Dynamics of innate immunity are key to chronic immune activation in AIDS

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Abstract

Purpose of review—We propose here that the dynamics rather than the structure of cellular and viral networks plays a determining role in chronic immune activation of HIV infected individuals. A number of novel avenues of experimental analysis and modeling strategies is discussed to conclusively address these network dynamics in the future.

Recent findings—Recent insights into the molecular dynamics of immune activation and its control following SIV infection in natural host primates has provided possible alternate interpretations of SIV and HIV pathogenesis. Concomitant with insights gained in other host-pathogen systems, as well as an increased understanding of innate immune activation mechanisms, these observations lead to a new model for the timing of innate HIV immune-responses and a possible primordial role of this timing in programming chronic immune activation.

Summary—Chronic immune activation is today considered the leading cause of AIDS in HIV-infected individuals. Systems biology has recently lent arguments for considering chronic immune activation a result of untimely innate immune responses by the host to the infection. Future strategies for the analysis, comprehension, and incorporation of the dynamic component of immune activation into HIV vaccination strategies are discussed.

Keywords

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1. Introduction

Despite prodigious efforts, the definition of an effective HIV vaccine has only made modest progress [1, 2]. Currrent strategies aim at establishing and/or amplifying both innate and adaptive immune responses [3••]. The central idea being that HIV evades efficient, durable recognition by the human immune system and that therefore a successful vaccination strategy needs to provide for such increased recognition by presetting a humoral immune response [4, 5••]. Similarly, AIDS resistance in SIV natural host primates has been formerly believed to be caused by a lack of innate and adaptive immune activation (IA) contrary to Asian and New World non-human primates (NHPs) which develop AIDS following SIV or HIV infection. Recently, four comparative systems biology studies have shown independently and remarkably concordantly that just like AIDS progressors, natural hosts stage a comparable, in magnitude and composition, innate immune response to SIV infection [6••,7••,8••,9••, see also: 10•]. The major difference in SIV responses between AIDS progressors and non-progressors in NHPs is the duration of this innate response which is attenuated in natural hosts and becomes chronic in AIDS progressor species [11, 12•, 13, 14••, 15, 16]. It is hence the control of excessive immune activation, rather than absence of immune activation, which protects natural hosts from developing AIDS. Importantly, natural host primates tolerate comparable levels of SIV particles in their system which in progessor-species lead to AIDS [6••,7••,8••, 9••, 17]. It is thinkable that protection from AIDS in humans could be achieved by similarly establishing HIV tolerance as opposed to attempts to eradicate the virus from the body [10•, 14••, 15, 16, 18•, 19]. Hence, rather than boosting immune responses, vaccine strategies might want to explore shielding HIV from chronic immune recognition. Furthermore, it should be considered that humans, with the possible exception of longterm non-progressors (LTNPs) and elite controllers [20, 21], and similarly to Asian and New World non-human primates, also stage effective innate immune responses during the acute phase of HIV infection and that only the absence of attenuation/control of this innate response leads to chronic IA and thus AIDS. The current hypothesis of how attenuation or control of IA is established in natural hosts is the presence of active signaling to attenuate IA in natural hosts which would not be present/active in progressors species, or, alternatively, the presence of active signaling to promote continued AI in progressors and being absent in natural hosts [14••, 16]. The molecular, longitudinal profiles of transcriptional responses in AIDS progressors and non-progressors are currently being scrutinized in order to identify such signaling events, and it will be of outmost interest, also beyond the field of HIV research, to see whether candidate pathways to control or promote chronic IA can be identified [10•, 14••, 16, 22, 23]. Here, we discuss an alternate hypothesis for the absence of chronic IA in natural hosts which is based on a purely dynamic interpretation of the events following viral infection in general. While being, given the limited number of available studies, currently only modestly carried by direct experimental observations, this hypothesis not only has the benefit of simplicity, if true, it also would call for a very different approach for HIV vaccine development

2. The West Coast Model for IA

Rather than building the hypothesis we want to discuss here from different arguments, we put upfront a simplified model, and then discuss the evidences that are in support or argue

against this proposition (Figure 1). Assume for the sake of argument that acute viral infection be a wave at the beach, let further immune activation be symbolized by mounting a surf-board. Mounting your board too late (case I) will lead to slow sinking; mounting too early (case II) will get you washed away; only the right timing will let you surf (case III). Note that case I can also lead to case II if a second wave approaches. We propose this model as indeed a relevant way to look at viral infections: SIV-infected NHPs and HIV-infected human AIDS progressors would thereby mount their innate immune response too slow or rather too late leading to an inconclusive situation and thus chronic 'waiting' for something already gone by. This unresolved innate IA wears down the system and leads consequently to 'sinking' (in AIDS: decline in CD4+). Other viruses such as Ebola family viruses elicit such rapid (early) and massive innate IA leading to devastating break-down of the entire immune system (case II) [24, 25, 26, 27, 28]. Finally, natural hosts for SIV, such as sooty mangabeys, African green monkeys, and mandrills display timely responses to infection leading to resolution of IA and long-term tolerance of the virus (surfing).

Several, however yet inconclusive, arguments can be made in support of such an hypothesis: SIVagm is elite controlled in macaques. Despite triggering a strong innate IA apparently comparable to the IA in AGMs, SIVagm leads to adaptive immunity in RM demonstrating that acquired immunity against SIVagm is possible [29••]. Why does this not happen in AGMs themselves? Two options: (i) no can, (ii) no need. The latter is more likely and favored here. In AGMs the innate IA is resolved and the adaptive IA is likely not even triggered, which leads to persistent presence of the virus, however, without sufficiently significant consequences to the organism to be selected against. Another interesting question arises: Why are RMs capable of elite controlling SIVagm but not SIVmac? A possible explanation would be that SIVagm, unlike SIVmac, is not subjected to selective evolutionary pressure to evade adaptive immunity as its natural host does not stage an adaptive immune response. Comparative transcriptome profiling between SIV infected natural hosts and progressors has unrevealed a lag-time of IFNγ (as proxy for innate IA) signaling in progressors [6••]. This lag-time (≈6 days) might, however, be due to different effective doses of infection and different amplification kinetics of the SIVagm and SIVmac viruses in the respective species. On the other hand, only a ≈2 days lag can be justified when investigating the SIV amplification kinetics and measured viral titers. Hence, these experiments might provide the first direct evidence of differential activation kinetics for the innate IA fitting above model. Finally, a purely theoretical argument can be made in favor of the hypothesis. Timing of innate IA in this model would be an inherent property of the system and thus not require any dedicated signaling pathways or switches. In humans, it might thus turn out that the absence of an effective adaptive immune response is not *per se* a problem, but that rather inconclusive (case I) innate IA leads to chronic triggering as seems to be the case in non-human primate AIDS progressors. A mechanisms, where the rapid innate immune activation in AGMs and other natural hosts is presetting its proper attenuation to avoid chronic immune activation, is reminiscent of kinetic or conformational proofreading in molecular discrimination [30]. Interestingly, T-cell receptors use kinetic proofreading to enhance discrimination of *bona fide* ligands from other proteins to ensure correct signaling [31], and kinetic proofreading could well be at the basis of RIG-I or TLR mediated recognition of foreign in innate immunity [32••, 33, 34]. Kinetic proofreading

allows, through expenditure of energy, to increase discrimination of *bona fide* ligands or interaction partners from closely related molecules with modestly different free energies of binding. It has been first proposed based on theoretical grounds and later demonstrated to be the mechanism by which aminoacyl tRNA synthetase operates [30, 35]. Proposing a mechanisms reminiscent of kinetic proofreading for the coupling between innate and adaptive immunity is appealing as it combines simplicity with fidelity. Thereby, innate IA, with its obvious role of identifying foreign from self, would in the same time serve as a guard against inappropriate initiation of adaptive immunity by being a signal amplifier or dampener where appropriate. In other words, the energy spent on the innate IA increases the capacity of adaptive immunity to increase selectivity. This would require strong coupling between both processes, which is increasingly recognized to be the case. In the case of HIV and SIV infection in AIDS progressors the West Coast Model would thus predict that despite an strong activation of innate immunity, the innate IA remains inconclusive with respect to the function of providing sufficient strong recognition as non-self and triggering adaptive immunity (Figure 2). While innate IA continues to be triggered through the presence of virus, it never reaches the threshold required to trigger subsequent adaptive IA leading to chronic, inconclusive activation. In natural hosts, SIV triggers innate IA and reaches an apparently conclusive situation of non-recognition as foreign and consequent auto-inhibition/attenuation. Despite stimulation of innate IA, SIV is thus not triggering a productive immune response and a equilibrium of co-existence between virus and host emerges. This model thus predicts either better discrimination between inoffensive and foreign by innate immunity in natural hosts. From this follows that for some recognition/binding event during innate IA the difference in free energy is increased when compared to AIDS progressors. A greater free energy will result in a more rapid and earlier activation kinetic of innate IA, and is thus in agreement with the hypothesis developed here.

3. Propositions

If one considers the West Coast Model for IA a relevant hypothesis in the context of HIV/AIDS research, a new way of approaching HIV vaccine strategies needs to be considered. As a first measure, however, one would want to investigate some of the stronger hypotheses generated by the model experimentally [36•, 37, 38]. A much higher time-resolved investigation of the innate IA in progressors and non-progressors before peak-viremia using functional genomics and proteomics tools would allow to directly establish IA kinetics and compare them. The SIVagm infection of RMs thereby would be a key control system [29••], as the model would predict that elite control in this system requires rapid, conclusive innate IA compared to a RM response to SIVmac. Appropriate modeling tools would provide for a definitive answer on whether the time-lag is linked to the virus [39] or the host [19], the latter being favorable with respect to the model. Can one cause AIDS in natural hosts by delaying or dampening the innate IA following SIV infection? Current experimental vaccination strategies focus on developing protection in AIDS-progressors. It might be very difficult to find products that would accelerate rather than only amplify innate immune activation and thus very difficult to test present hypothesis this way. On the other hand, delaying innate IA in natural hosts would lead by current model to AIDS in these species, and thus would equally well proof the concept [40••, 41••]. Tampering with innate IA

kinetics in non-human primates, however, might be out of reach in both scenarios as this might require reprogramming epigenetic control [42•]. The only viable strategy would hence rely on generating reassortant viruses between for instance SIVagm and SIVmac in order to identify the components of the virus that more efficiently trigger innate IA in natural hosts than in progressor species [39, 43, 44•]. As a corollary, it would be interesting to see whether or not SIVagm lost selective evolutionary pressure to evade adaptive immunity [44•]. As SIVagm is elite controlled in RMs such an analysis might provide additional insights into the model presented here [29••].

4. Conclusions

The works reviewed here have established that: (i) SIV infection is accompanied by innate IA in AIDS progressors and nonprogressors. (ii) Innate IA does not necessarily lead to adaptive immunity in AIDS progressors or non-progressors with the apparent exception of SIVagm infection in macaques. SIVagm might be a truly exceptional case where the virus is no longer under selective pressure to evade adaptive immunity as its natural host never triggers adaptive immunity. HIV and SIV other than SIVagm either evades successfully adaptive immunity, or adaptive immunity is never triggered in humans and AIDS progressor primates. (iii) Innate and adaptive immunity are tightly linked, the former being an activator of the latter [45•, 46, 47, 48•, 49••]. (iv) Innate IA continues until the trigger (here: virus) is cleared from the system or it is actively attenuated as must be the case in natural hosts and possibly in human LTNPs. (v) Viral load at peak viremia is correlated with outcome in AIDS progressors including human and natural hosts provided they were infected with low, more physiological doses of virus. It can furthermore reasonably be assumed that: (i) HIV infection will cause innate IA in humans. (ii) Humans other than LTNPs could similarly as LTNPs and natural hosts live with the high viral titers observed in chronically infected individuals provided innate IA is attenuated and chronic IA avoided. (iii) Innate immunity does not only serve as first line of defense but also is a driver of adaptive immunity and thereby could serve as a proofreading mechanism to avoid, together with regulatory T-cell signaling, IA for self or non-harmful agents. (iv) Attenuation of innate IA might result from active signaling (or discontinuation thereof), or, be an inherent feature of the activation process itself. Indeed, the easiest way of controlling activation is a direct feed-back circuit which likely would be coupled to viral amplification kinetics. Combining above we propose:

- Innate immune activation obligatorily follows SIV/HIV infection.

- Innate IA is not actively attenuated via a distinct signaling event in natural hosts, but sufficiently early to reach a kinetically encoded set-point, which probably, but not necessarily, is distinct from viral set-point. IA is thus autoattenuated following a mechanism likely reminiscent to kinetic proofreading.

- AIDS progressors display too late (with respect to peakviremia) innate IA to ever reach this set-point.

- Anything beyond set-point is without relevance to the system as AIDS non-progressors will not develop chronic IA and progressors can no longer avoid chronic IA [50••].

- The question of whether an adaptive immune response can be mounted against HIV/SIV is irrelevant and should no longer be focus of vaccine research strategies [3••, 4, 48•, 51•].

- Accelerating innate IA in AIDS-progressors will lead to protection from AIDS, decelerating innate IA in natural hosts will cause AIDS.

In conclusion, we might want to start to understand and manipulate the kinetics of innate immune activation. And yes, we all three do enjoy a good surf on the West Coast, whether that be in the U.S. or in France.

Acknowledgments

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Key points

A. Innate IA is not actively attenuated via a distinct signaling event in natural hosts, butsufficiently early to reach a kinetically encoded set-point leading to auto-attenuation.

B. Auto-attenuated thus follows a mechanism reminiscent to kinetic proofreading.

C. AIDS progressors display too late (with respect to peak-viremia) innate IA to ever reach this critical set-point.

D. Anything beyond set-point is without relevance to the system as AIDS non-progressors willnot develop chronic IA and progressors can no longer avoid chronic IA.

E. The question of whether an adaptive immune response can be mounted against HIV/SIV isirrelevant for the design of a preventive vaccine.
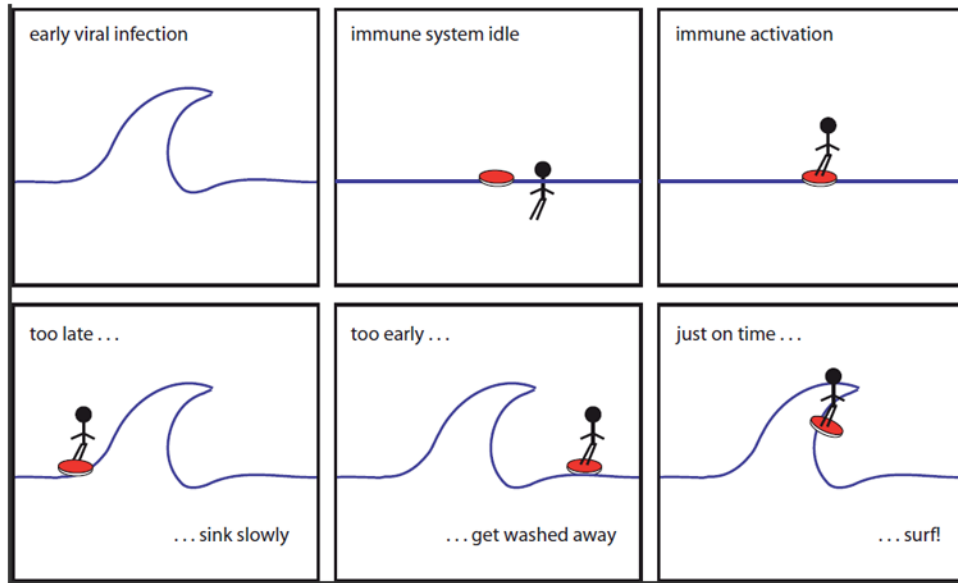
Figure 1.

The West Coast Model for IA. From left to right, top to bottom. Let *acute viral infection* be a wave at the beach, let further *mounting your surf-board* be symbol for IA. Then, as every surfer knows, mounting your board too late (case I) will lead to slow sinking; mounting too early (case II) will get you washed away; only the right timing will let you surf (case III). Note that case I can also lead to case II if a second wave approaches. We propose this model as indeed a relevant way to look at viral infections: SIV-infected NHPs and HIV-infected human AIDS progressors would there by mount their innate immune response too late leading to an inconclusive, chronic situation and consequently sinking (here: decline in $CD4^+$). Other viruses such as Ebola family viruses elicit such rapid (early) innate IA leading to devastating breakdown of the entire immune system (case II). Finally, natural hosts, such as sooty mangabeys, African green monkeys, and mandrills for SIV-infection display timely responses leading to tolerance of the virus (surfing).
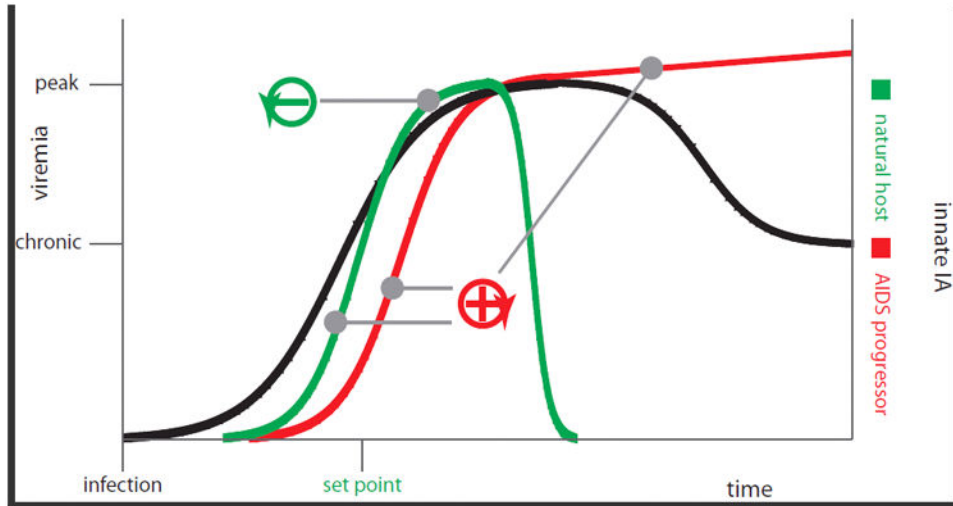
Figure 2.
Is the coupling between innate and adaptive IA reminiscent of kinetic proofreading? Innate immune activation obligatorily follows SIV/HIV infection. It is not actively attenuated via a distinct signaling event in natural hosts, but sufficiently early to reach a kinetically encoded set-point and thus autoattenuated. AIDS progressors display too late (with respect to peak-viremia) innate IA to ever reach this set-point. Anything beyond IA set-point is without relevance to the system as it can no-longer reach the auto-attenuation signal