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Chronic infection and the origin of adaptive immune system

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Abstract

It has been speculated that the rise of the adaptive immune system in jawed vertebrates some 400 million years ago gave them a superior protection to detect and defend against pathogens that became more elusive and/or virulent to the host that had only innate immune system. First, this line of thought implies that adaptive immune system was a new, more sophisticated layer of host defense that operated independently of the innate immune system. Second, the natural consequence of this scenario would be that pathogens would have exercised so strong an evolutionary pressure that eventually no host could have afforded not to have an adaptive immune system. Neither of these arguments is supported by the facts. First, new experimental evidence has firmly established that operation of adaptive immune system is critically dependent on the ability of the innate immune system to detect invader-pathogens and second, the absolute majority of animal kingdom survive just fine with only an innate immune system. Thus, these data raise the dilemma: If innate immune system was sufficient to detect and protect against pathogens, why then did adaptive immune system develop in the first place? In contrast to the innate immune system, the adaptive immune system has one important advantage, precision. By precision I mean the ability of the defense system to detect and remove the target, for example, infected cells, without causing unwanted bystander damage of surrounding tissue. While the target precision *per se* is not important for short-term immune response, it becomes a critical factor when the immune response is long lasting, as during chronic infection. In this paper I would like to propose new, “toxic index” hypothesis where I argue that the need to reduce the collateral damage to the tissue during chronic infection(s) was the evolutionary pressure that led to the development of the adaptive immune system.

Discussion

Why adaptive immune system?

The rise of adaptive immune system based on V(D)J recombination in jawed vertebrates has been traced back to 400 million years ago [1]. It is thought that mechanism of V(D)J recombination that potentially allows generation of unlimited pathogen-specific receptor diversity enabled host to detect and guard against pathogen(s) that could have otherwise evaded less variable receptor based detection system of innate immunity. In other words, the presence of adaptive immune system was an evolutionary advantage to the host in biological warfare against fast-evolved pathogens. Two conclusions could be drawn from this idea: first, adaptive

Conflicts of Interest Statement

None Declared

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immune system must operate independently from innate immunity. Second, it is fair to suggest that once adaptive immunity had developed, the natural consequence of this evolutionary arms race between pathogen(s) and host(s) would have wiped out any host with only innate immunity. In reality, however, neither of these two postulates is valid. First, the proper functioning of adaptive immune system requires the instructive signals from the innate immunity. Second, absolute majority of animal kingdom survives just fine with innate immunity only. So, why the adaptive immune system developed?

Paradigm change

During the 60s–80s of the 20th century, it was widely accepted that adaptive immune system represented new, more sophisticated layer of host defense that operated independently of innate immunity [2–5]. Because of random events of V(D)J recombination, productively assembled B and T cell receptors were thought to have the potential to recognize any piece of protein called epitope coming from pathogen(s), referred as nonself, as well as coming from own tissue (s), referred as self. The main focus of discussions or experiments was devoted to explain how self-tolerance was established and maintained [6,7]. However, in the 90s, this concept came into disarray after first it was proposed and then shown experimentally that proper functioning of adaptive immune system was dependent on innate immunity [8–10]. In fact, it is now firmly established that the variety of pathogen pattern-recognition receptors of innate immune system is responsible for detection of exogenous and endogenous danger signals that leads to the activation of innate immunity and that in turn leads to the activation of the adaptive immune system [11–15].

Dilemma

This new concept, however, challenges the age-old idea about the origin of the adaptive immune system. The paradox is that if activation of adaptive immunity depends on innate immunity, then innate immunity must detect every single pathogen. In fact, almost all recent studies on innate immunity have shown that it is indeed capable of detecting every pathogen studied [15]. So, if innate immunity can detect every pathogen examined so far, then what selection pressure drove the rise of the adaptive immunity?

Innate versus adaptive immune system

To try to find an answer to this question one needs to analyze both innate and adaptive immune systems. There are three major differences between innate and adaptive immune systems. First difference is in response time. Adaptive immune response usually takes longer to mature upon pathogen recognition compared to innate immunity [16]. This delay could have not given any advantage to the host against invader-pathogen, so it is reasonable to assume that it could have not been the evolutionary pressure that led to the development of adaptive immunity. Second difference is in the pathogen-specific receptor diversity [7]. Adaptive immune system is capable of generating unlimited pathogen-specific receptor diversity. However, as discussed earlier, the innate immune system is also capable of detecting every potential invader-pathogen. Moreover, a new study showed that innate immune system in some jawless vertebrates is quite sophisticated and its receptor repertoire is as diverse as that of adaptive immune system in jawed vertebrates [17]. Thus, pathogen-specific receptor diversity *per se* could not have been the evolutionary pressure that led to the development of adaptive immunity. Third difference is an accelerated response upon secondary encounter to the same pathogen or its derivative(s), commonly known as an immunological memory. Adaptive immune system usually generates long-lasting immunological memory in contrast to innate immune system which usually does not generate long-lasting immunological memory [18]. It must be mentioned here that the majority of studies about immunological memory were done using acute viral or bacterial infections with the typical immune response phases, while chronic infections are characterized

by continuing immune responses that lack a typical memory phase. The long-lasting immunological memory endowed by adaptive immunity to the host against invader-pathogen could have potentially shortened the time of being sick and/or substantially reduced the severity of infection and could have been the evolutionary pressure that led to the development of adaptive immunity [16]. However, if immunological memory were so important in evolution of defense strategy, why then would the innate immune system itself not have developed long-lasting immunological memory on its own? In fact, the new study on natural killer cells (NK cells), that are a component of innate immunity, has shown that Ly49H receptor positive subset of NK cells displayed typical adaptive-like response to its specific ligand, mouse cytomegalovirus (MCMV)-encoded m157 molecule, including long-lasting memory phase [19,20]. So, immunological memory *per se* could have not been the evolutionary pressure that led to the development of adaptive immune system.

“Toxic index” hypothesis

Here, I would like to propose the new “toxic index” hypothesis for the origin of the adaptive immune system. Both innate and adaptive immune systems fight off infection by elaborating effector molecules toxic for invader-pathogen(s). However, the same effector molecules are toxic for healthy tissue too, especially if made in excess or for an extended time [21,22]. Assuming that the immune response is inherently toxic to both pathogen and tissue, there are two ways to employ it against pathogen without much toxicity to healthy tissue: either it must be effective enough to be able to rid off the invader-pathogen in the shortest time possible or it must be less toxic if it takes longer to clear the pathogen from the tissue. Though effector molecules of innate immune system are very effective against pathogen(s), they are also highly toxic to healthy tissue because innate immune system lacks precision. By precision I mean the ability of defense system to identify and remove the target(s), for example, infected cells, without causing much bystander damage of surrounding healthy tissue. Precision *per se* is not important but it becomes a very critical factor if the immune response is long lasting, as it is during chronic infection(s). Because innate immune response lacks precision it potentially can damage larger area of tissue whenever invader-pathogen is detected, so it cannot be kept in active state for an extended time. Chronic infection especially poses a special threat in this regard. The V(D)J recombination-based detection system of adaptive immunity had an advantage to precisely identify target(s) and therefore had reduced inherent toxicity towards healthy tissue. Thus I propose that the evolutionary pressure to reduce collateral damage to healthy tissue during chronic infection was the critical factor that led to the development of the adaptive immune system. The longer it takes for a defense system to fight off invader-pathogen, the immune response should become the more precise and less toxic to the tissue. I believe the same rule applies to different classes of adaptive immune response. Adaptive immune response against tissue-resident infection would thus transit through the stages from short-lived and more toxic to long-lived and less toxic immune class as the immune response progresses. Any failure to switch to less toxic class during ongoing adaptive immune response will lead to immune pathology.

Conclusion

In summary, I believe the paradox of adaptive immune system lies in the understanding that not the invader-pathogen itself but how to reduce the collateral damage to the tissue during chronic infection was the critical factor that led to its development.

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