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Perspective

Innate and Adaptive Immune Memory: an Evolutionary Continuum in the Host's Response to Pathogens

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Immunological memory is an important evolutionary trait that improves host survival upon reinfection. Memory is a characteristic recognized within both the innate and adaptive arms of the immune system. Although the mechanisms and properties through which innate and adaptive immune memory are induced are distinct, they collude to improve host defense to pathogens. Here, we propose that innate immune memory, or "trained immunity," is a primitive form of adaptation in host defense, resulting from chromatin structure rearrangement, which provides an increased but non-specific response to reinfection. In contrast, adaptive immune memory is more advanced, with increased magnitude of response mediated through epigenetic changes, as well as specificity mediated by gene recombination. An integrative model of immune memory is important for broad understanding of host defense, and for identifying the most effective approaches to modulate it for the benefit of patients with infections and immune-mediated diseases.

Innate and Adaptive Immunity

Classically, host immunity is divided into innate and adaptive immune responses. The former reacts rapidly and non-specifically to pathogens, whereas the latter responds in a slower but specific manner, with the generation of long-lived immunological memory (Farber et al., 2016). This dichotomy has dictated the last half century of immunological research, and a vast number of studies have defined the cellular and molecular substrates on each of these two major components of host defense. Innate immunity is mediated by innate immune cell populations such as myeloid cells, natural killer (NK) cells, and innate lymphoid cells (but non-immune cells in specific circumstances as well), as well as by ancient humoral systems such as defensins and complement. Adaptive immunity is a relatively new evolutionary trait based on the immunoglobulin family and cells such as B- and T-lymphocytes in jawed vertebrates (Danilova, 2012) and on variable lymphocyte receptors (VLR) comprised of leucine-rich-repeat (LRR) segments in jawless vertebrates (Boehm et al., 2012).

During an infection, the innate immunity is the first to be triggered (the inflammatory reaction), taking no longer than minutes to hours to be fully activated (Netea et al., 2017). This is crucial for the host defense in the first phase of a new infection. While innate immunity is generally able to eliminate the pathogens efficiently, initial clearance of infection can fail due to the high number or virulence of invading pathogens. In these situations, lymphocytes and adaptive immune mechanisms are activated, which allows specific recognition and elimination of the pathogen. Establishment of adaptive immunity needs 1–2 weeks and is important for host defense during the latter phases of an infection and during secondary infections due to its capacity to "remember" and respond more effectively to restimulation (Farber et al., 2016).

The innate and adaptive immune processes were initially seen as relatively compartmentalized responses in time, but research in the last two decades has clearly demonstrated strong links and an efficient network between them. Activation of the adaptive immune response and induction of classical immune memory in lymphocytes are dependent on the innate immune system, in particular on antigen-presenting cells such as dendritic cells. The downstream effects of lymphocyte activation are then exerted by amplifying innate immune responses such as phagocytosis and killing of pathogens by certain innate immune cells.

Two properties that discriminate innate and adaptive immunity are on the one hand specificity, and on the other hand the capacity to build long lived immunological memory. Innate immune responses are traditionally thought to be non-specific and without the capacity to adapt, whereas adaptive immune responses recognize with great precision different pathogens using gene recombination processes in the immunoglobulin gene family, and subsequently build immunological memory (Danilova, 2012) (Figure 1). The concept that innate immunity is non-specific has been challenged by the discovery of pattern recognition receptors (PRR). These receptors expressed on a variety of cells within the innate immune system recognize specific components of microorganisms, and the combination of PRRs expressed by an immune cell can lead to partially specific recognition of the type of microorganism encountered: for example, innate immune cells recognize the difference between a Gram-negative and a Gram-positive bacteria, but not between two

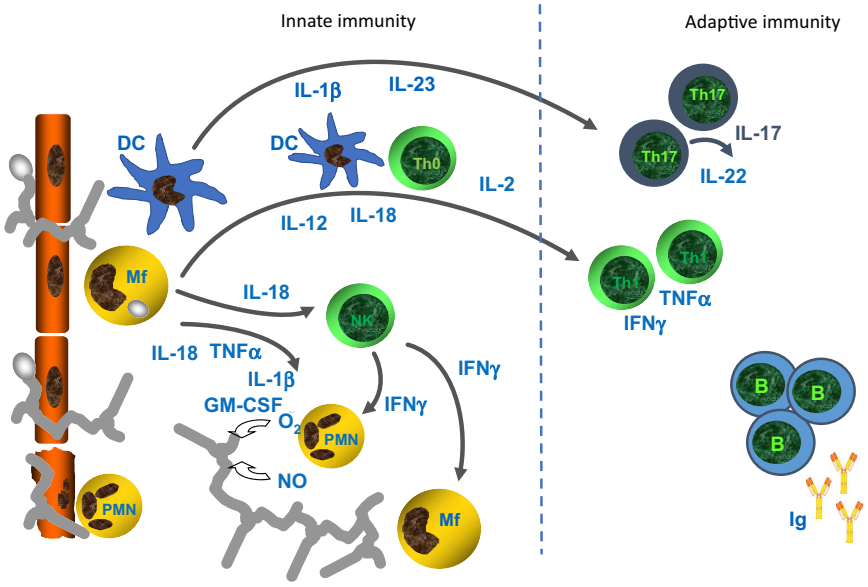

Figure 1. Innate versus Adaptive Immune Responses

During the first hours and days of an infection, invasion by pathogens induces activation of innate immune cells such as macrophages, monocytes, or NK-cells or humoral factors such as complement. These pathways strongly activate an inflammatory reaction and eliminate the pathogens (innate immunity). In the few cases when infection is not eliminated, pathogens are ingested and processed by antigen-presenting cells, followed by antigen presentation and stimulation of a specific activation of T- and B-lymphocytes. In turn, this leads to clonal expansion and activation of effector mechanisms (e.g., release of cytokines, immunoglobulins) (adaptive immunity).

closely related species or strains (Medzhitov and Janeway, 2000). We will not discuss the progress in understanding the pathogen recognition through PRRs in this review, as this is the subject of many excellent recent overviews in the literature (e.g. O'Neill et al., 2013).

Here, we will focus on the second property discriminating innate and adaptive host defense mechanisms: induction of immune memory. In contrast to early literature, a growing body of evidence shows that innate immune responses exhibit adaptive characteristics (Bowdish et al., 2007; Netea et al., 2011). In plants and invertebrates that lack adaptive immunity, sustained protection against reinfection has been reported (Kurtz, 2005). Studies in mammals have demonstrated that there is cross protection against infections with different pathogens (Quintin et al., 2014), while experimental studies of mice devoid of functional adaptive immune cells have shown partial protection in certain models of vaccination (Bistoni et al., 1986; van 't Wout et al., 1992). It is thus apparent that innate immunity can be modulated by previous encounters with microbes or microbial products, and this property has been termed "trained immunity" and represents a *de facto* innate immune memory.

However, there are distinct molecular mechanisms that mediate the two types of immune memory. Based on molecular, immunological, and evolutionary arguments, we propose that innate immune memory is a primitive form of immune memory present in all living organisms, while adaptive immune memory is an advanced form of immune memory representing an evolutionary innovation in vertebrates. Based on the complementary properties of the two types of immune memory, and on a range of biological arguments as described below, we argue in this Perspective that the development of innate and adaptive immune memory represents an evolutionary continuum. We also propose that these two forms are two evolutionary steps toward the development of effective mechanisms of adaptation to an environment teaming with potentially pathogenic microorganisms.

Immunological Memory as an Adaptive Evolutionary Trait

The dogma that immunological memory is confined to the adaptive immune system faces a conceptual difficulty when considered from an evolutionary perspective. That immune memory is advantageous from an evolutionary point of view is well illustrated by deadly ancient diseases such as smallpox: while mortality was historically 20%–60% for first infections, individuals became completely immune to the disease thereafter (Riedel, 2005). Therefore, it is difficult to envision that immune memory evolved only in vertebrates, which represent approximately 1%–2% of living species (Gourbal et al., 2018). In contrast, other important advantageous traits, such as vision, evolved independently several times during the evolution of various groups of animals (so called "convergent evolution") (Gehring, 2004). Interestingly, immunological memory within the vertebrate lineage evolved not just once, but twice. First, the development of VLR-based memory in the jawless fish (such as the lamprey) and, second, the development of the Ig-based memory (which is also the basis for the development of B- and T-lymphocyte memory) in all the other jawed vertebrates. That there would be two separate events leading to immune memory in vertebrates (Cooper and Alder, 2006), while being completely absent in all other metazoans, is very unlikely.

In line with this, a large number of studies of plant immunology have demonstrated that plant host defense includes adaptive characteristics, a response termed Systemic Acquired Resistance (SAR) (Jaskiewicz et al., 2011; Kachroo and Robin, 2013; Reimer-Michalski and Conrath, 2016). The molecular mechanisms and biochemical mediators of SAR are largely known (Kachroo and Robin, 2013), with epigenetic-based rewiring of host defense being suggested to play a central role (Luna and Ton, 2012). In addition, increasing evidence has challenged the belief that invertebrate innate immunity lacks memory traits (Kurtz, 2005). Adaptive properties of innate immune responses have been reported in several invertebrate lineages; for example microbiota have been shown to induce innate immune memory to protect mosquitoes against *Plasmodium* (Rodrigues et al., 2010), the social insect *Bombus terrestris* to display innate immune memory against three different pathogens (Sadd and Schmid-Hempel, 2006), and the tapeworm *Schistocephalus*

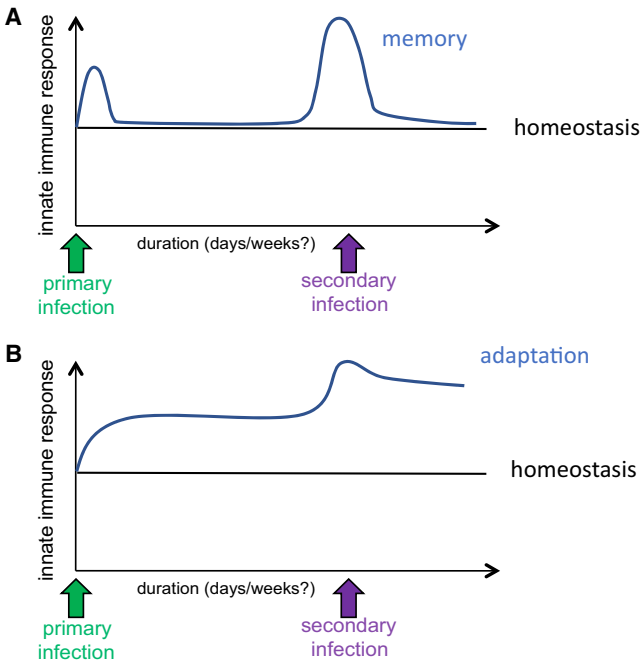

Figure 2. Immune Memory versus Immune Adaptation
Immune memory is defined as a changed status of the immune system of a host after an acute infection (or vaccination), leading to a more effective response against reinfection. Importantly, during induction of immune memory, between the first infection and the re-infection, the immune status functionally returns to a low basal state, while the capacity to respond stronger to restimulation is imprinted at epigenetic level (A). In contrast, adaptation is defined as the long-term change in the immune response determined by a constant change in the environmental conditions, or due to a chronic insult (e.g., a chronic infection), leading to a new functional state. Importantly, the functional immune status during adaptation does not return to the low basal state existing before the insult (B).

solidus to induce memory in the copepod crustacean (Kurtz and Franz, 2003), and innate immune memory is a defense mechanism in snails (Pinaud et al., 2016). These studies have been complemented by data in vertebrates showing that it is possible to induce partial protection to reinfection in experimental murine models even in the absence of functional adaptive immune responses (Bistoni et al., 1986; van 't Wout et al., 1992). Moreover, epidemiological studies have shown heterologous protection by human vaccines against a broad spectrum of infections (Benn et al., 2013), with mechanisms likely independent from classical adaptive immune responses. Therefore, it is reasonable to conclude that immunological memory can be found not only in vertebrates but also in plants and lower animals (Kurtz, 2005; Netea et al., 2011) that do not harbor a classical adaptive immune system.

Innate and Adaptive Immune Memory: an Evolutionary Process

If these data strongly argue for the presence of immune memory in all groups of higher organisms, how can this be defined? A simple definition is that immunological memory refers to the ability of the immune system to respond more rapidly and effectively to a pathogen. This definition encompasses all processes described as immune memory in plants, invertebrates and vertebrates, although it does not discriminate between the differences in action observed within various organismal groups. In a recent review, Pradeu and Du Pasquier (2018) propose a multidimensional model of immune memory, in which they discriminate no less than six varieties of immune memory: classical adaptive memory in vertebrates, NK-cell immune memory, trained immunity in myeloid cells, priming in invertebrates, immunological memory in plants (e.g., SAR), and Crispr/Cas-based memory in bacteria and archaea (Pradeu and Du Pasquier, 2018). These forms of immunological memory differ in their properties based on a number of basic characteristics of the response: strength, speed, extinction (reversal to the basal state), duration, and specificity. However, while this classification is useful for understanding the ubiquitous presence of immune memory in all living organisms, we believe that this compartmentalization of immune memory does not reflect the common molecular, biological, and functional substrate of the memory characteristics in different organisms.

In this Perspective, we propose a unifying model of immune memory that is based on two concepts:

- There is conceptual difference between two forms of immune adaptation: immune memory and immune differentiation.
- An evolutionary continuum links innate and adaptive immune memory.

The first concept that needs to be defined is represented by the difference between immune memory and immune adaptation. We define immune memory as a changed status of the immune system of a host after an acute infection (or vaccination), leading to a more effective response against re-infection. Importantly, during induction of immune memory, between the first infection and the reinfection, the immune status functionally returns to a low basal state, while the capacity to respond stronger to restimulation is imprinted at epigenetic level (Figure 2A). In contrast, we define immune differentiation as a form of adaptation through long-term changes in the functional program of a system (including immune response), determined by a constant change in the environmental conditions or due to a chronic insult (e.g., a chronic infection), leading to a new functional state. Importantly, the functional immune status during differentiation does not return to the low basal state existing before the insult (Figure 2B). There are many biological situations characterized by adaptation though immune differentiation: one such situation may be induced for example by stable changes in gut microbiota, that is known to induce long-term effects on the local immune responses. The process of immune differentiation is the subject of many other excellent reviews, and it will not be the focus of this Perspective.

Another important distinction to make is between priming and memory. Priming is also a term that has been used to describe increased responses to a secondary stimulus, however this is often an acute process that does not involve long-term memory effects. For example, during acute malaria infection there is a well-known hyper-responsiveness of immune cells to Gram-negative microorganisms that can lead to severe acute symptoms: the immune cells are primed to respond acutely with

higher cytokine release. However, that does not imply a memory response that would persists for months or years.

Here, we will focus on the concept of immune memory, which we believe characterizes all living organisms. We propose that there is an evolutionary continuum between innate and adaptive immune memory based on two fundamental properties mediated by distinct mechanisms:

- **Increased magnitude and kinetics** of the immune responses upon reinfection, which is mediated by epigenetic processes and characterizes both innate and adaptive immune memory (present in all organisms)
- **Specificity** of the memory responses, mediated by gene recombination, a property specific to adaptive immune memory (described until now only in vertebrates)

Innate Immune Memory

While in vertebrate immunity it has long been assumed that innate immune responses cannot adapt after an infection, and upon reinfection an identical response is elicited each time, this assumption was never followed in plants or invertebrate immunity. In addition to studies on plants and invertebrate host defenses described above (see Immunological Memory as an Adaptive Evolutionary Trait), several mechanisms have been proposed to account for the induction of innate immune memory in invertebrates, including upregulation or "training" of regulatory pathways such as Toll or Imd (Boutros et al., 2002) and quantitative and phenotypic changes in immune cell populations (Rodrigues et al., 2010). Some investigators have also proposed the presence of diversity-generating mechanisms in insects. Such candidate mechanisms may involve fibrinogen-related proteins with high rates of diversification at the genomic level (Zhang et al., 2004) or upregulation of expression of specific receptors such as peptidoglycan recognition molecules and lectins (Steiner, 2004).

Important clues that vertebrate innate immunity also has adaptive characteristics have been reported in experimental studies in mice. Several of such studies have shown that priming or training mice with microbial ligands can protect against lethal infection. For example, trained immunity induced by β-glucan (derived from fungi) induces protection against bacterial infection with *Staphylococcus aureus* (Di Luzio and Williams, 1978; Marakalala et al., 2013). Similarly, the bacterial peptidoglycan component muramyl dipeptide induces protection against *Toxoplasma* (Krahenbuhl et al., 1981), and CpG oligodeoxynucleotide administration protects against sepsis and *Escherichia coli* meningitis (Ribes et al., 2014). Furthermore, flagellin from Gram-negative bacteria can induce protection against the Gram-positive bacterium *Streptococcus pneumoniae* (Muñoz et al., 2010) and rotavirus (Zhang et al., 2014a). In addition to microbial ligands, there is evidence that certain proinflammatory cytokines may induce trained immunity: injection of mice with one dose of recombinant IL-1 three days before an infection with *Pseudomonas aeruginosa* protected mice against mortality (van der Meer et al., 1988). The nonspecific character of the trained immunity effects argues against a classical memory effect mediated by adaptive immunity and suggests activation of nonspecific innate immune mechanisms. An important aspect that will need to be investigated is the duration of the protective effects of trained immunity. Studies in mice and humans have shown effects after 3 months and even one year (Kleinnijenhuis et al., 2014), although epidemiological data based on the protective heterologous effects of vaccines suggests that they will be functional at least 3–5 years.

Trained immunity may mediate at least some of the protective effects of vaccination. Compelling evidence comes from studies showing that vaccination with the tuberculosis vaccine bacillus Calmette Guerin (BCG), the most commonly used vaccine worldwide, induces T cell-independent protection against secondary infections with *Candida albicans*, *Schistosoma mansoni,* or influenza in animals (Spencer et al., 1977; Tribouley et al., 1978; van 't Wout et al., 1992). Human data complete these studies: BCG vaccination in human volunteers protects against an experimental infection with yellow fever vaccine virus (Arts et al., 2018), while large epidemiological studies have reported protective heterologous effects for BCG and measles vaccination (Benn et al., 2013; Goodridge et al., 2016). In addition, herpesvirus latency increases resistance to the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis* (Barton et al., 2007) with protection achieved through enhanced production of IFNγ and systemic activation of macrophages. Similarly, infection with the helminthic parasite *Nippostrongylus brasiliensis* induces a long-term macrophage phenotype that damages the parasite and induces protection from reinfection independently of T and B lymphocytes (Chen et al., 2014).

The main cell populations that have been reported to be responsible for innate immune memory are monocytes, monocyte-derived macrophages, and natural killer (NK) cells. Whereas macrophage-dependent secondary protection from infection is nonspecific, NK cell-mediated immune memory may provide increased specificity. The first evidence of NK cell memory comes from observations of different T and B cell deficient mice (RAG knockout, SCID, and nu/nu) being able to mount robust recall responses to hapten-based contact sensitizers (O'Leary et al., 2006). NK cells can mediate hapten-specific contact hypersensitivity (CHS) in these animals, yet the NK cell memory is restricted to liver-resident cells of the NK.1.1+DX5−CXCR6+CD49a+ phenotype (O'Leary et al., 2006; Paust et al., 2010; Peng et al., 2013). Mouse liver-resident NK cells can develop specific memory toward variety of haptens and other antigens, including virus-like particles (VLPs); however, the antigen recognition mechanism is not known (Paust et al., 2010). Antigen-specific and long-lasting (splenic and hepatic) NK memory cell responses were also observed in rhesus macaques, suggesting that antigen-specific memory NK cells may also exists in humans (Reeves et al., 2015).

NK cells can be activated by cytomegalovirus: after infection with murine cytomegalovirus (mCMV) (Nabekura et al., 2015; Schlums et al., 2015; Sun et al., 2009; Sun et al., 2012), NK cells bearing the Ly49H receptor proliferate, persisting in lymphoid and non-lymphoid organs during the contraction phase of the NK cell response. Upon reinfection, the "memory" NK cells undergo a secondary expansion, rapidly degranulating and releasing cytokines, thus inducing a protective immune response (Sun et al., 2009). A number of possible mechanisms have been put forward to explain the memory properties of NK cells, involving either the IL-12/IFNγ axis (Sun et al., 2012) or

the activation of the co-stimulatory molecule DNAM-1 (DNAX accessory molecule-1, CD226) (Nabekura et al., 2014).

CMV-induced NK memory appears to be specific: mouse studies demonstrated no enhanced responsiveness of mCMV-induced NK memory cells against other infections such as influenza or *Listeria* (Min-Oo and Lanier, 2014). Similarly, human studies show no responsiveness of NKG2C+CD57+ NK cell population expanded in human (H)CMV+ individuals (Hendricks et al., 2014). Cytokine-primed NK cells have been suggested also to develop memory-like properties. Mouse as well as human NK cells stimulated with a combination of IL12, IL15, and IL18 showed enhanced IFNγ production in response to the secondary stimulation with cytokines or tumor cells weeks after cytokine priming (Cooper et al., 2009; Keppel et al., 2013; Romee et al., 2012).

Innate lymphoid cells group 2 (ILC2) that share the common lymphoid progenitor with NK, B, and T cells, do not possess antigen receptors but can be activated by cytokines. They also show the potential to ''remember'' their activation status and generate enhanced responses upon secondary stimulation. In the lung, inhaled allergens stimulate ILC2s to produce IL-5 and IL-13 in an IL-33-dependent manner (Halim et al., 2014). After allergen-induced activation, lung ILC2s undergo expansion followed by a contraction phase in which they do not produce cytokines. A population of allergen-experienced ILC2s persist in the lung and lymph nodes. Upon a secondary challenge with unrelated allergens, memory-like ILC2s mount a more robust immune response. Sensitization of mice with IL-33 was sufficient to generate memory ILC2s responsive to allergen secondary stimulation indicating the non-antigen specific character of ILC2s memory (Martinez-Gonzalez et al., 2016).

These observations may also highlight the unique positioning of ILCs and NK cells at the evolutionary crossroads between innate and adaptive immunity.

Taken together, these complementary murine and human studies demonstrate that innate immune responses have the capacity to be ''trained'' and thereby exert a new type of immunological memory upon reinfection, for which the term trained immunity has been proposed (Netea et al., 2016; Netea et al., 2011). An extension of the trained immunity concept has been recently proposed to contain also non-immune cells types, such as epithelial cells (Cassone, 2018).

Central versus Tissue Innate Immune Memory

To understand the mechanisms responsible for the induction of trained immunity, we need to define the two levels at which trained immunity acts. The first level is represented by the cell populations undergoing reprogramming (e.g., hematopoetic stem cell progenitors; see below), and the second level is the intracellular processes responsible for the reprogramming of each cell (e.g., epigenetic and metabolic reprogramming of the cell; see Epigenetic Mechanisms Mediate Induction of Innate Immune Memory).

Since the vast majority of myeloid cells, such as monocytes, granulocytes, and dendritic cells, are short-lived, the question arises how innate immune cells maintain and propagate the observed innate immune memory phenotype beyond their own life-span over a period of up to 3 months and longer. Several seminal studies have shed light on some of the mechanisms contributing to these processes. Specifically, it was shown that systemic application of the fungal cell wall component β-glucan leads to a modulation of the transcriptomic, metabolomic, and functional properties of the hematopoietic progenitor cascade in the bone marrow, in turn generating more myeloid cells with a faster kinetic at the expense of the lymphoid lineage (Mitroulis et al., 2018). Mechanistically, these effects were attributed to IL1β and GM-CSF signaling events, with induction of cholesterol metabolism and enhanced glycolysis leading to a more robust production of myeloid effector cells upon LPS re-challenge. Similar studies in mice injected with BCG demonstrated the effect of vaccination on remodeling myelopoesis, that in turn mediates an improved innate host defense against mycobacteria (Kaufmann et al., 2018). Moreover, in a model of high-fat-diet-induced innate immune training, similar effects on the myelopoesis have been shown, highlighting the potentially deleterious effects of life style on the reactivity of the immune system at least partly explaining the overt immune activation phenotypes observed in obese individuals (Christ et al., 2018).

So far, studies have only elucidated the effects of systemically applied training stimuli. However, physiologically, topical innate immune training seems very likely as the lung, the mucosae, or the skin are regularly exposed to a wide array of microbial constituents. Indeed, innate immune training can be induced in a skin wound healing model utilizing topical administration of the TLR3 ligand Poly I:C, leading to an enhanced ability to regenerate the skin after injury. This process of enhanced wound repair was dependent on sustained signaling of AIM2 within the reservoir of epithelial stem cells within the affected area of the skin, clearly showing that innate immune training can also be elicited locally, independent of immune cells (Naik et al., 2017). Moreover, earlier studies in the lung suggest that innate immune cells in the lung are indeed able to remember their inflammatory history. Studies investigating the effect of two unrelated subsequent viral infections, LCMV and influenza A virus, clearly showed that a first infection exerts the ability to alter a secondary innate immune response indicating a degree of innate immune training in these models of viral infections (Mehta et al., 2015). Beyond host defense, the consequences of topical innate immune training or inflammatory memory for the development of autoimmune and auto-inflammatory disorders remain to be investigated. Recently, a study highlighted the importance of prior immune activation on the development of asthma in the setting of a latent gammaherpesvirus infection, which in turn protected affected mice from the development of allergic asthma (Machiels et al., 2017). Interestingly, this protective phenotype was accompanied by a replacement of the embryonically derived alveolar macrophage pool with monocyte-derived alveolar macrophages displaying an immune-regulatory phenotype, thereby raising the question of what role tissue-resident macrophages play in the induction and/or maintenance of organ-specific innate immune training.

Taken together, these studies provide evidence that innate immune memory is induced *in vivo* in two main compartments: centrally in the bone marrow influencing the functional program of immune cell progenitors, and peripherally in the tissues. Especially tissues exposed to the outside world possess the capacity to mount an innate immune training response. This raises the question of how this process is balanced to provide enhanced

host defense and to counteract development of auto-inflammatory disorders.

Epigenetic Mechanisms Mediate Induction of Innate Immune Memory

The central feature of trained innate immune cells is the ability to mount a qualitatively and quantitatively different transcriptional response when challenged with microbes or danger signals. Evidence supports the convergence of multiple regulatory layers for mediating innate immune memory, including changes in chromatin organization, DNA methylation, and probably non-coding RNAs such as microRNAs (miRNAs) and/or long non-coding RNA (lncRNAs). In myeloid cells, many loci encoding inflammatory genes are in a repressed configuration during homeostasis (Ramirez-Carrozzi et al., 2006, 2009; Saccani et al., 2001). Upon primary stimulation, there is a strong gain in chromatin accessibility, increased acetylation, and RNA polymerase II recruitment. These changes are driven by the recruitment of stimulation-responsive transcription factors (e.g., NF-κB, AP-1, and STAT family members) to enhancers and gene promoters, which are usually pre-marked by lineage-determining transcription factors such as PU.1 (Barozzi et al., 2014; Ghisletti et al., 2010; Heinz et al., 2010; Smale and Natoli, 2014). In turn, transcription factors control the recruitment of coactivators (including histone acetyltransferases and chromatin remodelers) (Ramirez-Carrozzi et al., 2009; Ramirez-Carrozzi et al., 2006) that locally modify chromatin to make it more accessible to the transcriptional machinery. Maintenance of such enhanced accessibility underlies the more efficient induction of genes upon restimulation (Foster et al., 2007). One interesting paradigm is provided by latent or *de novo* enhancers (Kaikkonen et al., 2013; Ostuni et al., 2013); these are genomic regulatory elements that are unmarked in unstimulated cells but gain histone modifications characteristic of enhancers (such as monomethylation of histone H3 at K4, H3K4me1) only in response to specific stimuli. *In vitro*, upon removal of the stimulus, a fraction of latent enhancers retain their modified histones and can undergo a stronger activation in response to restimulation (Ostuni et al., 2013).

Recent studies have investigated the changes in epigenomic programs in innate immune cells during induction of trained immunity. One early study proposed that changes in epigenetic status underlie the repression of inflammatory genes during LPS tolerance (Foster et al., 2007). In contrast, during LPS tolerance, the genes involved in anti-microbial responses were either not affected, or their expression was increased (Foster et al., 2007). In turn, exposure of monocytes/macrophages to *C. albicans* or β-glucan modulated their subsequent response to stimulation with unrelated pathogens or PAMPs, and the changed functional landscape of the trained monocytes was accompanied by epigenetic reprogramming (Quintin et al., 2012; Saeed et al., 2014). BCG vaccination has also been shown to result in the increase in inflammatory mediators in monocytes from healthy volunteers, which correlated with parallel changes in histone modifications associated with gene activation (Arts et al., 2018; Kleinnijenhuis et al., 2012), as well as with changes in the pattern of DNA methylation (Verma et al., 2017).

Similar to monocytes and macrophages, the induction of CMV-induced NK cell memory is accompanied by dynamic chromatin structure changes (Lau et al., 2018) and at least partially relies on epigenetic reprogramming, which is linked to reduced expression of the transcription factor promyelocytic leukemia zinc finger (PLZF) (Schlums et al., 2015) and the tyrosine kinase SYK (Lee et al., 2015). Interestingly, a recent comparative study of chromatin structure on genome wide level in mCMV-induced memory NK and CD8 T cells revealed that epigenetic signatures of NK and CD8 T cells, even though very different in naive cells, become similar in effector and memory cells. The few genes that share epigenetic and transcriptional programs in memory NK and CD8 T cells (for example Bach2, Tcf7, and Zeb2) are known to drive differentiation of CD8 T cells to memory phenotype, suggesting common epigenetic mechanisms underlying memory formation in adaptive and innate immune cells (Lau et al., 2018). Human CMV also drives epigenetic imprinting of the *IFNG* locus in NK cells, which leads to consistent IFNγ production in NKG2C(hi) NK cells, providing a molecular basis for the adaptive feature of these cells (Luetke-Eversloh et al., 2014).

Thus, it can be concluded that epigenetic rewiring is the molecular substrate that sits at the basis of the enhanced response of innate immune cells upon a secondary stimulation (Figure 3).

Classical Adaptive Immune Memory

Changes in chromatin structure accompany not only innate immune memory formation but also that of adaptive immune memory. The adaptive immune system consists of B and T lymphocytes, which express highly antigen-specific receptors, namely B cell receptor (BCR) and T cell receptor (TCR) emerging during somatic gene recombination (Figure 4), a feature unique to these cells. There have been excellent reviews about the role of T and B cells during an immune response (De Silva and Klein, 2015; Kurosaki et al., 2015) and the developing of memory T and B cells once an immune reaction has been resolved. More recently, memory T and B cells have been further subdivided by their location and differential functionalities (Jameson and Masopust, 2018; Kumar et al., 2018).

Although neither naive nor memory T and B cells express effector molecules and they possess largely similar transcriptional programs, their response to secondary TCR or BCR stimulation differs qualitatively and quantitatively (Akondy et al., 2017; Klein et al., 2003). Therefore, the question arises: what are the mechanisms responsible for more effective yet specific response of lymphocytes during the infection with the same pathogen? These two properties of the adaptive immune response are mediated by two fundamentally different types of mechanisms: first, the higher magnitude and speed of the response is mediated by epigenetic programming, while, second, the specificity of the response is insured by gene recombination of TCR and BCR and clonal expansion of specific cell subpopulations upon antigen recognition.

Epigenetic Programming in Memory Lymphocytes

To achieve the faster and more pronounced reactivity of T and B lymphocytes upon reinfection with the same pathogen, epigenetic regulation is an ideal regulatory system allowing differential functionality of a cell without losing its identity. On the molecular level, epigenetic mechanisms are essential for regulation of gene expression (Jaenisch and Bird, 2003). DNA methyltransferases, chromatin remodeling, and histone modifying enzymes rearrange chromatin structure at gene regulatory elements and regulate accessibility of DNA for the transcriptional machinery. miRNAs silence gene expression at the level of transcription or

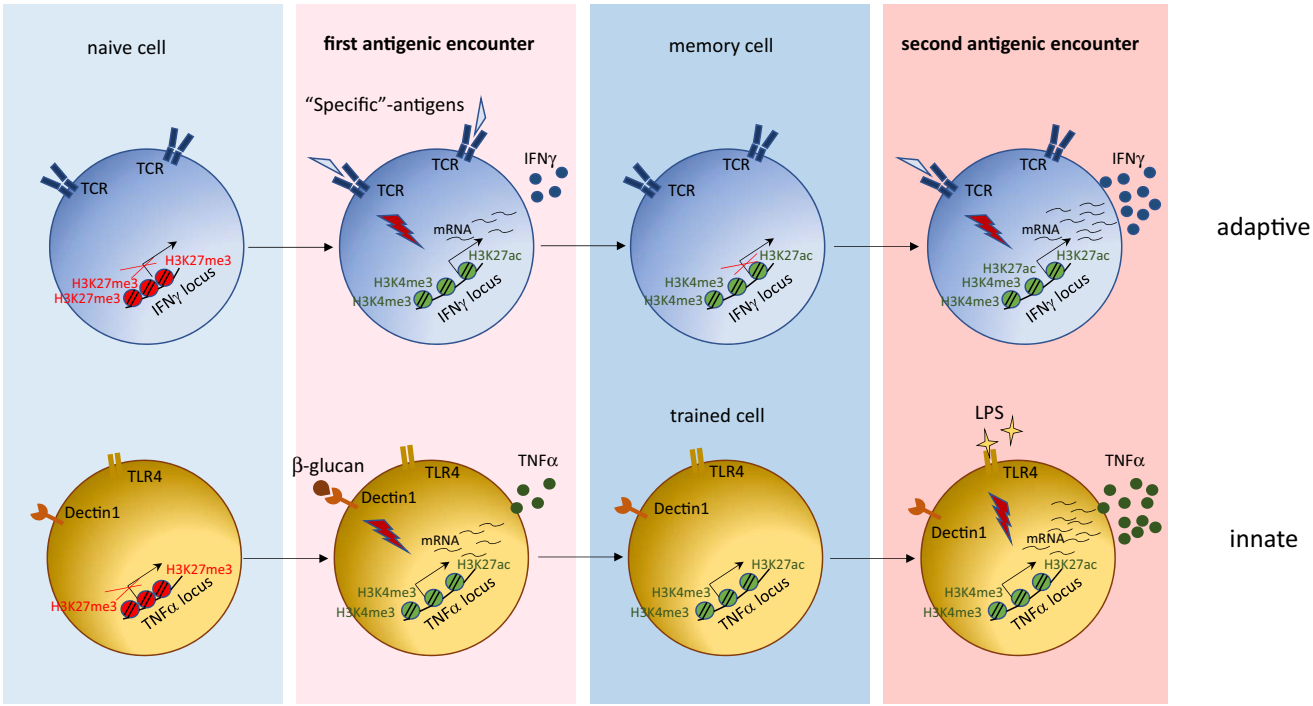

Figure 3. Amplitude of Immune Memory: Epigenetic Mechanisms
Epigenetic rewiring underlies both the adaptive characteristics of innate immune cells during trained immunity and amplification of the response in memory adaptive immune cells. Silencing of effector genes in naive immune cells is maintained by suppressive histone marks, such as H3K27me3. Initial activation of gene transcription is accompanied by loss and gain of specific chromatin marks such as H3K27me3 and H3K4me3, respectively, which are only partially maintained after elimination of the stimulus. The enhanced status of the innate immune cells, mirrored by persistence of histone marks such as H3K4me3- and H3K4me1-characterizing "latent enhancers," results in a non-specific stronger response to secondary stimuli upon re-challenge.

translation and lncRNAs can either foster or inhibit chromatin interactions. (Houri-Zeevi and Rechavi, 2017). Notably, once induced, epigenetic changes persist over time and are preserved through cell divisions, reflecting the past of a cell and allowing them to pass these "memories" to a daughter cell. Therefore, epigenetic regulation might not only be a hallmark of developmental and differentiation processes but explains molecularly the cellular hallmark of T and B cell memory, namely *increased magnitude and faster onset of response*. Importantly, transcriptional and epigenetic regulation also controls cell proliferation and clonal expansion, a key process of T and B cell memory.

Recently, the German Epigenome Programme (DEEP) generated a genome-wide epigenetic dataset for human peripheral naive, central, and effector memory CD4$^+$ T cells (Durek et al., 2016). This study showed a progressive loss of DNA methylation, the epigenetic mark mainly associated with gene silencing, from naive to central to effector memory CD4$^+$ T cells. Many regulatory elements that showed decreases in DNA methylation during naive to memory CD4$^+$ T cell transition were linked to genes known to be involved in CD4$^+$ T cell differentiation, such as T-bet, IL2 receptor subunits, RUNX3. DNA methylation changes also accompany differentiation of naive CD8$^+$ T cells into memory cells. Interestingly, DNA methylation was shown to be enriched at loci coding for genes characteristic for naive T cells, such as CD62L or CCR7. Vice versa, genes associated with memory CD8$^+$ T cells including T-bet and EOMES show enriched DNA-methylation in naive CD8$^+$ T cells, again suggesting that epigenetic regulation allows differential gene expression between naive and memory T cells (Abdelsamed et al., 2017; Youngblood et al., 2017). If loss of DNA methylation is one of the epigenetic mechanisms allowing memory T cells to react faster and with a higher magnitude, one would propose that gene loci for T cell effector molecules should be de-methylated in memory T cells but not in naive T cells. In fact, loci of genes responsible for CD8$^+$ T cell effector function such as IFNg, Perforin, GranzymeB (GZMB) and GZMK are methylated in naive CD8$^+$ T cells and become demethylated in memory CD8$^+$ T cells. Moreover, the methylation profile remains largely unchanged during homeostatic proliferation of memory CD8$^+$ T cells in the absence of an antigen (Abdelsamed et al., 2017; Youngblood et al., 2017).

A rearrangement of the DNA methylome has also been observed during differentiation of naive B cells to germinal center (GC) B cells and to memory cells, with more profound changes between naive and GC B cells than between GC cells and memory and plasma cells (Kulis et al., 2015; Lai et al., 2013). In fact, memory B and plasma cells, although relatively distinct transcriptionally, possess similar DNA-methylomes, while naive and memory B cells show more differences in DNA-methylomes despite their similar transcriptional programs. Moreover, among differentially methylated regions were enhancers enriched in transcription factor (TF) binding sites, especially those involved in B cell differentiation (Kulis et al., 2015; Lai et al., 2013). These observations suggest that decreased levels of DNA

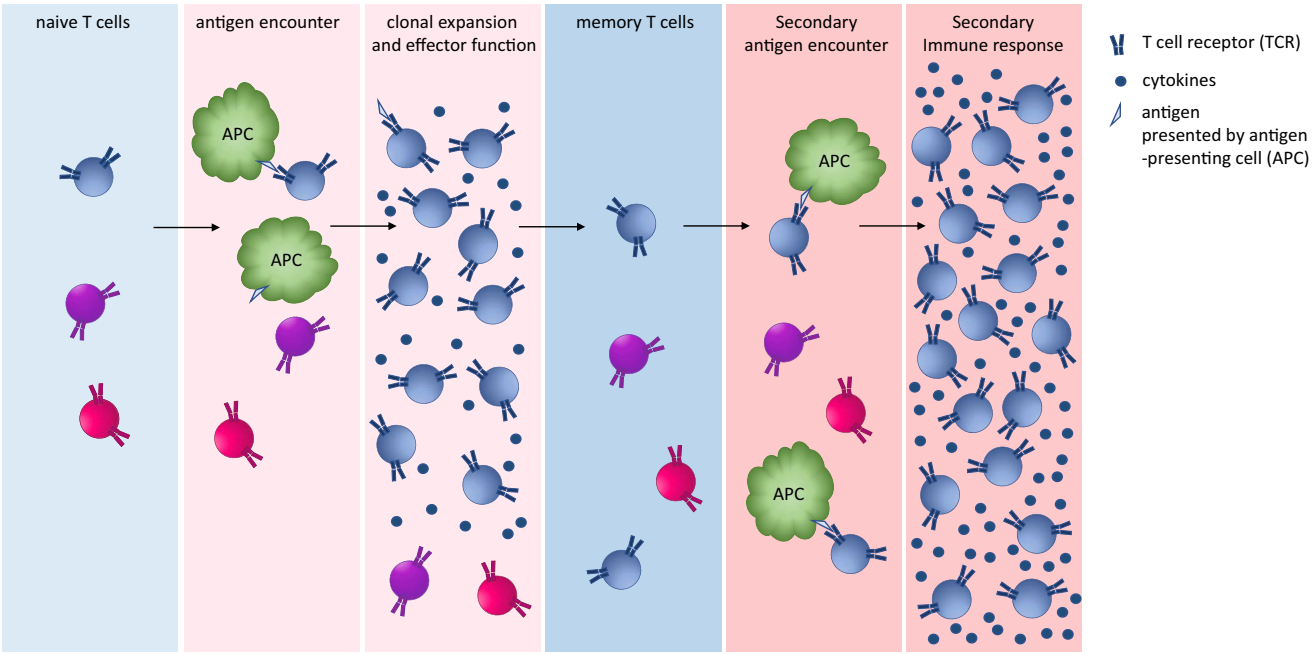

Figure 4. Specificity of Immune Memory: Antigenic Recognition and Clonal Expansion
Classical adaptive immune memory is induced by antigen presentation to specialized lymphocytes in the lymph nodes. After proliferation, elimination of the pathogen and contraction, a small number of memory lymphocytes persists to insure long-time specific memory to the target pathogen.

methylation at regulatory elements of effector molecules reflects the history of antigen encounter and facilitate faster and more pronounced expression of the effector genes upon reencounter of antigen.

DNA-methylation is not the only epigenetic modification that changes during naive T- and B-cell activation and persists in memory cells. In addition, histone modification patterns on regulatory elements allow the prediction of the subsequent gene expression status. Several studies addressed these changes during T-cell differentiation. A genome-wide analysis of histone modifications (H3K4me1, H3K4me3, and H3K27ac) in human naive, central memory, and effector memory CD4+ T cells revealed that loci coding for various cytokines including IFNγ, IL4, IL13, IL17, and IL22 are enriched in activating histone marks as compared to naive cells. In addition, they are more rapidly induced in memory than in naive T cells upon stimulation (Barski et al., 2017; Durek et al., 2016). Similar patterns were observed at gene loci coding for T-bet and RORC transcription factors known to be important regulators for effector molecules induced in memory $CD4^+$ T cells upon stimulation that, for instance, drive IFNγ and IL17 expression, respectively. Furthermore, there is a positive correlation between gain of H3K4me3 in memory CD4+ T cells at gene loci that are more inducible in memory cells than naive T cells, suggesting their poised status in memory cells (Barski et al., 2017).

Additionally, epigenetic studies have been conducted on $CD8^+$ T cells populations (Henning et al., 2018). The loss of activating H3K4me3 and H3K9ac histone marks and gain of suppressive H3K27me3 were observed on genes downregulated in effector $CD8^+$ T cell (such as FOXO1, KLF2, LEF, and TCF7), while the loss of H3K27me3 and/or gain of H3K4me3 were found on genes coding for effector molecules (such as Eomes, TNFa, IFNg, GZMB, CD27, BLIMP1, CCR7, or SELL) in memory cells (Araki et al., 2008; Russ et al., 2014). Interestingly, activating H3K9ac modification was increased in memory cells at loci of genes part of signaling pathways downstream of the TCR. This suggests that not only effector molecules but also early signal transduction can be quickly boosted upon secondary antigen-experience in memory T cells (Rodriguez et al., 2017). Whether this effect is also responsible for the higher magnitude seen in memory T cells requires further investigation.

Furthermore, activating H3K4me1 and H3K27ac histone modifications were shown to be enriched in effector and memory $CD8^+$ T cells at gene loci induced upon activation of naive cells, IL7r and Id2 for example (Yu et al., 2017) (Crompton et al., 2016). Similar to $CD4^+$ T cells, genes highly inducible upon stimulation in memory $CD8^+$ T cells were characterized by enriched H3K4me3 and depleted H3K27me3 modifications at their respective gene loci when compared to naive cells (Araki et al., 2009; Russ et al., 2014). Moreover, the genome-wide distribution of H3K4me3 and H3K27me3 marks in memory cells was more similar to effector than to naive $CD8^+$ T cells (Crompton et al., 2016; Russ et al., 2014).

An interesting group of cells who might bridge the development from naive to effector T cells are recently described stem-cell-like memory CD8+ T(scm) cells. Tscm possess partially naive phenotype ($CD44^{low}$ $CD62L^{hi}$) and memory characteristics: high expression of $IL2R\beta^+$ and $CXCR3^+$, increased proliferation potential and cytokine release in response to antigen re-stimulation (Gattinoni et al., 2011; Gattinoni et al., 2009; Zhang et al., 2005), and dependence on IL-15 and IL-7 for

homeostatic turnover (Cieri et al., 2013). The development of Tscm cells is also accompanied by epigenetic changes (Abdelsamed et al., 2017; Akondy et al., 2017). Transcriptomic and histone modification analysis in *in vitro* generated human Tscm suggest that this cell population consists of a developmental continuum from naive via Tscm to effector and memory T cells. Crompton et al. showed a progressive upregulation and downregulation of signature genes from naive T cells, Tscm, effector T cells to T memory cells, accompanied by progressive acquisition of H3K4me3 and loss of H3K27me3 histone marks (Crompton et al., 2016). Chromatin structure changes were further expanded to the DNA methylome analysis which showed a progressive loss of DNA methylation during development of Tscm cells from naive T cells (Abdelsamed et al., 2017), indicating that Tscm derive from naive T cells. This hypothesis was challenged however by the observation of long-lived CD8+ T cells generated in yellow fever vaccinated individuals, these authors proposing that Tscm generated from effector T cells (Akondy et al., 2017). Although the origin of Tscm needs to be better investigated, it is clear that the chromatin structure consists of a basis of enhanced cytokine response and proliferative potential of Tscm.

These data suggest that the elevated expression potential of a gene in memory T cells is encoded in its chromatin structure and molecularly resembles the functional hallmarks of a higher magnitude and faster response onset. It is primarily gained upon antigen-specific cell activation of naive T cells, then preserved in memory T cells during *in vivo* homeostasis.

Less is known about histone modifications in naive and memory B cells, but assessment of H3K4me1, H3K4me3, H3K36me3, H3K27me3, and H3ac showed that human B cell subpopulations have very distinct and specific epigenetic profiles. Transition from naive to GC B cells was found to be associated with a gain of activating histone marks H3K4me1, H3K4me3, and H3ac on genes induced during GC formation and a loss of these marks on genes that become silenced (Zhang et al., 2014b). Despite little knowledge being available about changes in histone modification landscapes during B cell commitment to memory subsets, several studies show the importance of histone modifying enzymes in memory B cell formation.

New research has also shed light on the enzymes and mechanisms responsible for the epigenetic programming of memory in lymphocytes. Histone acetyltransferase monocytic leukemia zinc finger protein (MOZ) is a histone modifier found to be important for proper GC and memory B cell formation (Good-Jacobson et al., 2014). MOZ is required during B cell activation and it was suggested that MOZ-induced histone modification during a primary response can alter the dynamics of secondary responses by affecting the memory B cell repertoire. As DNA methylation plays a role in memory B cell formation mutation of DNA, methylatransferase 3 beta (Dnmt3b) is correlated with a lack of plasma and memory B cells in ICF syndrome (immunodeficiency, centromere instability, and facial anomalies syndrome) (Blanco-Betancourt et al., 2004; Hansen et al., 1999; Xu et al., 1999). Dnmt3 deletion early during $CD8^+$ T effector cell differentiation resulted in decreased DNA methylation levels and re-expression of genes associated with naive cell state, therefore attenuating the formation of memory cells (Youngblood et al., 2017). In $CD4^+$ T cells, several histone-modifying enzymes, including H3K9 methyltransferase SUV39H1 and Jumonji Domain Containing 3 (Jmjd3) H3K27 demethylase, control naive T-cell commitment to effector cells by regulating effector cytokines and transcription factor expression. In the absence of SUV39H1 or Jmjd3, once committed Th1, Th2, or Th17 cells start to re-express cytokines of another lineage, suggesting that histone modifying enzymes are required in $CD4^+$ T cells to "remember" their original transcriptional programs (Allan et al., 2012; Li et al., 2014).

All in all, a large body of evidence demonstrates the important role played by epigenetic programming for mediating the changes in the magnitude and kinetics of T and B lymphocytes during induction of immune memory (Figure 3).

The second important property of the adaptive immune memory is represented by specificity of the responses. It is ensured by expression of highly specific receptors and immunoglobulins (Ig) by T and B cells. To be effective, highly specific immune response requires huge diversity of receptors and antibodies, which is achieved by somatic rearrangement of gene segments coding for TCR and Ig. In the classical process of V(D)J recombination, hundreds of gene segments, called variable (V), diversity (D), and joining (J), are assembled into one V-D-J exon. This "cut and paste" process is driven by RAG enzymes (encoded by recombination-activation genes) specifically expressed and indispensable in maturating lymphocytes. V(D)J recombination results in millions of TCR and antibody variants able to recognize and neutralize millions of various antigens. After successful rearrangement of its receptor, mature B or T cells express functional BCR (composed of transmembrane Igs) or TCR, respectively, ready for an antigen encounter. The presence of RAG proteins is strictly associated with the DNA rearrangement process, and the appearance of RAG genes during evolution has been believed for decades to be a core stone for development of adaptive immunity. To date, RAG homologs have been described in many jawed vertebrates but not in jawless vertebrates such as lampreys or hagfishes (Kumar et al., 2015). Despite the lack of recombination-activation genes, the immune response of jawless vertebrates does exhibit characteristics of adaptive immunity. This is mediated through lymphocytes carrying antigen-specific variable lymphocyte receptors (VLR) that emerge during somatic DNA rearrangement. Some VLRs can be secreted extracellularly and serve as antibodies (Herrin and Cooper, 2010).

The lymphocyte that carries an antigen-specific receptor undergoes clonal expansion upon activation by the antigen enriching the poll of immune cells in those able to recognize the encountered antigen. Clonal expansion of antigen-activated B and T cells not only assures a better defense during primary infection, but also makes the immune response more efficient upon secondary infection by the same agent. Elevated numbers of memory cells and antibody-producing plasma cells generated during clonal expansion augment chances of an encounter with antigen, making the secondary immune response much faster and more efficient (Campos and Godson, 2003). However, despite changes in numbers and relocation of memory cells to sites with increased chances of meeting an antigen (Aiba et al., 2010; Sathaliyawala et al., 2013), there might be intrinsic changes that allow memory cells to react more pronounced and faster to secondary immune challenges (Barski et al., 2017).

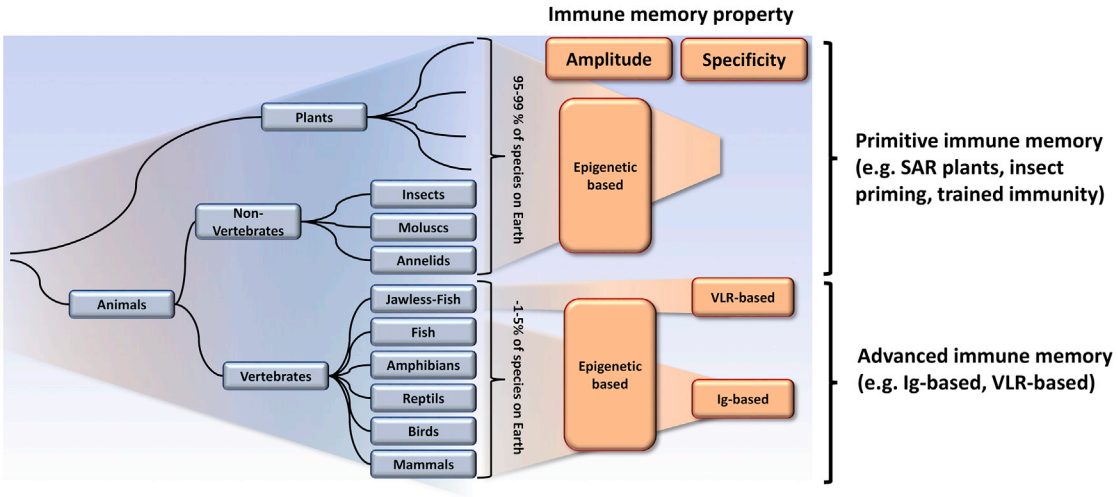

Figure 5. A Proposed Two-Step Model for the Evolution of Immune Memory
The first step is represented by ancient evolutionary epigenetic processes that insure an increased magnitude of the response to a second infection, and this characterizes both innate and adaptive memory. The second step evolved in vertebrates and insures that the memory is highly specific toward a certain pathogen, by involving the development of specific memory cells selected from a large repertoire obtained through gene recombination.

An Evolutionary Model Involving Two Steps for the Development of Immune Memory

In this Perspective, we reappraised the various mechanisms responsible for the induction of the two major forms of immune memory: classical adaptive immune memory and innate immune memory. Both forms are characterized by an improved response of the host after reinfection and have evolved to enhance the chances of host survival in an environment teeming with potentially lethal pathogenic microorganisms.

Based on the data presented above, we would like to propose a comprehensive concept as a basic framework of understanding the properties of immune memory in various groups of multicellular organisms. In this model, we propose that immune memory is a general characteristic of host defense of all living organisms. Evolution of immune memory in various groups of organisms is a continuum that started with the development of epigenetic mechanisms responsible for increasing the magnitude and speed of the immune response upon reinfection and continued thereafter with the build-up of specificity in vertebrates by mechanisms including gene recombination and clonal selection. Magnitude and kinetics amplification by epigenetic rewiring characterizes thus a more primitive form of innate immune memory, while both higher magnitude/kinetics and specificity characterizes the refined adaptive immune memory in vertebrates (Figure 5).

This is not to be seen as a static model, but it can change upon novel discoveries in the years to come. We can envision, for example, that new forms of adaptive immune memory will be described in complex invertebrate animals. Indeed, in line with the assessments that the advantages of building adaptive immune memory are especially obvious in long-lived organisms, it is conceivable and maybe even likely, that forms of specific adaptive immunity will be described also in some groups of complex invertebrate animals.

From a molecular perspective, we need to better understand how the epigenetic changes following an initial immune activation are translated to achieve more pronounced secondary responses with a faster onset. What are the epigenetic mechanisms that allow such an adaptation in behavior of immune cells? When is this behavior evolutionary beneficial? Why do only some stimuli lead to such a cellular response? And, as a consequence, can we identify rules that would allow us to predict immune memory responses to a given chemical entity? What are the modern-life situations that trigger immune memory outside our evolutionary understanding? Is immune memory in these incidences always detrimental? Very recent examples suggest that an unexpected induction of innate immune memory by Western Diet (Christ et al., 2018) or in the context of Alzheimer's disease (Wendeln et al., 2018) show the flop-side of an evolutionarily conserved immune mechanism. Furthermore, what is the role for locally induced innate immune memory, and how do tissues erase these memories if needed?

Other questions relate to the specificity of the epigenetic mechanisms and changes induced during induction of immune memory. Why are only some gene loci affected, and are they from certain classes? Mechanistically, what are the similarities and differences between the epigenetic changes observed in adaptive and innate immune memory? An important area of future research will be to identify and describe the memory characteristics of non-immune cells (e.g., epithelial cells, stromal cells, etc.). Indeed, very recent studies have shown epigenetically-mediated long-term changes in epithelial precursors (Naik et al., 2017; Ordovas-Montanes et al., 2018), with important roles in tissue defense and regeneration. The use of newly developed technologies, including single-cell omics sequencing, will represent an important support to answer many of these questions within the next decade.

Finally, in addition to the better understanding of immune memory at mechanistic and conceptual levels, we hope that the description of both adaptive and immune memory will lead to a more efficient design of vaccines. Indeed, one can envision that vaccines that are capable of inducing both forms of immune

memory at the same time would be more effective. A clear understanding of the processes driving immune memory at all levels is crucial to achieve this aim.

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