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The race between infection and immunity – how do pathogens set the pace?

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Infection is often referred to as a race between pathogen and immune response. This metaphor suggests that slower growing pathogens should be more easily controlled. However, a growing body of evidence shows that many chronic infections are caused by failure to control slow growing pathogens. The slow growth of pathogens appears to directly affect the kinetics of the immune response. Compared with the response to fast growing pathogens, the T cell response to slow pathogens is delayed in its initiation, lymphocyte expansion is slow and the response often fails to clear the pathogen, leading to chronic infection. Understanding the 'rules of the race' for slow growing pathogens has important implications for vaccine design and immune control of many chronic infections.

The race

The classic paradigm of the “race between infection and immunity” is one of the cornerstones of undergraduate immunology, and one of the basic tenets of vaccination [1]. Many pathogens can grow extremely fast, doubling every hour in the case of some bacteria, and every 2-3 hours in the case of influenza virus [2]. By contrast, T cells can divide only every 5-6 hours [3]. During primary infection, antigen-specific T cells have a very low precursor frequency, and cells undergo extensive division and differentiation to produce an ‘effector’ response. During this early phase of infection the relatively slow division time of lymphocytes means that they might be ‘outrun’ by fast-replicating bacteria or viruses. The ultimate control and elimination of infection occurs as the immune response ‘catches up’ to the pathogen and mediates clearance. Within the context of this ‘race’, vaccination is thought to give the immune system a ‘head start’ so it can control infection more quickly.

The race metaphor for infection would seem to predict that slowly growing pathogens should be more easily controlled by the immune system. However, many slow pathogens appear, paradoxically, to be associated with chronic persistence of infection. For example in monkey models of HIV [4] and in hepatitis C virus (HCV) infection [5], the virus doubles only every ~10 hours. In hepatitis B virus (HBV) infection, growth is even slower, as the virus doubles as slowly as every 2-3 days [6,7]. Growth of tuberculosis (TB) and trypanosomes is similarly slow, with doubling times of 28 hours [8] and >18 hours [9,10] respectively. Since these pathogens divide much more slowly than lymphocytes are able to do, why doesn’t the immune system just ‘outrun’ these

pathogens? It seems that there are a number of features of this 'slow' race that impair the outcome (summarized in Figure 1).

Slow out of the blocks:

The early stages of CD8⁺ T cell activation can be extremely rapid, and activation has been detected as early as 6 – 8 hours after infection when it involves direct inoculation of high doses of virus [11]. In animal models of acute infection such as Listeria, lymphocytic choriomeningitis virus (LCMV), and influenza virus infection, rapid T cell growth is detected by day 3 - 6 post-infection, and thereafter cell numbers double every 5-6 hours. Despite the ability of T cells to respond rapidly to these fast growing infectious agents, with slowly growing pathogens there is often a significant delay before activation and expansion are evident. For instance in monkey models of HIV infection, there is a delay of around 10 days before virus-specific CD8⁺ T cell numbers begin to rise [4,12]. This delay occurs even in vaccinated animals, and the delay in T cell activation coincides with a failure of vaccine-induced cells to control early viral growth [4]. This delay is not limited to HIV, as a similar delay in T cell activation is seen with other slow growing pathogens, such as HBV[13], HCV [14,15], TB [8,16-18], Salmonella [19], toxoplasma [20], and Trypanosoma [9,21,22] infection.

Delayed antigen presentation:

How does slow pathogen growth lead to delayed T cell activation? Initial T cell activation requires antigen presentation by dendritic cells (DC) [23]. So it is not simply the number of infected cells that is crucial, but the level of antigen presentation by DC. The DC themselves require not just the presence of antigen, but also activation, migration

to lymph node, and maturation. This DC activation and maturation is usually driven by innate immune recognition of the pathogen and / or tissue damage in early infection. Studies of the kinetics of antigen presentation in early infection demonstrate that the number of antigen presenting cells (APC) increases in early infection, and that this increase coincides with the peak period of lymph node swelling [24]. In influenza virus infection in mice, lymph node swelling and APC production don't get underway until ~24 hours after infection [24,25]. This seems related to the time taken for virus to proliferate to high levels and / or begin to cause tissue damage in influenza infection. For example, lymph node swelling and antigen presentation can be seen significantly earlier when high levels of herpes simplex virus are directly injected into the footpad [11,24,25]. This suggests that a certain level of virus or tissue damage is needed to trigger innate immune responses, lymph node swelling and DC recruitment. Likewise, recent studies comparing T cell activation and bacterial numbers in the lymph node during TB infection have suggested that a 'threshold' level of bacteria is required for T cell activation [16]

If innate immune activation requires a certain level of pathogen or tissue damage to be triggered, this level will be reached later with slow pathogens. In addition, pathogens such as *M. tuberculosis* have a relatively inert cell wall compared to more acute infections such as *Listeria*, and thus for equivalent bacterial numbers would be expected to elicit much less inflammation (and thus less lymph node cell recruitment and APC production). This is clear in infections like TB and HIV, where slow, non-tender lymph node swelling is seen. Other slow pathogens such as a cytomegalovirus have mechanisms

that directly block DC recruitment [26]. In addition to this, many pathogens prevent presentation of their antigens on MHC molecules by directly interfering with antigen processing and presentation pathways [27]. Thus, slow pathogen growth, weak stimulation of innate immunity, and specific mechanisms to inhibit antigen presentation may work in concert to delay and reduce the production of APC.

A 'threshold' level of antigen presentation to activate T cells.

An individual T cell requires a minimum density of peptide-MHC on the surface of an APC to be activated [28]. In vivo, the T cell population may also require a minimum number of APC to ensure that all precursors have a high probability not only of being activated, but also of continuing to receive further stimulation during clonal expansion [29]. If such a threshold number of APC is required, the rate at which APC are produced will be an important factor in determining the timing of T cell activation. Studies of APC recruitment in acute infection demonstrate that in primary infection APC are rapidly recruited over a few days, and then decay exponentially with a half-life of 1-2 days [24,25]. In slow infections there is only slow lymph node swelling, and thus APC are likely to be produced only very slowly. The relatively short half-life of APC means that in slow infection they might be lost almost as fast as they are produced, and take much longer to accumulate to the threshold level (see Figure 2). Together these factors conspire to delay and reduce antigen presentation and T cell activation, so that T cells react "too little too late" to mediate early immune control [4].

Catching up slowly:

Once T cell growth is initiated, T cell numbers can double as often as every 5 - 6 hours in

acute infection. This is sufficient to easily outgrow many slowly growing pathogens with doubling times over 10 hours. However, slow pathogen growth seems to stimulate slow T cell growth. The doubling time of CD8⁺ T cells in monkey models of HIV is only around 18-24 hours, and seems to parallel slow growth in viral loads [4]. Similar slow growth of both the CD4⁺ and CD8⁺ T cell response is seen in tuberculosis infection [8,16,18], trypanosome infection [21,22], and toxoplasma infection [20]. It is not clear whether this slower T cell growth represents slower division or increased death of T cells (see Figure 3). However, the similarity between T cell growth rates and pathogen growth rates suggest that growth is somehow 'antigen limited', and the level (and growth) of T cells may be driven by the level of pathogen.

The effect of slow T cell growth on ultimate T cell effector function and survival is not well understood. If slow growth is due to increased cell death (with the same underlying division rate of cells), then for a given number of T cell responders observed, the cell population with the higher death rate will have undergone more divisions. This might directly affect the phenotype and function of responding cells, since cell division affects differentiation and memory formation, as well as leading to senescence [30,31]. Thus, slow pathogen growth in early infection may directly impact the effectiveness of T cells in controlling virus during chronic infection.

Matching stride with infection – the establishment of persistence:
Thus far, we have referred to pathogens simply as 'fast' and 'slow'. However, pathogen growth rate also seems associated with the ability to persist in the host: The fast

pathogens we have used as examples are generally acute infections that can be completely eliminated by the immune system ('sterilizing immunity'). By contrast, the slow pathogens are agents that can persist in the host, causing chronic infection and chronic immune stimulation. Can pathogen pace itself be a determinant of persistent infection?

In fast infections, the rapid growth of pathogens and cytotoxic T lymphocytes (CTL) often leads to the number of CTL significantly 'overshooting' the number required for pathogen containment, and thus there is a high ratio of T cells to pathogen later in infection facilitating pathogen clearance. In slow infections, the apparently parallel growth kinetics of T cell and pathogen can lead to a dynamic equilibrium state, where the levels of CTL and virus are balanced so there are 'just enough' CTL to control infection [32,33]. The 'equilibrium state' is in fact persistence of pathogen and chronic infection. However, unlike the stable levels of antigen-independent 'memory' T cells after clearance of acute infections, the cells that persist in chronic infection are often antigen-dependent. This is demonstrated in HIV and trypanosome infection, where anti-retroviral or antibiotic treatment leads to the decay of both pathogen and the T cell response [34,35]. Thus in persistent infection, antigen is required to maintain T cell levels and the presumed 'host-pathogen equilibrium'. However, this equilibrium involves the chronic activation of T cells, which may eventually lead to their exhaustion or senescence. Thus, what appears to be a stable population of cells might in fact involve continual recruitment of new cells and clonal turnover of the response [36-38].

A new mechanism for immune evasion – pathogen pace:

Pathogens have evolved a number of strategies to avoid immune control, including mechanisms to impair antigen presentation and innate immune responses, or antigenic variation to avoid adaptive responses. We need to add 'slow pathogen pace' to the list of strategies that pathogens use to evade immune control, because slow pathogen growth in early infection appears an important determinant of later pathogen persistence. An obvious question in this context is whether this slow growth is intrinsic to the pathogen, or whether it reflects the balance of fast intrinsic pathogen growth tempered by strong innate immune control. Two arguments appear to favor the argument for an intrinsically slow growth rate: (i), at least some slow pathogens such as *M. tuberculosis* have slow growth rates even in vitro; (ii) if slow growth were determined by high innate immune activation, then we might expect that slow pathogens would be more inflammatory than fast ones if inoculated directly. Again, inoculation with *M. tuberculosis* does not elicit a rapid inflammatory response, suggesting that it does not induce high innate immune activation.

Obviously, growth rate alone is not a black and white determinant of persistence.

Lymphocytic chorio-meningitis virus (LCMV), for example, grows extremely rapidly in acute infection, and appears to establish persistence by immune exhaustion [39,40]. HBV grows more slowly than HCV, and HCV is more likely to establish chronic infection in adults. Still, considering the breadth of different potential 'race strategies' that can be adopted by infectious agents, it is tempting to speculate that they may might fall into two general tactics: Fast pathogens try to "outrun" the immune response, by having such a

high growth rate that peak levels of infection are reached before the adaptive immune response has time to respond to them in primary infection. They reach high early levels of pathogen and rely on rapid early transmission. Slow pathogens avoid a head-to-head race, and instead aim to 'sneak past' the immune response [41] and persist at low levels. The disadvantages of slow early growth may be traded off against the advantages of producing only a slowly developing immune response, and long-term persistence and shedding of infection. These strategies of growth within a host also have implications for the strategy 'adopted' by the pathogen to spread in a population, as fast growing pathogens only have a short time to be transmitted (see Table 1).

Vaccination – finding a new race strategy for slow infections?

The traditional approach to vaccination is to give the immune system a 'head start' in the race against the pathogen. This head start is made by having high antibody titer or a higher number of responding cells, as well as a qualitatively better response because cells are more differentiated and may have undergone antigen selection for higher avidity. In the secondary response, memory cells are rapidly activated and control infection without the need to wait for division and differentiation of low frequency naïve precursor population. This head start is an effective strategy for a 'sprint race', where host and pathogen run flat out. If the 'memory' levels of antibody are sufficiently high (the head start sufficiently large), the pathogen may be unable to grow at all, and the immune response will win the race before it starts. However, many of the advantages of the head start may be lost with slow growing pathogens; If the timing of activation is determined by a 'threshold' level of pathogen, then the response will still be delayed (and the delay

may might even be increased [42]). If latently infected cells are produced during the period of early uncontrolled viral growth, persistence might be established before the immune response even 'sees' the infection [4]. Similarly, if the growth rate of T cells is constrained by competition for antigen, then the higher T cell number following vaccination might lead to lower T cell growth rate, especially in slow growing pathogens [42]. If the pathogen strategy is to elude the immune system by growing slowly, then just making more memory cells might be fundamentally the wrong approach.

The delay in immune control in vaccinated animals with slow infection is most likely due to a delay in the conversion of quiescent memory cells into active effectors, since if animals have recently been vaccinated (and cells are already in an activated effector state) the effects of vaccination on viral control can be seen within the first week of infection [43]. Thus, three potential solutions present themselves; (i) Persistent activation of T cells with live attenuated viruses, bypassing the need for infection to activate memory cells (ii) Increasing the avidity of the T cell response should effectively lower the threshold number of APC needed to trigger a response, allowing recognition of virus earlier in infection. (iii) Finally, strategies to induce more potent innate responses to infection should accelerate APC production and immune recognition.

Understanding pathogen pace:

Although there is evidence for the link between slow pathogen pace and persistent infection, there are relatively few studies that have investigated the kinetics of pathogen growth as a factor in infection. Systematic studies to measure pathogen growth and

correlate this with clinical outcome across a wider range of infections are important to understanding the links between 'pace' and 'persistence', and the role of different immune evasion mechanisms in promoting chronic infection. Coupled with these studies of natural infection, in vivo studies that can independently manipulate the dynamics of antigen load and innate immune stimulation are necessary. By using different dosing schedules of peptide and adjuvant, we can dissect the effects of slow antigen accumulation and slow inflammation on the initiation, growth, and long-term phenotype of the immune response. Such studies are relevant not only for slow infection, but also for cancer, where slow tumor growth may have similar effects. An understanding of the rules of this 'slow race' might be the essential element in the development of a new generation of vaccines for chronic infectious diseases.

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Table 1:
Transmission of fast and slow pathogens:

	Within-host behavior	Between-host behavior	Potential examples
“Fast” pathogens	<ul style="list-style-type: none"> High pathogen growth rates outpace immune system early after infection, leading to early peak in viral load. Early initiation of immune response and fast division rate. Immune response ‘overshoots’ pathogen growth, leading to clearance. Pathogen ‘cleared’ in days or weeks. Good immune memory may prevent re-infection with the same strain. Effective vaccines for many agents. 	<ul style="list-style-type: none"> High pathogen load lasts a short time in infected hosts. Rapid modes of transmission required (e.g: by respiratory route). Effective inoculum is high, leading to competition between the transmitted strains in early infection (favoring faster growing strains). 	<ul style="list-style-type: none"> Influenza virus Listeria Vaccinia virus
“Slow” pathogens	<ul style="list-style-type: none"> Slow pathogen growth rates. Delayed activation of innate and acquired immune responses. Slow growth of immune response. Long-term persistence of pathogen, with equilibrium levels of infection and immunity. Control of infection may be lost over time. Less amenable to conventional vaccines. 	<ul style="list-style-type: none"> Pathogen persists for extended periods in infected hosts. Slower modes of transmission possible (e.g: by intimate contact, / sexual transmission, / blood borne, / vertical transmission). Effective inoculum is low, reducing ‘within host’ competition for faster growth rate in early infection. 	<ul style="list-style-type: none"> HIV HCV tuberculosis

Box:

Outstanding questions:

- How closely is slow pathogen growth linked to the persistence of infection across diverse pathogens? How important is it as a determinant of vaccine failure?
- Does variation in pathogen growth between individuals infected with the same pathogen determine who will control infection and who will progress to develop chronic infection?
- How do the kinetics of infection dictate the kinetics of antigen presentation? What are the relative roles of innate immune recognition and antigen levels in recruiting and loading APC, and stimulating the adaptive immune response?
- How does slow pathogen growth determine slow T cell growth? What are the effects of this on T cell phenotype and senescence?
- There is abundant data to support slow T cell responses to slow infection. How does slow infection affect the kinetics and phenotype of antibody responses?

Box: Glossary

Slow pathogen pace: slow growth rate of a pathogen, so that it divides more slowly than the potential for division of immune cells (*i.e.*, taking more than six hours to double in number).

Figures:

Figure 1: (Summary schematic)

Pathogens set the pace of the immune response:

The different phases of the immune response for fast infection (left) and slow infection (right) are shown.

Figure 2: (DC schematic)

Innate immunity to slow pathogens:

Does slow dendritic cell (DC) recruitment contribute to low levels of antigen presentation? In the resting lymph node (top left) there is a slow turnover of non-activated DC. Fast infections (top right) result in fast recruitment of DCs into the lymph node, and these are loaded with antigen to become APCs. Because APC accumulate rapidly, most cells are simultaneously present at the peak of the response, and then decay over the following days or weeks: if 1000 APC are recruited, this leads to a peak number of ~1000 APC. In slow infection (bottom), there is only weak activation and recruitment of DC, which slowly leak into the lymph node. Because the decay rate of antigen presentation is relatively high (half-life of around a day) [24], APC do not get the chance to accumulate. If 1000 APC are recruited slowly over time and have time to decay, the peak number of APC present at any one time will be much lower.

Figure 3:

Mechanisms of slow T cell division:

Fast infection and rapid T cell division (A) can involve most cells dividing as often as

every 5-6 hours. However, the mechanisms of slow T cell division are unclear. It may involve all cells dividing, just like rapid division, but with the time between divisions greatly extended (B). But it is also possible that the underlying division rate of cells is the same, but that death rate of dividing cells is larger, reducing the growth rate of the cell population as a whole (C). For example, an increased proportion of annexin V positive T cells in BCG infection supports this as a mechanism of slow T cell growth [18].

[Suggested cover art – photo of running race]

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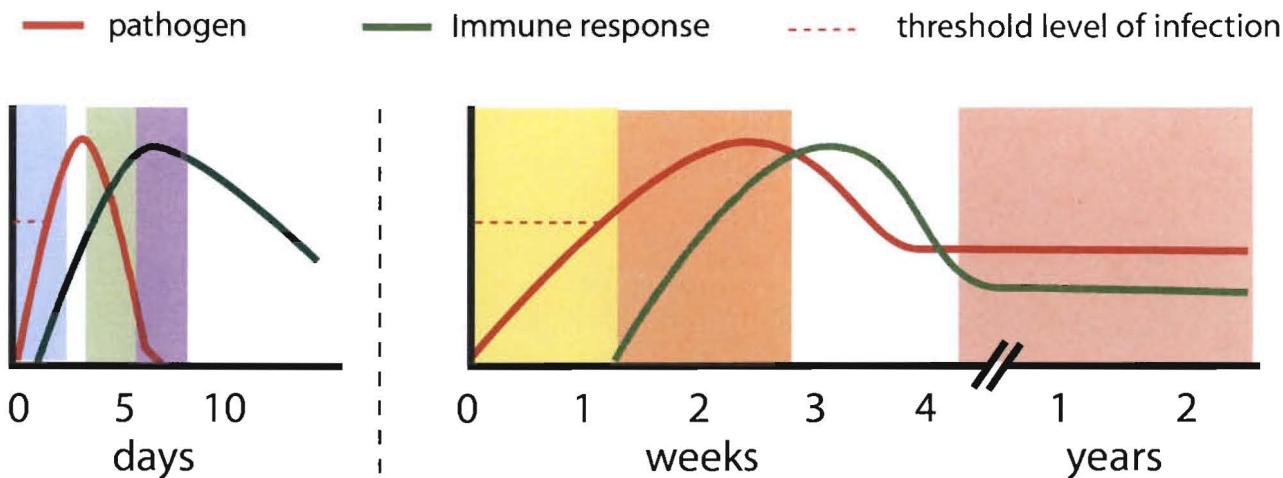
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Figure 1



Fast pathogens

Rapid early pathogen growth 'outruns' immune response.
"Threshold" level of infection crossed quickly, triggering T cell response.

T cells proliferate maximally (about every 5-6 hours).

T cells 'overshoot' pathogen. Pathogen controlled and completely removed by response.

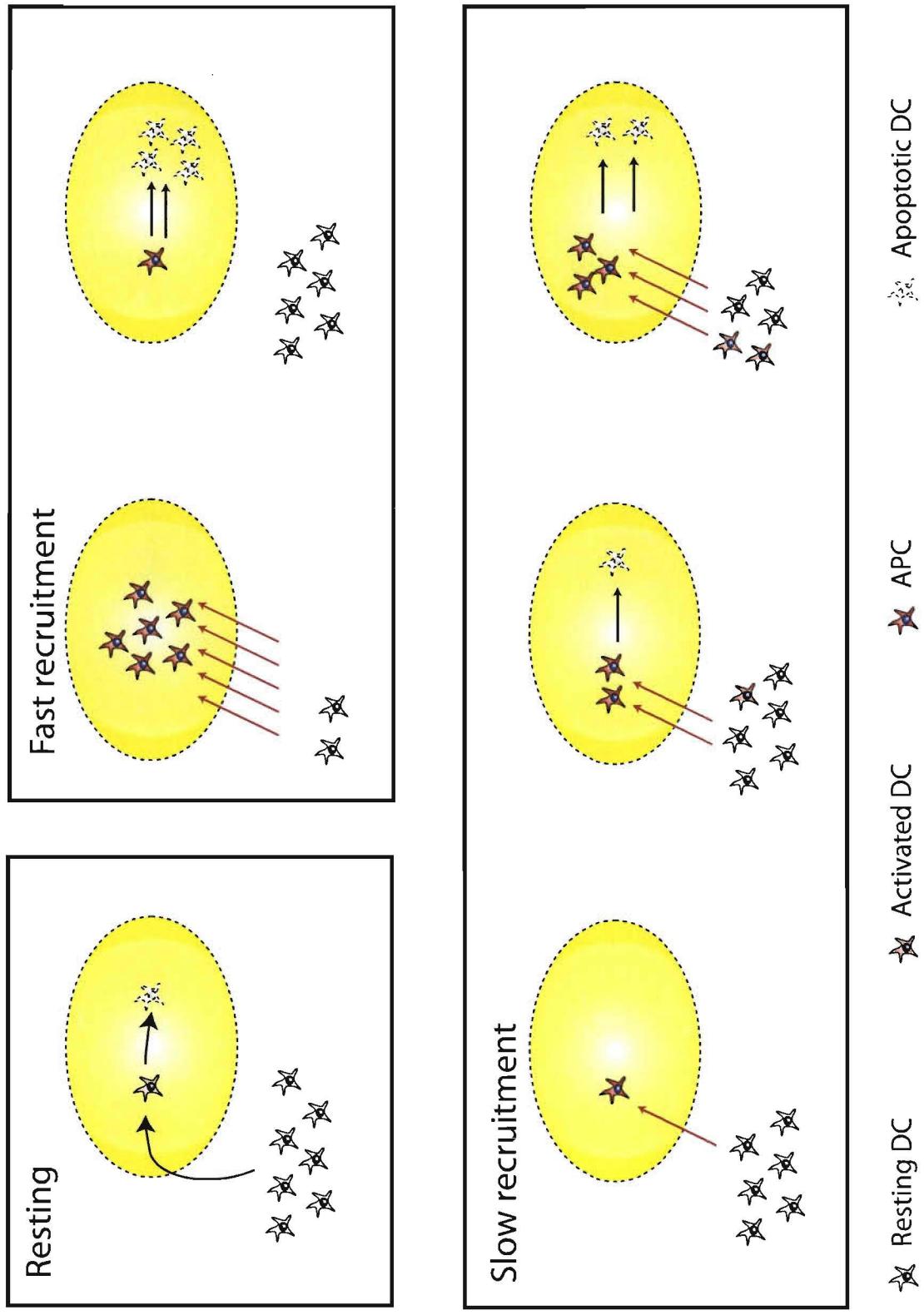
Slow pathogens

Slow pathogen growth, T cell response delayed until pathogen reaches a 'threshold' level of infection.

Slow growth of T cells.

Balance of pathogen growth and immune response leads to persistence and chronic infection.

Figure 2



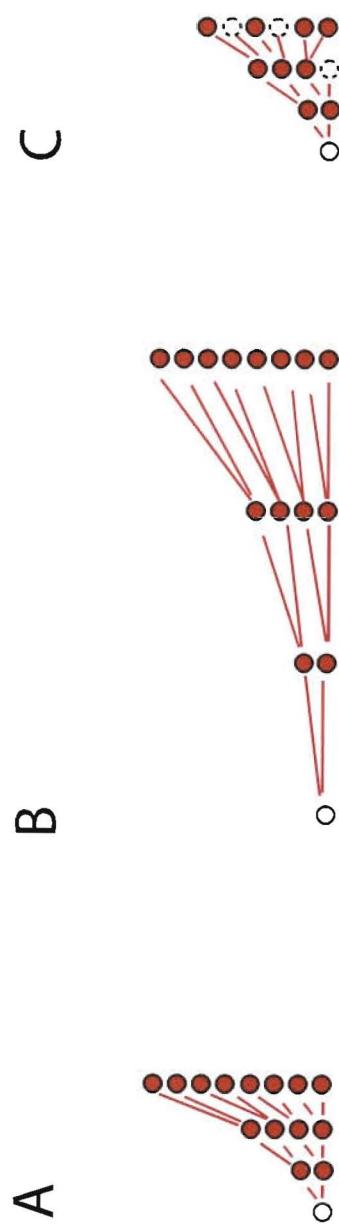


Figure 3