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Generalized immune activation and innate immune responses in SIV infection

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Abstract

Purpose of review—Chronic immune activation is a key factor driving the immunopathogenesis of AIDS. During pathogenic HIV/SIV infections, innate and adaptive antiviral immune responses contribute to the chronic immune activation. In contrast, non-pathogenic SIV infections of natural hosts such as sooty mangabeys (SMs) and African green monkeys (AGMs) are characterized by low immune activation despite similarly high viremia. This review focuses on the role of innate immune responses in SIV infection.

Recent findings—Several studies have examined the role of innate immune responses to SIV as potential drivers of immune activation. The key result of these studies is that both pathogenic SIV infection of macaques and non-pathogenic SIV infections of natural hosts are associated with strong innate immune responses to the virus, high production of type-I interferons by plasmacytoid dendritic cells, and up-regulation of interferon stimulated genes (ISGs). However, SIV-infected SMs and AGMs (but not SIV-infected macaques) rapidly down-modulate the interferon response within 4–6 weeks of infection, thus resulting in a state of limited immune activation during chronic infection.

Summary—Studies in nonhuman primates suggest that chronic innate/interferon responses may contribute to AIDS pathogenesis. Further, the ability of natural host species to resolve innate immune responses after infection provides a novel avenue for potential immunotherapy.

Keywords

Simian Immunodeficiency Virus; SIV; Chronic Immune Activation; Innate Immune Responses; Plasmacytoid Dendritic Cells; Type I Interferon; IFNa; Interferon Stimulated Genes (ISGs)

Introduction

The nonhuman primate models of Simian Immunodeficiency Virus (SIV) or Simian/Human Immunodeficiency Virus (SHIV) infection represent the most biologically relevant and widely used animal model for HIV infection and AIDS. There are two basic types of SIV/SHIV infections, the pathogenic infection of the experimental (i.e., non-natural) Asian

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macaque hosts and the nonpathogenic infection of African natural hosts such as sooty mangabeys (SMs), African green monkeys (AGMs), and numerous others. Experimental S I V infection of macaques results in a disease characterized by high level virus replication, progressive CD4+ T cell depletion, chronic immune activation, and establishment of a mucosal and systemic immunodeficiency that closely resembles human AIDS. For this reason, pathogenic SIV infection of macaques has been used in many studies of HIV transmission, pathogenesis, prevention, and therapy that have been extremely influential in the field. In contrast, SIV infection of natural hosts is typically non-pathogenic despite robust virus replication, and results in a substantial preservation of the immune system function, lack of chronic immune activation, and a lifespan similar to SIV uninfected individuals [1–2]. An exception to the rule that natural SIV infections are nonpathogenic is the relatively understudied natural SIVcpz infection of chimpanzees that can progress to AIDS, albeit at a lower frequency than HIV-1-infected humans or SIV-infected macaques [3]. Over the past decade, many studies have investigated the factors underlying the benign nature of natural SIV infections, with numerous mechanisms proposed including (i) lack of chronic immune activation, (ii) reduced infection of central memory CD4+ T cells, (iii) preserved or enhanced immune regeneration, (iv) absence of microbial translocation, and (v) ability to mediate T helper function by CD3+CD4−CD8− T cells [1–2]. In this review, we will discuss the role of chronic, generalized immune activation as a factor discriminating pathogenic and non-pathogenic SIV infections, and analyze in detail the similarities and differences between these two models in terms of innate immune responses to the virus.

Chronic immune activation in pathogenic HIV and SIV infections

Chronic immune activation was proposed as a key determinant of AIDS pathogenesis in the late '80s/early '90s [4–6]. Shortly thereafter, Giorgi and colleagues reported that the level of immune activation, as determined by the fraction of CD8+ T cells expressing CD38, is a very strong and independent correlate of disease progression [7]. Strong support for the crucial role of immune activation in AIDS pathogenesis was then provided by studies of non-pathogenic SIV infections of natural hosts, in which high levels of virus replication are associated with low levels of immune activation [8]. The HIV-associated chronic immune activation is characterized by a constellation of immunological signs including increased frequency of lymphocytes expressing activation markers, high levels of activation-induced apoptosis, accelerated T cell turnover as measured by direct labeling, and high plasma and tissue levels of pro-inflammatory mediators (Reviewed in [9]). Importantly, these signs of chronic immune activation are clearly present during pathogenic SIV infection of macaques, thus emphasizing the relevance of this model in terms of HIV immunopathogenesis [9]. While there is a broad consensus that chronic immune activation is a consistent feature of pathogenic HIV/SIV infections and plays an important role in the pathogenesis of AIDS, there is still controversy as to what causes the HIV-associated immune activation. Factors that have been proposed to contribute to this phenomenon include (i) the direct effect of specific virus proteins (Env, Nef, Tat, etc), (ii) the generation of innate and adaptive immune responses to the virus, (iii) an ineffective regulation of antiviral immune responses; (iv) a bystander activation of T and B lymphocytes caused by increased production of pro-inflammatory cytokines (e.g., TNF-α, I L-1, IL-6, and several others); (v) the translocation of microbial products from the intestinal lumen to the systemic circulation, where they can activate the immune system by binding to certain Toll-like receptors (TLRs), and (vi) the presence of clinical or sub-clinical co-infections [10]. More recently it was proposed that preferential infection of central-memory CD4+ T cells (as opposed to effector-memory CD4+ T cells) is a factor favoring the maintenance of chronic immune activation by concentrating the bulk of antigenic load in central lymphoid tissues [2]. Regardless of the mechanisms responsible for its establishment, chronic immune activation is thought to disrupt CD4+ T cell homeostasis and overall immune function by several mechanisms

including: (i) increased number of available target cells for the virus (i.e., activated CD4+ T cells), (ii) exhaustion of antiviral CD8+ T cells, (iii) excessive lymphocyte apoptosis, (iv) suppression of T cell regeneration, (v) accelerated proliferative senescence of lymphocytes, and (vi) disruption of the lymphoid tissue niche necessary for the proper functioning of naive and central-memory T cells [10–11].

In the following sections of this article we will focus on the potential role of innate antiviral immune responses as key mediators of the chronic immune activation associated with pathogenic SIV infection of macaques, and how rapid regulation of these responses may be responsible for the low immune activation found in the chronic phase of infection of natural SIV hosts.

Innate immune responses in SIV-infected Asian macaques

The role of the innate immune response to HIV has been the subject of intense study over the past few years. In SIV-infected macaques, recent reports have examined the role of specific innate leukocyte subsets and/or effector molecules (macrophages, NKT cells, γδ T cells, defensins, etc). Here we will mainly discuss the contribution to AIDS pathogenesis of the axis of innate antiviral immunity represented by plasmacytoid dendritic cells (pDCs), type I interferon production, and up-regulation of interferon stimulated genes (ISGs). In both humans and non-human primates, pDCs represent ~0.2–0.5% of total peripheral blood mononuclear cells and are identified phenotypically as Lineage-HLADR+CD123+/BDCA2+ and functionally as producing type I IFNs (α,β) as well as a number of pro-inflammatory cytokines and chemokines (i.e., TNFα, IL-6, CXCL10, CCL4, and CCL5) [12]. It should be noted that BDCA2 is not commonly used to define pDCs in macaques due to poor cross-reactivity of reagents, but has been used successfully in other NHP species. Importantly, pDCs express high levels of two key Toll-like receptors, TLR7 and TLR9 [13–15], that mediate the response to viral ssRNA and DNA, respectively, with the production of type I IFNs in response to TLR-7/9 stimulation being dependent on the phosphorylation and nuclear translocation of the transcription factor IRF7 [16]. Upon activation *in vivo*, pDCs upregulate CCR7 and CD62L, migrate to lymph nodes, and mature into typical antigen-presenting cells [17–18]. While pDCs are not the only cell type capable of producing type I IFNs, most studies indicate that they are the key cells that dictate the tempo and magnitude of the *in vivo* type I IFN response to a viral infection.

In HIV-infected humans, the observations that pDC are both depleted and dysfunctional when compared to uninfected controls led to the formulation of a model in which pDCs contribute to the immune control of HIV via their ability to induce antiviral responses and augment CTL and NK responses [19]. The longitudinal kinetics of pDC levels were more rigorously defined in SIV-infected macaques, in which these cells increase rapidly in blood during the first few days of infection, then rapidly decline to levels ~50% of baseline by the time of peak viremia (days 10–14 post infection) and remain reduced throughout the chronic phase of SIV infection [20–24]. Of note, the SIV-associated decline of circulating pDCs is associated with increased levels of these cells in lymph nodes [22–25]; however, it remains unclear whether this increased pDC homing to lymph nodes persists during the chronic phase of SIV infection [21–24]. Collectively, these studies of pDCs in SIV-infected macaques appeared to support the model in which these cells play a protective role against disease progression.

Several recent findings, however, have suggested that pDC activation and type I interferon responses may not be wholly beneficial to the HIV/SIV infected host and, in fact, may be detrimental by promoting immune activation and/or bystander apoptosis. First, the observation that ISGs are upregulated during chronic SIV infection of macaques indicated

that even though pDCs are partially depleted from the blood and/or lymph nodes, they (or complementing cell types) are able to promote strong type I interferon responses [26–28]. Second, in vitro and ex vivo studies have shown that HIV-activated pDCs may acquire the ability to induce apoptosis of CD4+ T cells via a TRAIL/DR5 dependent mechanism [29–30]. Third, stimulation of human pDCs with HIV RNA induces the production of indoleamine 2,3 dioxygenase (IDO), thereby promoting the differentiation of T regulatory cells, thus potentially suppressing a number of antiviral immune responses [31]. Fourth, acute SIV infection is associated with significant migration of pDCs to the intestinal mucosa, where these cells persist throughout the chronic phase of infection in association with high levels of local immune activation [32–34]. A recent report has suggested that during SIV infection pDCs are depleted to near absolute levels in SIV infected macaques and, therefore, could not contribute to immunopathogenesis [35]. In this regard, the observations that pDCs localize in the gut after infection are particularly important because they indicate that (i) the depletion of pDCs from peripheral blood during SIV infection is likely due to mucosal retention, rather than to a net loss of pDCs due to cell death, and (ii) pDCs remain in the gut well into chronic infection and cannot be ruled out as candidate drivers of immune activation. Finally, as discussed in detail in the next section, natural SIV hosts display robust pDC activation and interferon production during acute SIV infection that is rapidly resolved upon the transition to chronic infection (reviewed in [36]). In light of these data, and in combination with recent human studies demonstrating chronic activation and dysregulation of pDCs in HIV infection [37–39], an alternative model has been proposed by several investigators in which pDCs and/or the type I interferon response may represent a major cause of immune activation and immunopathogenesis during pathogenic HIV and SIV infections [40–41].

Innate immunity in non-pathogenic SIV infection of African natural hosts

The role of innate immune responses to SIV during non-pathogenic infections of SMs and AGMs has been the subject of several recent studies aimed at testing the hypothesis that attenuated innate immunity to the virus is responsible for, or at least associated to the low levels of immune activation observed during the chronic phase of these infections. In this regard, all published works indicate that, despite robust virus replication, the key markers of innate immune activation, such as production of type I interferons by pDCs, up-regulation of ISGs, and activation of macrophages and natural killer cells, are not elevated during chronic SIV infection of natural hosts [25,42–47]. A number of hypotheses have been proposed to explain this intriguing phenomenon, including an intrinsic defect in the ability of pDCs to respond to Toll-like receptor (TLR)-7 and 9 signaling, the presence of active inhibitory mechanisms (acting either at the level of pDCs or through cross-talk with other cell types), and changes in the maturation and/or trafficking of these cells that limit their interaction with viral products (reviewed in [10]).

The possibility that innate immune responses to SIV are intrinsically deficient in natural SIV hosts was proposed by Mandl et al. based on a comparative *in vitro* study of pDC function in SMs and macaques [25]. This study described a reduced production of IFNα protein levels in response to TLR-7 and -9 stimulation of SM pDCs when compared to the same cells of macaques [25]. These authors concluded that divergent TLR-7 and -9 signaling was present in macaques compared to SMs, even though a similarly strong upregulation of type I IFN mRNAs in response to inactivated SIV was observed in both species [25]. More recently, several independent *in vivo* studies conducted using different groups of animals have more reliably assessed the dynamics of innate immune responses to SIV in natural hosts using various combinations of high-throughput genomic analysis, multiparametric flow cytometry, detection of plasma levels of cytokines, and immunohistochemistry [42–47]. These studies have conclusively shown that, in both pathogenic infections of macaques and non-

pathogenic infections of SMs and AGMs, the acute phase of SIV infection is associated with a robust innate immune response to the virus. This response involves major changes in the transcriptome consistent with activation of the innate immune system, including a massive up-regulation of ISGs in both peripheral blood and lymphoid tissues [42–45]. Consistent with these observations is the fact that high levels of IFN-I-producing pDCs can be detected by immunohistochemistry in the lymph nodes of SIV-infected SMs and AGMs during acute infection [46]. This large set of *in vivo* studies indicates that an intrinsic deficiency of pDCs to stimulate a strong type-I IFN-mediated response to the virus is neither a feature of natural SIV infections nor a requirement to reach a state of non-pathogenicity.

Importantly, a key difference between pathogenic SIV infection of macaques and non-pathogenic SIV infection of natural hosts is that the latter resolves the widespread expression of innate effector molecules during the post-acute phase of infection (i.e., by day 30–45 post-infection) [42–43], reviewed in [48]. The observed similarities in the overall pattern of SIV-induced transcriptional changes in SMs and AGMs suggest a common evolutionary pathway of disease resistance in natural hosts that relies on the active regulation of an otherwise normal innate immune response to the virus [36]. In stark contrast, SIV-infected macaques maintain their elevated expression of innate immune response genes, including ISGs, throughout the chronic phase of infection [42–43]. The observation of chronically high levels of ISGs in SIV-infected macaques is consistent with the finding of high levels of ISG mRNAs during chronic HIV infection in humans [49–50]. In addition, recent work characterizing the transcriptomes of a rare population of chronically HIV-infected humans that do not exhibit CD4+ T cell depletion despite plasma viremia exceeding 100,000 RNA copies/ml demonstrated remarkable overlap with those of sooty mangabeys, including a reduced ISG response compared to patients with a rapid progressor phenotype [51]. Collectively, these comparative studies of innate immune responses during pathogenic and non-pathogenic SIV infections delineate a model in which natural SIV infections are characterized by a robust and extensive innate immune response to the virus that—in contrast to pathogenic infections—resolves during the transition from acute to chronic infection despite ongoing virus replication (Figure 1). This model of immune resolution also suggests that active immune regulatory mechanisms are responsible for the low immune activation of chronically SIV-infected SMs and AGMs. While resolution of the pDC/interferon response was reported by multiple groups, the mechanism by which natural hosts arrest IFNα production despite persistent virus replication remains a key unanswered question. Several recent studies detailing virus/DC interplay at the cellular level provide intriguing potential mechanisms by which natural hosts may halt the interferon response (summarized in Figure 2) including: (i) active immunoregulatory mechanisms; (ii) restriction of infection of DCs [57]; (iii) reduced DC trafficking to mucosal tissues [32–33]; (iv) desensitization/maturation of pDCs [39]. Consistent with a mechanism of immune regulation is the observation that the return to baseline expression levels of innate immunity genes in SIV-infected SMs is temporally coincident with a marked up-regulation of immune regulatory genes such as IDO and ADAR [42]. An intriguing, non-mutually exclusive possibility is that the rapid regulation of pDC- and type I IFN-mediated responses in SIV-infected SMs is related to the low levels of virus replication in the central-memory CD4+ T cells of these animals [58]. Further studies will hopefully elucidate the role of these and other immunomodulatory factors in determining the low immune activation state of chronically SIV-infected SMs and AGMs.

Conclusion

The role of innate immunity and chronic immune activation in the immunopathogenesis of AIDS has been recently investigated by comparative studies of experimental, pathogenic SIV infection of Asian macaques and natural, non-pathogenic SIV infection of African non-

human primates. These studies have shown that both pathogenic and non-pathogenic SIV infections are characterized by a robust innate immune response to the virus. However, this response is transient in natural hosts, but persistent in Asian macaques, thus suggesting that this down-regulation of innate immunity may protect SMs and AGMs from chronic immune activation and progression to AIDS. Importantly, it is hoped that further elucidation of the genes and molecular pathways involved in maintenance of a state of low immune activation in chronically SIV-infected SMs and AGMs will identify targets for therapeutic interventions aimed at limiting or abrogating the aberrant immune activation that is associated with HIV infection in humans.

Key points

- The role of innate immunity and chronic immune activation in AIDS pathogenesis has been recently investigated by comparative studies of pathogenic SIV infection of macaques and non-pathogenic SIC infection of sooty mangabeys and African green monkeys.
- During pathogenic SIV infection, innate immune responses to the virus may favor the immune-mediated control of virus replication, but also act as immunopathogenic mechanisms by mediating the chronic immune activation/inflammation that characterizes this infection.
- Both pathogenic and non-pathogenic SIV infections are associated with robust innate immune responses, significant plasmacytoid dendritic cell activation, and massive type I IFN stimulated genes (ISG) up-regulation during the acute phase of infection.
- In natural, non-pathogenic SIV infections the innate immune response to the virus is dramatically reduced during the transition between the acute and the chronic phase of infection.

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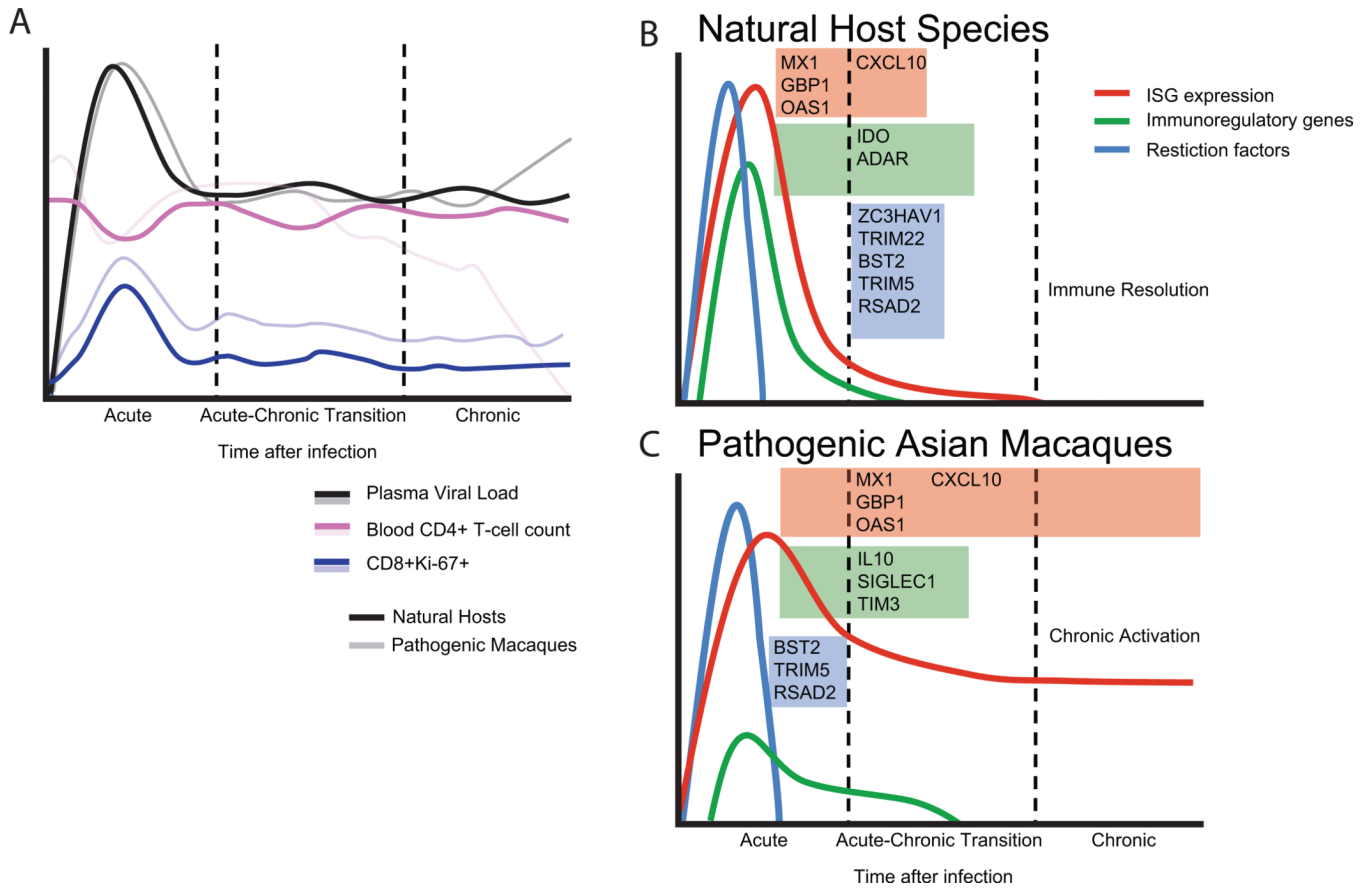

Figure 1. Transcriptional profiles of pathogenic and nonpathogenic SIV infection

(A) Virological and immunological parameters of prototypical SIV infection in natural host species contrasted with pathogenic infections. Solid lines denote natural hosts, transparent lines depict macaque species. Kinetics of viral loads are similar between species. In general, natural hosts do not undergo rapid peripheral CD4+ T lymphocyte depletion as observed in macaques; it should be noted that in a handful of natural hosts, CD4+ depletion has been observed in the absence of disease [52–53], and that long term SIV infection of sooty mangabeys is associated with a gradual, although clinically benign, decline of blood CD4+ T cells [54]. Immune activation as assessed by peripheral blood CD8+Ki67+ levels occurs in both animals during acute SIV infection [55–56], but returns to near-baseline levels after infection, in contrast to macaque species, which remain elevated. Transcriptional regulation in (B) natural host and (C) macaque species during SIV infection. Both species have massive upregulation of interferon stimulated genes (ISGs) during acute infection (depicted by red lines); during the transition to chronic phase the ISG response resolves in natural hosts but is maintained indefinitely in macaques. mRNAs for multiple restriction factors (blue lines) are present in blood during acute infection of both species but decline rapidly. Genes associated with negative regulation of the immune response (green lines) are expressed differentially between species.

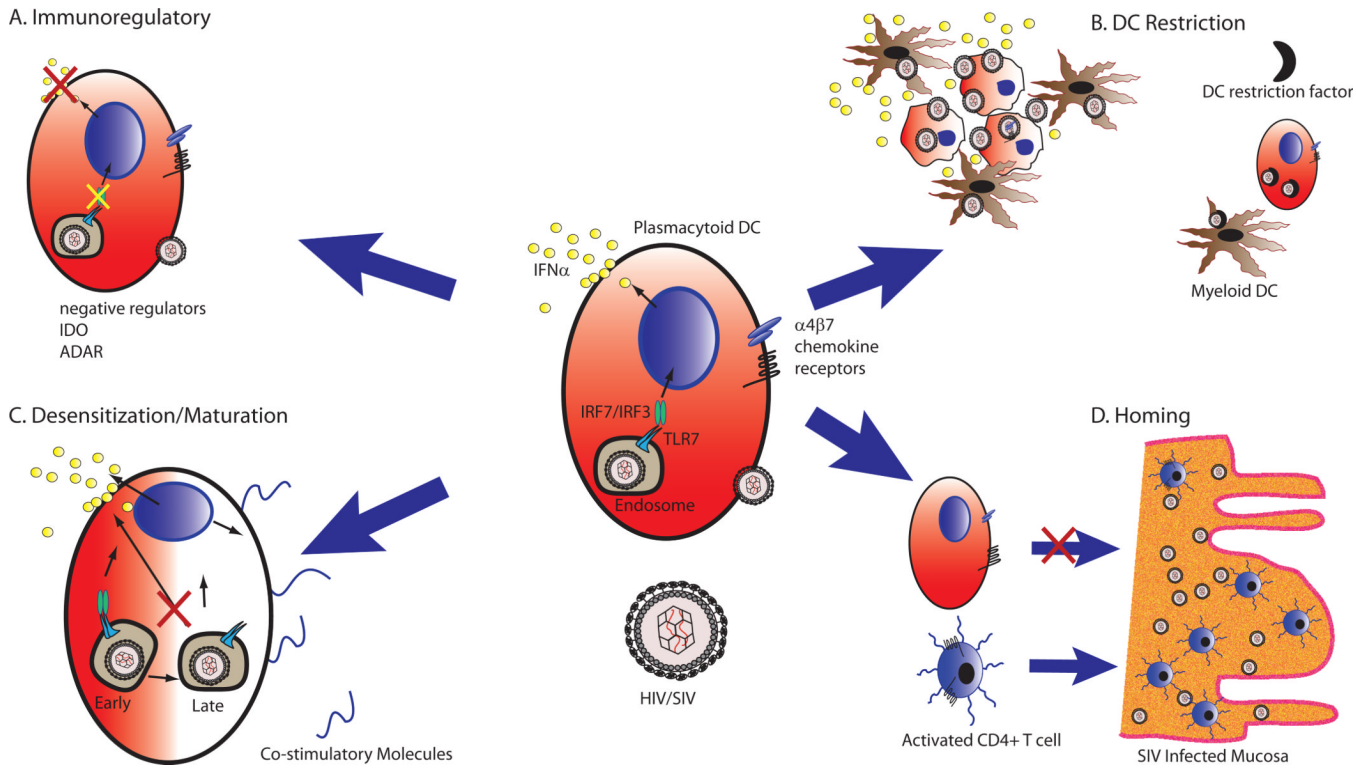

Figure 2. Potential mechanisms of resolution of ISG response in natural hosts during SIV infection

CD123+ Plasmacytoid DCs are the primary producers of IFNα in LNs of SIV-infected RMs, AGMs and SMs [46]. During chronic infection, pDCs in natural host species stop producing IFNα, concurrent with the resolution to baseline of ISG expression, despite continued high level viremia. Possible mechanisms by which the resolution occurs are (A) Immunoregulatory: transcript profiling data demonstrated elevated expression of immunomodulatory proteins such as ADAR and IDO in SMs; alternatively negative regulation of IFNα production in pDCs by ITAM mediated pathways has been demonstrated in mice, but data are lacking in the context of pDC/HIV interactions. (B) DC-specific HIV Restriction: Recent data has demonstrated that productive infection of DCs by HIV is blocked by an uncharacterized restriction factor [57]; circumvention of DC restriction yields a high level of virus production and secretion of Type I IFNs. During acute infection there is widespread induction of restriction factors, and inhibition of DC infection may remove the nidus for IFNα production. (C) Reduced mucosal homing - pDCs in natural hosts have attenuated recruitment to vaginal and rectal mucosa in comparison with macaques during chronic infection. Lowered gut homing may reduce pDC exposure to sites of high level virus replication, and limit their potential for driving immune activation in mucosal lymphoid tissue. (D) Dysregulated pDC Desensitization/Maturation - Recent work has shown that HIV, unlike other viruses recognized by pDC TLRs, signal predominately in early endosomes, resulting in partially mature pDCs that have a continual ability to make IFNα and poor expression of costimulatory molecules[39]. pDCs in natural hosts may have altered interactions with SIV that allow for full maturation and cessation of interferon production.