immune responses. We suggest that bystander chronic infections affect different stages of host responses and may impact transmission and recognition of other pathogens, innate immune responses, priming and differentiation of adaptive effector responses, as well as the development and maintenance of immunological memory. Further understanding of the immunological effects of coinfection should provide opportunities to enhance vaccine efficacy and control of infectious diseases.

Introduction

Diseases from persistent infections impact a large portion of humanity. Chronic infections with intestinal helminths, *Mycobacterium*, *Plasmodium*, and hepatitis viruses affect more than a third of the global population. In developing countries, in particular, infection with at least one persistent pathogen is common. Although major efforts are focused on the control of persistent pathogens, current vaccines and treatments for many of these infections are lacking, ineffective, or unavailable.

In addition to diseases directly caused by these pathogens, mounting evidence suggests that persistent infections can alter immunity to unrelated pathogens and vaccines. In some cases, coinfections may provide a benefit to the host (Barton et al., 2007; Xiang et al., 2001). However, much of the existing epidemiological evidence suggests a negative impact of chronic coinfections on host immune responses. The high incidence of coinfection with multiple chronic pathogens suggests an increased susceptibility to secondary infections. Moreover, responses to many vaccines are reduced in chronically infected patients, rendering those individuals (often young children) more susceptible to subsequent infections. Although numerous observational studies have associated bystander chronic infections with altered immune responses to unrelated pathogens or vaccines, the immunological mechanisms underlying these effects remain poorly understood.

In this review, we discuss the effects of bystander chronic infections on immune responses to secondary pathogens and vaccines based largely on epidemiological and clinical observations. Many variables, such as nutritional or socioeconomical status, age, and gender may affect the outcome of chronic infections or efficiency of vaccines, but here we focus on the potential immunological pathways that might be altered by bystander chronic infections. The dramatically reduced vaccine efficacy that has been noted in developing versus industrialized countries (Cherian et al., 2012) suggests that a more systematic understanding of the effects of bystander chronic infections could improve vaccines and treatments for infectious diseases worldwide.

High Incidence of Coinfection Suggests that Chronic Infections Increase Susceptibility to Unrelated Infections

Epidemiological studies suggest that chronic infections can predispose patients to secondary infections. Since many pathogens causing chronic pathology are coendemic, one could argue that the high rate of coinfection is simply due to enhanced coexposure. Although the geographical overlap of pathogen spread cannot be excluded as a potentially contributing factor, mathematical models suggest that chronic infections, such as malaria and human immunodeficiency virus (HIV), actively contribute to the increased rate of infection with unrelated pathogens (Abu-Raddad et al., 2006). In the following sections, we discuss evidence that representative chronic parasitic, bacterial, or viral infections with high global prevalence impact immunity to secondary pathogens or vaccines. The majority of epidemiological data support a negative effect of chronic bystander infections in regulating immunity to subsequent unrelated infections. However, studies suggesting that other chronic infections provide some immunological benefits to the host will be also discussed in a later section. The pathogens discussed here are not intended to be an inclusive set, and many other data sets exist from epidemiological and/or animal model studies, some of which are summarized in Table 1. The examples below are chosen, rather, to illustrate key points that may give insights to common underlying immunological mechanisms.

Although considerable epidemiological data suggest that chronic bystander infections affect susceptibility to unrelated pathogens, it is challenging to compare studies that examine different ethnic backgrounds, age groups, and/or different stages of the chronic infection. Thus, data from small-scale

Table 1. Representative Examples of Chronic Bystander Infections Affecting Susceptibility to and/or Outcome of Unrelated Infections

Bystander Chronic Infection	Unrelated Infection Affected	Outcome of Coinfection	Representative References
Helminths	*Plasmodium*	Exacerbation of malaria during acute phase; reduced severity during chronic phase	Nacher et al., 2002; Le Hesran et al., 2004; Sokhna et al., 2004; Briand et al., 2005
	Mycobacterium	Increased pathology	Resende Co et al., 2007
	HCV	Increased risk of developing chronic disease; advanced liver disease	Kamal et al., 2001
	HIV	Increased susceptibility to HIV; controversial results on viral loads	Gopinath et al., 2000; Wolday et al., 2002; Modjarrad et al., 2005; Brown et al., 2005
Plasmodium	*Mycobacterium*	Exacerbation of disease, reactivation of latent infection	Hawkes et al., 2010
	EBV	Reactivation of EBV	Donati et al., 2006
	HIV	Increased viremia	Pisell et al., 2002; Kublin et al., 2005
Mycobacterium	*Plasmodium*	Amount of IFN produced determines susceptibility to malaria in resistant/susceptible murine strains	Page et al., 2005; Leisewitz et al., 2008
	HIV	Enhanced AIDS disease and mortality	Whalen et al., 1995
Viral Hepatitis	*Plasmodium*	Reduced and slower progression to parasitemia	Ouwe-Missi-Oukem-Boyer et al., 2011; Andrade et al., 2011
	Schistosoma	Increased pathology and mortality	Zaki et al., 2003
	HIV	Advanced AIDS disease and mortality	d'Arminio Monforte et al., 2009; Chun et al., 2012
HSV	HIV	Increased HIV replication and transmission	Schacker et al., 2002; Freeman et al., 2006
Helicobacter	*Mycobacterium*	Reduced risk of progression to active disease	Perry et al., 2010
	Toxoplasma	Increased parasite replication and disease severity	Stoicov et al., 2004
Leishmania	HIV	Increased viral replication	Cacopardo et al., 1996

Studies mentioned here represent only a portion of available epidemiological data existing to illustrate underlying mechanisms of interactions.

observational studies can be challenging to interpret broadly. However, when viewed together, some general themes emerge that should allow hypothesis generation for future larger and/or mechanistic studies.

HIV infection represents a special case for the discussion of bystander chronic infections, given that HIV infects and kills CD4 T cells, resulting in overt immunosuppression. In some cases, poor immune responses to other antigens during HIV coinfection do not correlate with CD4 T cell deficiency or HIV viral loads (Brydak et al., 1999; Bickel et al., 2011), suggesting that mechanisms besides overt immunodeficiency may exist. However, the role of chronic HIV as a bystander infection affecting responses to unrelated pathogens will not be explored in detail here. Instead, further discussion of coinfections involving HIV will focus on HIV not as the "bystander" but as the "unrelated" or "secondary" infection, and how other chronic infections may impact responses to HIV.

Helminths and Coinfections: A Role for Cytokine Skewing?

Persistent infections with parasitic helminths affect more than a billion people, and coinfections with helminths and unrelated parasitic, bacterial, or viral pathogens are very common, particularly in developing countries. Nevertheless, the interaction between helminths and *Plasmodium*, the causative agent of malaria, is controversial. Some studies suggest that chronic helminth infections protect from cerebral malaria and reduce parasite burden (Nacher et al., 2002; Briand et al., 2005). In contrast, other studies have shown an increased risk of developing malaria and increased severity of malaria symptoms due to bystander helminth infections (Le Hesran et al., 2004; Sokhna et al., 2004). These broadly discussed discrepancies could, in part, be attributed to the fact that the acute phase of infection with the trematode *Schistosoma* promotes a Th1 type of inflammation, which is predominantly associated with cell-mediated immunity and resistance to intracellular pathogens and could potentially increase *Plasmodium*-induced pathology. By contrast, the chronic phase of helminth infections is associated with a Th2/regulatory cytokine milieu, which can attenuate Th1 responses that are immunopathogenic for malaria (Hartgers and Yazdanbakhsh, 2006). These discordant epidemiological findings illustrate the immunological complexities of chronic coinfection, where the timing of acquisition of the second pathogen might be critical in the context of a dynamic immunological environment due to a pre-existing bystander infection.

Chronic helminth infections also affect responses to viruses, such as hepatitis C virus (HCV) or HIV. Coinfection with *Schistosoma* increases the risk of proceeding from acute to chronic HCV infection and enhances viral burden and disease progression (Kamal et al., 2001). Similarly, helminths may promote susceptibility to HIV (Gopinath et al., 2000). However, the benefit of antihelminthic treatment during HIV infection has been the subject of considerable debate. In some studies, deworming was beneficial for reducing HIV viral load (Wolday et al., 2002); in others it was not (Modjarrad et al., 2005; Brown et al., 2005). A more systematic review of the literature, however, supported a beneficial effect of antihelminthic treatment for reducing HIV viral loads (Walson and John-Stewart, 2007). The inability to estimate the exact timing of acquisition of either infection, as well as the small sample sizes in many of these studies, may account for these discrepancies and have limited broad conclusions on this issue, emphasizing the need for further investigation.

Tuberculosis Infection Can Impact the Outcome of Unrelated Viral or Parasitic Infections

Coinfection with the intracellular bacterium *Mycobacterium tuberculosis* (Mtb) and HIV is one of the most prevalent and lethal combinations of coinfection. Development of active tuberculosis caused by Mtb accelerates the clinical course of HIV infection and is associated with increased mortality in HIV patients (Whalen et al., 1995). Mathematical models have predicted that treatment of latent and active tuberculosis delays the onset of AIDS (Bhunu et al., 2009), suggesting that the detrimental effects of this coinfection are not simply due to HIV-mediated immunosuppression but rather due to a reciprocal pathogen interaction. Animal studies support this hypothesis, as upon Mtb infection, macaques infected with simian immunodeficiency virus (SIV), a close relative of HIV, show increased viral load, enhanced CD4 T cell decline, and increased mortality (Zhou et al., 1999). Together, these data provide a strong rationale for the appreciated importance of early detection and management of tuberculosis in HIV-coinfected patients, but also suggest a complex set of immunological interactions during HIV/Mtb coinfections.

Mtb infections can also impact subsequent parasitic infections, such as malaria. Interferon (IFN) responses are crucial for sustaining immune control of chronic Mtb infection and may represent a predictive biomarker of Mtb disease (Berry et al., 2010). A fine balance in the amount of IFN-γ produced upon Mtb infection may determine the outcome of *Plasmodium*/Mtb coinfection: optimal amounts of IFN-γ may protect from subsequent *Plasmodium* infection, while uncontrolled IFN-γ production may result in enhanced susceptibility to malaria and/or pathogenesis (Page et al., 2005; Leisewitz et al., 2008). The potential contribution of additional mechanisms, such as intrinsic defects in lymphocyte subsets or proliferative defects caused by chronic Mtb infection, remains to be examined in these settings.

Malaria Affects Pathology Induced by Bacterial or Viral Infections

While mycobacterial infections can impact responses to malaria, the reverse interaction between *Plasmodium* and Mtb has also been observed, predominantly in animal models. In a mouse model of coinfection, *Plasmodium* infection exacerbated acute mycobacterial infection, increased bacterial growth by almost 60%, and induced reactivation of latent Mtb (Hawkes et al., 2010). Given the significant geographic overlap of these two infections, unraveling the mechanisms of how malaria might modify Mtb infection and vice versa could be of considerable clinical importance.

Plasmodium infection also impairs responses to viral pathogens, such as HIV. Mathematical models have suggested a mutual interaction between these two infections responsible for the spread of both pathogens in coendemic areas (Abu-Raddad et al., 2006). Patients with malaria present with higher HIV viral burden, an effect that could be abrogated upon parasite clearance (Pisell et al., 2002; Kublin et al., 2005). Since the timing of acquisition of HIV infection in relation to *Plasmodium* infection is usually unknown, animal models may provide a more controlled and mechanistic dissection of the immunological interactions between *Plasmodium* and HIV. Indeed, studies in rhesus macaques indicated that established malaria infection accelerates CD4 T cell decline upon subsequent SIV infection and enhances SIV disease progression (Koehler et al., 2009). Therefore, the high incidence of malaria/HIV coinfection cannot be completely attributed to HIV-induced immunodeficiencies. Rather, a bidirectional interaction between these two pathogens likely exists.

Chronic Viral Infections Affect Immune Responses to Other Pathogens

The high incidence of HIV/hepatitis B virus (HBV) or HIV/HCV coinfection has been attributed to the similar modes of transmission, as well as HIV-induced immunosuppression. However, the impact of hepatitis viral infections on the course of HIV infection remains controversial. Some studies have not detected an effect of HBV or HCV on the progression of HIV infection, but others have defined an up to 2.6-fold increase in the risk of developing AIDS-related illness due to HCV coinfection (Piroth, 2009; d'Arminio Monforte et al., 2009). These different observations might relate, at least in part, to different stages of HIV disease progression. Indeed, a recent study in a large cohort with known duration of HIV infection detected a 2-fold increase in the risk for progression to AIDS or death in HIV/HBV coinfected patients (Chun et al., 2012). Further, clinical evidence suggests that chronic hepatitis viral infections affect pathology and morbidity induced by *Schistosoma* infection (Zaki et al., 2003). Besides chronic hepatitis viruses, other persistent viral pathogens, such as herpes simplex virus type 2 (HSV-2), have a well-recognized role in affecting immunity to unrelated pathogens, such as HIV. HSV-2 infection has been associated with an ~3-fold increased risk in HIV acquisition, and reactivation of HSV-2 from latency increased HIV viral replication (Schacker et al., 2002; Freeman et al., 2006). These studies suggest that a critical factor in preventing or treating global health threats such as HIV, and even vaccine-preventable diseases such as polio and rotavirus, may be addressing the effects of coinfections.

Chronic Infections Impair Development of Protective Immunity following Vaccination

The examples discussed above have focused on clinical and experimental observations from different types of chronic parasitic, bacterial, and viral infections affecting the largest numbers of people globally. While these studies shed light on the effects of chronic coinfection, our understanding of the precise immunological pathways associated with altered immunity remains

limited. Two key issues complicate the interpretation of many data sets on coinfection. First, in settings where two different pathogens infect the same host, it is often difficult to define how the replication and/or pathogenesis of each infection might be altered. Subsequently, changes in pathogenesis can have a profound impact on the developing immune responses. Second, especially when examining coinfections in the developing world, the timing of acquisition of each infection is usually unknown, and ascribing "bystander" and "secondary infection" status to the different pathogens is often somewhat arbitrary. Studies on vaccination, on the other hand, allow a more controlled evaluation of the effects of chronic infections as "bystanders" to the vaccine.

The geographic overlap between poor immune responses to vaccination and persistent infections such as those discussed above suggests that, in addition to impacting other infections, bystander chronic infections may also negatively affect responses to vaccination. Several other factors, such as malnutrition, poor health practices, and nonadherence to vaccination protocols, should not be overlooked in these settings, but there is accumulating evidence that chronic infections actively impact efficacy of vaccines. These data on vaccination suggest that additional studies on coinfection are warranted, since the target population for vaccines against some of the most challenging global infectious diseases, such as HIV, malaria, and tuberculosis, is often chronically infected with other pathogens. In addition to the urgent need to understand how to enhance vaccine efficacy in the developing world, studies on vaccination in the context of chronic infections also provide insights into potential underlying immunological effects of bystander chronic infections. In these settings, the timing of initiating the vaccine-targeted response is known, and often the "optimal" response to the vaccine in noninfected cohorts has been defined.

Vaccination during Helminth Infections

Helminth infections have been associated with lower responses to vaccinations for tetanus toxoid (Sabin et al., 1996; Nookala et al., 2004), cholera (Cooper et al., 2001), and Bacille Calmette-Guerin (BCG), the vaccine for tuberculosis (Elias et al., 2001). Upon vaccination of helminth-infected individuals, reduced T cell proliferation and Th1 cytokine production, increased production of the cytokine interleukin (IL)-10, and lower levels of antibody isotypes IgG2, IgG3, and IgG4 were detected, effects that were in some cases overcome by antihelminthic treatment (Elias et al., 2001; Cooper et al., 2001; Nookala et al., 2004). Thus, the effects of helminth infection on vaccine-induced responses are consistent with observations from chronic helminth coinfections and suggest a major contribution of Th2 skewing but also possible effects on lymphocyte effector function.

Vaccination during Malaria

Children with malaria develop weaker antibody responses to *Salmonella typhi*, tetanus toxoid, meningococcal polysaccharide, and *Haemophilus influenzae* vaccination (Cunnington and Riley, 2010). Antimalaria treatment may enhance responses to meningococcal polysaccharide and tetanus toxoid vaccination, but not to measles vaccination (Rosen and Breman, 2004; Cunnington and Riley, 2010), suggesting that responses to different vaccine antigens may be differentially affected by a bystander *Plasmodium* infection. In a recent primate study, malaria was shown to reduce the efficacy of a DNA-based SIV vaccine by decreasing vaccine-induced CD4 and CD8 T cell responses (Yin et al., 2012). Thus, the clinical data indicate substantial defects in vaccine-induced antibody responses in malaria-infected individuals, while animal models also support the notion of T cell defects. Unlike chronic helminths, *Plasmodium* parasites promote Th1 responses. Therefore the mechanism(s) of how different bystander infections may impact new immune responses could extend beyond the disruption of Th1/Th2 cytokine equilibrium.

Vaccination during Chronic HCV Infection

Chronic HCV infection moderately affects responses to hepatitis A virus (HAV) or influenza virus vaccination (Majda-Stanislawska et al., 2004; Gaeta et al., 2002). More prominent is the effect of chronic HCV on HBV vaccination, with HBV seroconversion as low as 50% reported in HCV-infected subjects, independently of serum HCV titers (Wiedmann et al., 2000; Elefsiniotis et al., 2006; Moorman et al., 2011). Some data indicate that, despite later defects, early responses (i.e., 1 month) following HBV vaccination were normal (Lee et al., 1999), suggesting that the main defect caused by chronic HCV may be in the long-term maintenance of protective immunity. While most of these studies have examined only protective antibody production, they suggest that T cell responses (i.e., to help T-dependent antibody responses and perhaps development of immunological memory) may also be affected.

How Do Bystander Chronic Infections Affect Immune Responses to Unrelated Antigens?

The observations discussed above largely support the notion that chronic bystander infections affect immune responses to unrelated antigens, secondary infections, and vaccines. Indeed, conventional clinical practice is often to avoid vaccinating patients with fevers or infections. However, in the developing world, where chronic infections causing pathology and immunological alterations are the norm, vaccinating only individuals lacking bystander infections is likely impractical or impossible. Thus, a better understanding of how bystander chronic infections influence immunity to new antigens is needed. Several mechanisms may be responsible for the increased susceptibility to unrelated infections in chronically infected patients. Different stages of host-pathogen interaction and developing immune responses could be impacted by bystander chronic infections, including (a) initial pathogen entry or vaccine uptake and innate immune responses, (b) altered antigen-presenting cell (APC) function and initial priming of B and T lymphocytes, (c) development of host effector mechanisms and lymphocyte differentiation, and (d) development and/or maintenance of immunological memory (Figure 1). Each of these is discussed in more detail below.

Bystander Chronic Infections, Initial Pathogen Entry, or Vaccine Uptake and Innate Immune Responses

Many pathogens need to efficiently penetrate host epithelial barriers, and some important vaccines can be administered via mucosal routes. Several chronic infections discussed above could affect pathogen (and possibly vaccine) entry through mucosal barriers (Figure 1). For example, helminth infections affect the integrity of epithelial layers by disrupting epithelial tight junctions and increasing epithelial permeability (Su et al., 2011),

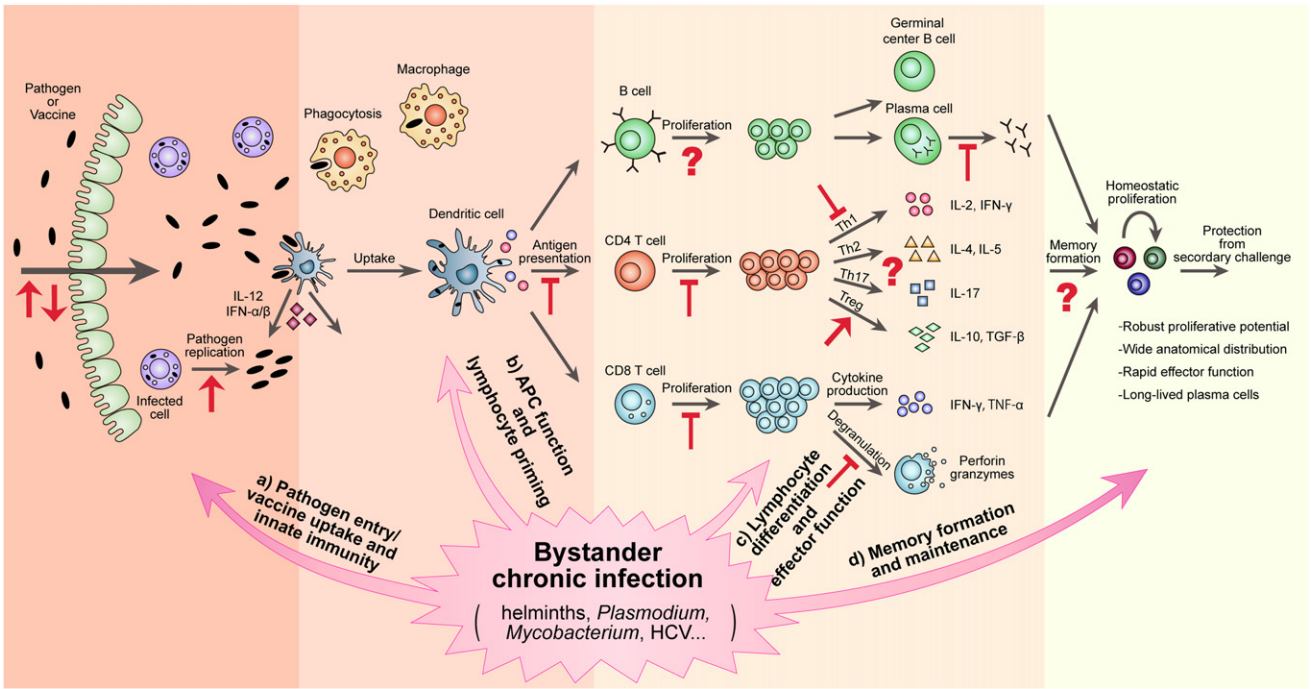

Figure 1. Potential Mechanisms by which Bystander Chronic Infections May Affect Immune Responses to Unrelated Antigens

Bystander chronic infections, such as helminths, malaria, tuberculosis, and viral hepatitis, may affect different stages of a developing immune response to unrelated pathogens or vaccines.

(A) Pathogen entry though mucosal/epithelial barriers or vaccine uptake is illustrated as an event that may be altered by bystander chronic pathogens. Dysregulation of innate immune responses and reduced production of early antimicrobial mediators could impact initial pathogen replication.

(B) Reduced or altered APC function including antigen processing and presentation, costimulation, and cytokine production may alter initial lymphocyte priming.

(C) Skewed lymphocyte differentiation could result in altered cytokine production, dysregulated humoral responses, and reduced cytotoxicity, manifesting in defective or altered effector functions.

(D) Effects on memory B and T cell development and maintenance may occur, but it remains unclear whether these are direct effects on memory B and T cell differentiation after the effector phase or reflect alterations in the early stages of the immune response.

thus potentially facilitating entry for unrelated mucosal pathogens. Furthermore, interaction of helminths with epithelial cells induces cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which promote goblet cell hyperplasia and mucus production (Artis and Grencis, 2008). Qualitative changes in goblet cell mucins during intestinal helminth infections (Khan, 2008) may alter the intestinal microenvironment and affect entry and/or survival of unrelated pathogens, while accumulation of excessive mucus may impact vaccine uptake at mucosal surfaces, decreasing vaccine efficacy (van Riet et al., 2007). Thus, an altered intestinal mucosal environment might affect initial entry of microbes and uptake of vaccines. In support of this hypothesis, intestinal viral infection with poliovirus or reovirus is impacted by the local microbial environment, since bacterial polysaccharides enhance the infectivity and pathogenesis of these enteric viruses (Kuss et al., 2011). In this example, the "bystander" microbe is nonpathogenic commensal bacteria species (see below), but these data illustrate the point that microbe-to-microbe interactions can influence the initial phases of infection. Other mucosal surfaces are also subject to disruption of barrier integrity and altered infectivity by pathogens. For example, epithelial cell damage in the genital mucosa during HSV reactivation (Horbul et al., 2011), as well as downregulation of mucosal immune mediators by HSV (Fakioglu et al., 2008), are thought to increase the rate of infection with HIV. These effects might not be limited to chronic infections, since disruption of epithelial integrity due to acute respiratory viral infections has since long been thought to facilitate secondary bacterial infections (McCullers, 2006).

In addition to affecting pathogen entry via mucosal surfaces, bystander chronic infections can also alter infectivity of target cells and pathogen replication. *Schistosoma* (Bahgat et al., 2010), Mtb (Zhang et al., 1995), and *Plasmodium* (Pisell et al., 2002; Hawkes et al., 2010) have been reported to increase replication of unrelated pathogens in their target cells. Several mechanisms might contribute to the increased cellular susceptibility to infection during a bystander chronic infection. First, cellular infiltration induced by chronic inflammation may increase the accumulation of target cells at the site of infection, thus promoting host cell-pathogen interactions. For example, HSV reactivation in mucosal tissues results in an influx of activated CD4 T cells, which may facilitate HIV transmission (Zhu et al., 2009), and a similar effect could be envisioned for other infections in the genital or intestinal mucosa. Similarly, *Plasmodium*-induced infiltration of dysfunctional monocytes at sites of tuberculosis granulomas, which are clusters of immune cells, may contribute to the inability to contain Mtb infection during *Plasmodium*/Mtb coinfection (Hawkes et al., 2010). Second, persistent pathogens may alter surface receptors expressed by bystander target cells, thus facilitating infection with secondary pathogens. For

example, enhanced spread of HIV in the presence of Mtb or *Plasmodium* infection may be facilitated by the increased expression of the HIV coreceptors CXCR4 and CCR5 (Hoshino et al., 2004; Moriuchi et al., 2002). These types of changes in initial pathogen entry and/or cellular infection could lead to major changes in early pathogen burden, substantially affecting downstream innate and adaptive immunity.

In addition to altering mucosal barrier integrity and cellular susceptibility to infection with unrelated pathogens, many chronic infections evoke substantial changes in innate immune cell development and function. Natural killer (NK) cell numbers are reduced in tuberculosis patients during concomitant intestinal helminth infection (Resende Co et al., 2007), as well as in chronic HCV patients (Morishima et al., 2006). Impaired NK cell development during chronic infection could play a role in the defective early control of subsequent viral infections. Cytokine production is another important mediator of innate immunity, considerably affected by bystander chronic infections. IFN-α/β responses by dendritic cells (DCs) and macrophages, crucial for early antiviral control, are inhibited by IL-4 and IL-10 (Varano et al., 2000; Sriram et al., 2007), a mechanism potentially relevant for the increased viral replication during coinfection with Th2-inducing parasites. Furthermore, production of the Th1 cytokine IL-1 by myeloid cells is suppressed by type I and type II IFN, providing a potential mechanism for the regulation of Mtb immunity by viral or other Th1-inducing coinfections (Mayer-Barber et al., 2011).

Finally, hematopoiesis and the generation of myeloid lineage cells can be dramatically impacted during chronic infections. Sustained production of cytokines including type I and type II IFN during chronic infections affects proliferation and differentiation of hematopoietic stem cells (Essers et al., 2009; Baldridge et al., 2010). While other examples of potential innate cross-regulation exist that might impact responses during coinfection, such as crosstalk between antiviral and antibacterial innate sensing pathways (Abt et al., 2012; Ichinohe et al., 2011), clearly more studies are needed to dissect how initial pathogen and vaccine entry, uptake, and innate sensing are altered by bystander chronic infections.

Bystander Chronic Infections, APC Function, and Initial Priming of B and T Lymphocytes

Intrinsic defects in innate immune cells caused by bystander chronic infections may lead to altered APC function, reduced antigen processing and presentation, and poor or altered priming of adaptive immune responses (Figure 1). The optimal initial priming of T cell responses requires that DCs efficiently acquire the antigen, home to the T cell zone of lymphoid tissues, process and present antigen to T cells, and express the appropriate array of costimulatory ligands to provide signal 2. Further, signal 3 from inflammatory mediators such as IFN-α/β, IL-12, IL-1, and possibly IL-33 is critical for optimal T cell activation (Curtsinger and Mescher, 2010; Bonilla et al., 2012).

This highly orchestrated set of events involved in initial priming can be disrupted by bystander chronic infections. DC maturation, costimulatory molecule expression, and cytokine production are affected by chronic infections. For example, interaction of DCs with helminth-associated antigens induces a partial maturation of DCs (van Riet et al., 2007), a mechanism that could be responsible for the subsequent reduced production of cytokines and chemokines (Metenou et al., 2012), inefficient antigen presentation, and induction of suboptimal T cell proliferation (Su et al., 2005). Disruption of the balance of costimulatory versus coinhibitory signals can lead to tolerance, anergy, and/or exhaustion rather than productive T cell priming (Macián et al., 2004). Additionally, altered IFN-α/β and IL-12 production by DCs during T cell priming decreases the efficiency of signal 3, which is critical for optimal T cell activation. Therefore, immature DCs providing suboptimal costimulation and cytokine signals during T cell priming may account for the reduced adaptive responses to unrelated antigens observed in several settings of bystander chronic infection.

Antigen processing and presentation are also affected during bystander chronic infections. For example, HSV impairs HIV degradation in Langerhans cells, or skin-resident DCs, by directly interacting with their degradation machinery (de Jong et al., 2010). Similarly, Mtb infection impairs the degradative processing and presentation of HIV by DCs (Reuter et al., 2010). On the other hand, the process of transinfection, whereby DCs deliver infectious virus to T cells without first being infected, is enhanced during tuberculosis infection (Reuter et al., 2010). Although a potentially fundamental mechanism for the increased transmission of HIV among tuberculosis patients, it is unclear if the enhanced ability of DCs to present virus in *trans* occurs in other settings of chronic bystander infections.

An additional recently appreciated effect of chronic infections is the dysregulation of lymphoid architecture. Both acute and chronic infections induce a transient downregulation of CCL21 and CXCL13, the key chemokines involved in DC and lymphocyte homing to, and within, lymphoid tissues (Mueller et al., 2007a). However, this period of altered chemokine production and responsiveness might persist longer during chronic infections. Additional disruptions in lymphoid architecture, including changes in follicular reticulocytes, could also lead to a dramatically different priming environment during chronic coinfections (Mueller et al., 2007b). While some evidence of altered lymphoid tissue architecture exists for chronic HIV and HCV infections (Dietrich et al., 1997; van Grevenynghe et al., 2008), the exact consequences of such changes in the context of chronic coinfection or vaccination of chronically infected individuals remain poorly defined.

Bystander Chronic Infections, Lymphocyte Differentiation, and Development of Effector Functions

Development of the appropriately tailored effector B and T cell responses is essential for control of many pathogens and is the basis for rationale vaccine design. Bystander chronic infections have the potential to skew these effector lymphocyte responses (Figure 1). For example, proliferative defects have been observed in T cells from patients with chronic helminth infections (Elias et al., 2001), or chronic HCV infection (Moorman et al., 2011), and in animals with chronic *Plasmodium* infection (Yin et al., 2012). At the time points examined, these proliferative defects likely reflect long-term changes in APC populations and/or altered populations of effector or memory T cells. CD8 T cell cytotoxicity, the hallmark of protective immunity against intracellular pathogens, can also be dysregulated in the presence of bystander chronic infection, as shown by reduced potential for degranulation and cytotoxicity, in the presence of helminth infections or chronic HCV (Harcourt et al., 2005;

McElroy et al., 2005). In most cases it remains unclear whether low proliferative potential or altered function is intrinsic to the T cells or reflects APC changes. However, in addition to altered costimulatory and cytokine signals provided by APCs, as discussed above, the increased expression of inhibitory molecules on bystander T cells from chronically infected patients (Babu et al., 2009; Moorman et al., 2011) suggests that at least some T cell intrinsic changes occur. Although the exact mechanisms and consequences of T cell dysfunction during bystander chronic infections remain to be more fully examined, blocking inhibitory pathways has recently been proposed to enhance immunity against unrelated antigens (Babu et al., 2009; Moorman et al., 2011).

Altered cytokine production during chronic infections is probably one of the main underlying immunological changes that could impact increased susceptibility to other infections or vaccine efficiency. Chronic helminth infections have been well characterized for skewing toward Th2 and regulatory responses (van Riet et al., 2007). This Th2 environment can dampen or prevent protective Th1 responses and alter antibody isotypes critical for protection or efficient vaccination against secondary pathogens such as *Plasmodium* (Su et al., 2005; Metenou et al., 2012), Mtb (Babu et al., 2009), HIV (Ayash-Rashkovsky et al., 2002), and HCV (Farid et al., 2005). Although the role of a global Th2 cytokine skewing in altering subsequent protective Th1 immune responses has been widely documented, it remains unclear whether this effect can be solely attributed to the inhibition of IFN-γ and other type 1-related pathways (e.g., T-bet-dependent pathways) by the Th2 cytokines IL-4 and/or IL-13 or to altered APC function as well. Moreover, how such skewing during bystander infections affects other CD4 T cell lineages, such as Th9, Th17, T regulatory (Treg) cells, and T follicular helper (Tfh) cells, remains poorly understood.

Besides the prominent impact of global cytokine skewing, there is also evidence for effects of sustained production of individual cytokines due to bystander chronic infections. The amount of IFN-γ produced during *Plasmodium*/Mtb coinfection correlates with the level of pathology observed (Page et al., 2005; Leisewitz et al., 2008). It is also not clear whether different innate inflammatory signals during priming impart important qualitative properties on T (or perhaps B) cells tailored to the specific infection. While there is some evidence that the program of an IL-12 "conditioned" effector T cell might differ from an IFN-α/β "conditioned" effector T cell (Xiao et al., 2009), it is not known how such effects might manifest during chronic bystander infections and whether they would impact protective immunity.

Humoral immunity is also influenced by chronic bystander infections. For example, skewing of antibody classes during chronic helminth infections has been suggested to affect responses to secondary pathogens, such as *Plasmodium* (Druilhe et al., 2005). Moreover, reduced antibody production upon vaccination of chronically infected patients suggests that a crucial common mechanism for the reduced vaccine efficacy during bystander chronic infections involves altered B cell differentiation and/or antibody production. Whether these effects are B cell intrinsic; reflect altered development of Tfh cells, which facilitate B cell development and antibody production and/or function; or both remains to be investigated. However, altered cytokine production by chronic infections can significantly affect the differentiation and survival of plasma cells that produce large amounts of antibody (Elgueta et al., 2010), resulting in defective antibody responses. Similarly, altered chemokine production due to chronic bystander infections could affect B cell migration and the formation of germinal centers where B cells differentiate and proliferate. Abnormal B cell subpopulations, such as exhausted or anergic B cells, are found in the periphery of HCV- (Charles et al., 2011) and HIV-infected subjects (Moir and Fauci, 2009), and at least for HCV, there appear to be polyclonal alterations affecting not only HCV-specific B cells. Further investigations of the effects of bystander chronic infections on the development of germinal center B cells and plasma cell differentiation, as well as the homing, survival, and function of these critical components of the humoral response, will clarify the mechanisms of altered antibody responses during chronic infections and potentially reveal opportunities for therapeutic interventions.

Bystander Chronic Infections and Memory Formation and Maintenance

A critical issue for vaccinating individuals with ongoing chronic infections is the development of effective, long-lasting immunological memory. Vaccination studies in chronically infected individuals have demonstrated a detrimental effect on the development of protective antibodies, suggesting possible defects in humoral and/or T cell memory. During memory development, B and T cells acquire or maintain several important properties, including the ability to perform rapid effector function, longevity via antigen-independent self-renewal or long life span (in the case of plasma cells), wide anatomical distribution, and the ability to mount robust recall responses (Figure 1). It is clear that the development of high-quality B and T cell memory after the effector phase of an immune response is a highly orchestrated and complex process. However, it has been difficult to determine whether the potential effects of bystander infections reflect a direct impact on development of immunological memory or indirect effects occurring during priming and effector differentiation earlier in the response.

Recent studies in mice have demonstrated that inflammatory cytokines can skew development of effector CD8 T cells toward terminal differentiation and away from long-term memory development (Joshi et al., 2007; Pham et al., 2009). While most studies in animal models examine scenarios in which exposure to antigen and inflammation is linked, these data raise interesting questions regarding the potential impact of chronic inflammation due to bystander infections (i.e., antigen-independent effects). There is some evidence of bystander attrition of pre-existing memory T cells during serial unrelated acute infections due to IFN-α/β and/or IFN-γ (Selin et al., 1999; McNally et al., 2001; Dudani et al., 2008). However, similar attrition of preformed memory CD8 T cells was not observed in other studies in which memory T cell numbers were tracked following multiple subsequent distinct acute infections in mice (Vezys et al., 2009) or during acute Epstein-Barr virus (EBV) infection in humans (Odumade et al., 2012). While the data on the numerical impact of bystander chronic infection on memory maintenance remains controversial, there is little information on how the differentiation pattern of developing memory B and/or T cells is impacted by bystander coinfections. Investigating the impact on memory development is complicated by the need to distinguish effects

that occur in the early stages of the immune response from events involved after priming that specifically impact memory development. However, understanding the potential direct effects of bystander chronic infections on memory cell quantity, quality, and function will open new avenues for optimization of vaccine strategies during bystander chronic infections and other inflammatory conditions.

Persisting Infections Benefiting the Host

Much of the evidence on bystander chronic infections supports a negative effect of chronic infections in regulating immune responses to unrelated pathogens. This is the case for many chronic viral, bacterial, or parasitic infections, as discussed above. There are, however, also data suggesting a beneficial effect of some persistent or latent infections in regulating host immune responses. Although there are a large number of studies supporting a negative effect of coinfection in host immunity, the lack of evidence for positive effects does not necessarily imply absence of potentially clinically unapparent beneficial combinations of coinfection. For example, during infection with the flavivirus GB virus C a clinical benefit of coinfection can be observed. GB virus C can inhibit HIV replication, and HIV-infected individuals who are coinfected with GB virus C have an almost 4-fold reduced rate of mortality (Xiang et al., 2001). Similarly, mice chronically infected with the protozoan parasite *Leishmania* were protected against subsequent bacterial challenge, potentially due to the induced splenomegaly and expansion of CD8 T cells (Polley et al., 2005).

Herpesviruses infect the majority of the human population and establish latent, life-long infections with the risk for reactivation. In a murine model of herpesviral infections, latent infection with gammaherpesvirus (γHV) or murine cytomegolovirus (MCMV) provided protection against subsequent bacterial infections with *Listeria monocytogenes* or *Yersinia pestis*, due to an increase in macrophage activation resulting from low-grade IFN-γ production (Barton et al., 2007). This protection provided by γHV was also reported for subsequent adenovirus infection (Nguyen et al., 2008). However, the benefit of γHV on subsequent infections was transient (Yager et al., 2009). These results suggest an interesting potential coevolutionary benefit of herpesviruses and their mammalian hosts. However, the stage of herpesviral infection at which the secondary pathogen is encountered could be a critical determinant of whether the bystander infection is beneficial or detrimental. During latency, γHV may provide protection against malaria. However, during acute γHV infection, morbidity and mortality of malaria infection were significantly enhanced (Haque et al., 2004). On the other hand, although there may be some benefit of γHV infection during latency, chronic low-grade inflammation from human CMV infection has been associated with increased disease progression and mortality during HIV (Emery et al., 1999), as well as with accelerated decline in immune function or immunosenescence (Koch et al., 2007). Thus, animal models support a transient beneficial effect of herpesviruses during latency; however, the exact conditions under which a similar beneficial effect may apply to humans remains to be defined.

It is not a major leap to expand these ideas to the effect of commensal microbes in host immune responses. Indeed, it could be argued that in the majority of immunocompetent humans, herpesviruses are commensals or pathobionts, resident micro-organisms that can cause disease. Extending the idea of interactions between different microbes and host immunity, there are also examples of similar effects caused by enteric bacterial flora. For example, commensal bacteria can facilitate infection by enteric viruses (Kuss et al., 2011) but have also been shown to modulate host responses to unrelated pathogens and/or help tune the innate immune system for optimal antiviral immune responses (Abt et al., 2012; Ichinohe et al., 2011; Ganal et al., 2012). In some settings, basal activation of the IFN system by commensal bacteria allowed subsequent antiviral IFN-α/β signaling to occur at optimal efficiency (Abt et al., 2012). Therefore, it appears that the mammalian immune system has evolved to use sensing of environmental microbes to maintain optimal immunological fitness and responsiveness. This ability to sense persisting microbial signals might be beneficial in some settings or detrimental in others. Understanding the precise regulation of these positive and negative effects on development and maintenance of immunity to other infections and vaccines should provide opportunities to improve treatment of chronic diseases in both the developed and the developing world.

Concluding Remarks

This review has summarized epidemiological studies of coinfection and discussed evidence of possible underlying immunological pathways altered due to bystander chronic infections. A fine balance of the inflammatory milieu may determine host responses to subsequent immunological challenges. Disrupting this balance either by decreasing basal inflammatory signals, by altering symbiotic microorganisms, or by increasing and/or altering inflammation with chronic bystander pathogenic infections can have detrimental effects on host immune responses and survival. Defining the immunological mechanisms underlying the effects of coinfections and then devising strategies to overcome these barriers to optimal immunological interventions and vaccines in coinfected populations remains a major goal.

Our current understanding is that chronic bystander infections affect immunity to unrelated pathogens and vaccines by targeting several different stages of the subsequent immune response. Though the details of such mechanisms require further investigation, it is obvious that different chronic pathogens may use diverse pathways to alter host immune responses against unrelated infections, affecting early pathogenesis and innate immune responses and/or later effector functions and adaptive immunity. One common effect of coinfections appears to be that many symptomatic chronic infections alter the initial stages of infection with an unrelated pathogen, usually due to alterations of infectivity or distribution of target cells. Unique mechanisms for different chronic infections may also exist, such as the increased ability of DCs for transinfection, induced by concomitant Mtb infection. Nevertheless, a major common theme for the effects of many coinfections is an altered host cytokine and/or inflammatory environment that can include increased or decreased cytokine production or disruption of signaling and responses to cytokines. These events, while they may differ in detail depending on the coinfection, have the potential to affect all stages of immune responses (Figure 1). However, further studies in experimental models are needed to dissect the details of how

individual chronic infections affect subsequent innate and adaptive immune responses. Given the large global population harboring pathogenic chronic infections, it is likely that developing world vaccine efforts will be improved by a deeper mechanistic and clinical understanding of the effects of coinfection on immunity to unrelated infections and vaccines.

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