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Short Conceptual Overview

Memory immune response: a major challenge in vaccination

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Abstract

A crucial challenge for vaccine development is to design vaccines that induce a long-lasting protective immune response, i.e., immune memory. The persistence of antigen-specific antibody titers over a protective threshold, and the ability to exibit a 'recall response' to a subsequent encounter with an antigen have long been the only measurable correlates of vaccine take and immune memory development, suffering from the disadvantage of relying on long-term monitoring of the immune response. In the last few years, advances in the technologies for the identification and characterization of the cell subsets and molecular pathways involved in the immune response to vaccination have allowed innovative approaches to the identification of early correlates of immune memory. In this review, we discuss recent data and hypotheses on early correlates of the development of immune memory, with special emphasis on the gene expression signatures that underlie the self-renewal ability of some lymphocyte subsets, and their similarities with gene expression signatures in stem cells.

Keywords: humoral response; immune memory; self-renewal; systems biology; vaccination.

Introduction

Immune memory, namely the ability to mount an enhanced response to an antigen that has been previously encountered, is a system-level property of the immune system that arises from an increase in the frequency of antigen specific B and T cells, as well as from the differentiation of antigen specific lymphocytes into specific 'memory' populations, which display faster response to antigen re-exposure and the ability to self-renew (1, 2). The development of immune memory is the basis of the persistent protection afforded by the resolution of some infections and is the goal of vaccination. However, memory still represents in many ways a 'black box', for which intervention is difficult, making vaccine development a long trial and error process (3).

The persistence of antigen-specific antibody titers over a protective threshold and the ability to exibit a 'recall response' to re-encounters with antigens have long been the only measurable correlates of vaccine 'take' and immune memory. However, these methods for the evaluation of immune memory suffer from the disadvantage of relying on long-term monitoring of the immune response. Moreover, while the magnitude of the humoral response correlates with protection for all vaccines currently in use, it cannot be excluded that, for those cases where the development of a vaccine has been an elusive goal, qualitative features of the response other than the antigen-specific antibody titer may be relevant to protection.

In this review, we discuss recent advances in the monitoring and modeling of immune responses to vaccination, emphasizing a novel hypotheses for the mechanisms that underlie immunogenicity. In particular, in the past few years, systems biology approaches have suggested new methods for measuring vaccine efficiency, and for identifying ahead of time the development of protective immune memory.

Lymphocyte populations in the immune response

Following exposure to cognate antigens, naive lymphocytes become activated, proliferate, and differentiate into effector cells. After the expansion phase the population of antigen experienced cells undergoes a contraction phase, and memory cells form, which are a long-lived, self-renewing population (Figure 1).

Some of the qualitative differences between naive and antigen-experienced immune cells, for instance, the enhanced affinity of antigen receptors in memory cells, derive from the population dynamics during the acute phase of the response, whereby clones bearing higher affinity antigen receptors expand and outgrow lower affinity clones. In the case of B cells, somatic hypermutation of rearranged immunoglobulin variable genes allows affinity maturation of the antigen receptor (4, 5), whereas changes in the organization of the T cell receptor (TCR) complexes, in particular an increase in the size of TCR oligomers, have been recently related to the increase in sensitivity of antigen-experienced T cells (6). Memory B and T cells differ from their naive counterparts in a variety of cell-autonomous features, incuding activation requirements, division rate and function, and represent the long-term outcome of a differentiation process triggered by antigen exposure.

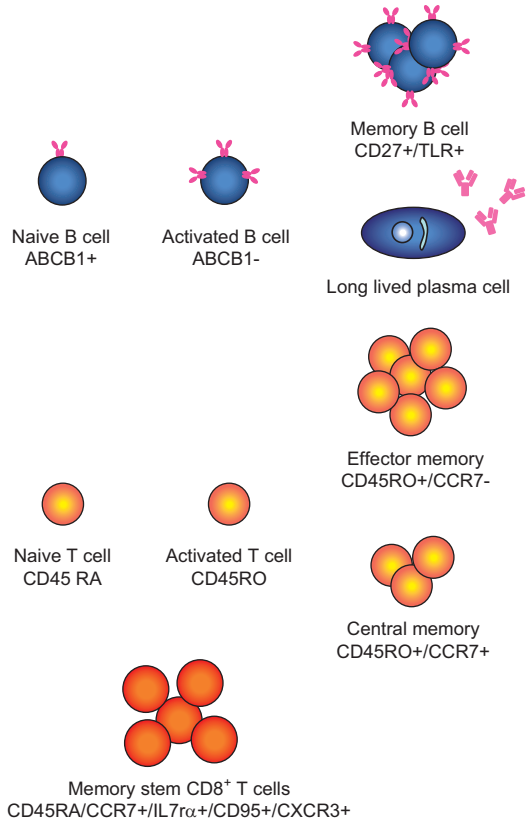

Figure 1 Development of memory B and T cells.
After infection or immunization, activated B cells differentiate into two long-term persistent subsets: memory B cells and long-lived plasma cells. Analogously activated T cells progress either towards a terminally differentiated effector memory phenotype or towards a central memory lineage. Memory T cells with stem-like properties have been identified in human blood.

Development of memory T cells

How memory T cell development occur is still a matter of study. The process is markedly linked to the metabolic state of T cells (7). In particular, an evolutionary conserved serine/threonine kinase, the mammalian target of rapamycin (mTor), has been recently identified to funnel multiple signaling pathways from inside and outside the cell (8). When activated, mTor promotes anabolic processes, enhances protein synthesis and cell growth and plays a role in immune functions (9, 10). In this context, the mTor pathway has also been described to be a major regulator of memory CD8 T cells (11–13). Moreover, during the acute phase of the response, cytokines play a role in the developmental process leading to memory cell formation, through the activation of transcription factors and the establishment of a characteristic epigenetic state of the nucleus (14, 15). In particular, in the case of $CD8^+$ T cells, the cytokines that have been implicated in the development of memory are IL6 (16), IL10 (17) and IL-21 (18). Although each of these cytokines has been associated with different functions, as IL-6 is associated with inflammatory responses, IL-10 plays an immunosuppressive role and IL-21 takes part in $CD4^+$ T cell-B cell collaboration in the germinal center reaction (19), signals from the IL-6, IL-10 and IL-21 receptors are all known to activate transcription factor STAT3 (19). Recent reports suggest that STAT3 activation is crucial in the development, maintenance and function of memory CD8 T cells (20). In particular, in the absence of either IL-10 and IL-21 or STAT3, virus-specific $CD8^+$ T cells retain terminal effector differentiation states and fail to mature into protective self-renewing central memory T cells (21). Dominant-negative STAT3 mutations cause, in humans, autosomal-dominant hyper-IgE syndrome (AD-HIES) that is characterized by immune conditions, including increased lymphoma prevalence, susceptibility to bacterial and fungal infections and a decreased ability to control varicella zoster virus and Epstein-Barr virus latency (20). AD-HIES patients have reduced numbers of central memory $CD4^+$ and $CD8^+$ T cells compared to healthy controls. Naive T cells from AD-HIES patients have lower expression of memory-related transcription factors BCL6 and SOCS3, a primary proliferation defect, and fail to acquire central memory-like surface phenotypes *in vitro* (20).

Humoral immune memory

Within the humoral immune response, memory is characterized by circulating antibodies (serological memory), memory B cells and long lived plasma cells (22). After infection or immunization, antigen-specific naive B cells proliferate and differentiate into memory B cells and short- and long-lived plasma cells (23). After the initial peak, the antibody titer declines but can remain above pre-immunization values for decades (22). Antigen-specific antibodies are detectable in the circulation for years after infection/vaccination and provide the first line of defense against pathogens. Long-lived plasma cells reside mainly in the bone marrow and constitutively produce and secrete antibodies. Unlike memory B cells, long-lived plasma cells contain minimal levels of B cell receptor (BCR) and cannot be stimulated to divide or boost the rate of antibody production.

In humans, memory B cells recirculate through the blood, but their main reservoir is lymphoid tissue. Under steady-state conditions, human memory B cells are slowly dividing, do not actively secrete antibody, and express a higher affinity B-cell receptor (24). In response to infection, memory B cells display a rapid recall response, quickly dividing and differentiating into antibody secreting plasma cells.

Defining lymphocyte subpopulations: surface markers

The identification of surface markers of memory T and B cells (reported in Tables 1 and 2 and Figure 1) has been instrumental to the understanding of the mechanisms underlying memory cell differentiation, self-renewal and function, which allows the enumeration of specific subpopulations within

Table 1 Markers of naive and memory cells.

Surface marker	Protein function	Expressing cell subsets	References
CD45RA	Tyrosine phosphatase (long isoform)	Naive T cells	(25, 26)
CD45RO	Tyrosine phosphatase (short isoform)	Antigen experienced T cells	(25, 26)
CCR7	Chemokine receptor (lymph-node homing receptor)	Central memory T cells	(27, 29)
CD62L	L selectin, adhesion molecule (leukocyte-endothelial cell interaction)	Naive T cells, Central memory T cells	(27, 29)
CD27	Tumor necrosis factor receptor (lymph-node homing receptor)	Memory B cells, plasma cells	(31, 32)
ABCB1	Multidrug resistance protein 1	Naive B cells,	(32)
Ki67	Nuclear protein associated with cellular proliferation	Circulating plasma blasts	(33)

complex samples and the isolation of specific subpopulations for molecular studies.

Different isoforms of protein tyrosine phosphatase CD45, generated by differential usage of three exons that code for an extracellular region close to the NH2 terminus, have been long used as surface markers of human naive and memory T cells, as the full-lenghth form CD45RA is expressed on naive T cells, whereas the shorter form CD45RO is expressed on antigen-experienced T cells (25, 26).

Expression of CCR7, a chemokine receptor that controls homing to secondary lymphoid organs, further divides human memory T cells into two functionally distinct subsets:

Table 2 Memory cell subsets.

Cell type	Surface markers	Function	References
Effector memory T cells	CCR7- (Express receptors for migration to inflamed tissues)	Immediate effector function Produce IFNg and IL4	(3, 14, 18, 27, 29, 35, 37, 40)
Central memory T cells	CCR7+ (lymph-node homing receptor) L-selectin+ (CD62L+)	Secrete IL2 High proliferative capacity. Differentiate into CCR7 effector cells upon restimulation	(3, 14, 18, 27, 29, 35, 36, 37, 40)
CD8 memory stem cells	CD45RA CCR7 CD62L Interleukin 7 receptor α CD95 IL-2Rb CXCR3 LFA-1	High self renewal capacity and therapeutic efficacy in a xenogtaft mouse model of adoptive cell therapy	(30)
Memory B cells	CD27 TLR ABCB1- CD19 CD20	Express high affinity BCR, mediate rapid recall response by quickly dividing and differentiating into antibody secreting plasma cells	(31, 32, 48, 66)
Plasma cells	CCR10 Beta 7 integrin CD27++ CD19- CD20- CD38 CD138	Contain minimal levels of BCR, costitutively produce antibodies, cannot be stimulated to boost the rate of antibody production	(33)
Plasma blasts	CD62L, HLA-DR, Ki67	Secrete less antibody than plasma cells, divide rapidly, are capable of internalize antigens, differentiate in plasma cells	(33)
Marginal zone B cells	IgM, Somatic mutated Ig genes	Response to bacterial polysaccharide	(34)

CD45RO$^+$ CCR7-memory cells, named effector memory cells, are relatively short-lived, express receptors for migration to inflamed tissues, display immediate effector function, and produce cytokines IFNγ and IL4; and CD45RO$^+$ CCR7$^+$ memory cells, named central memory cells, are long-lived and self-renewing, express lymph-node homing receptors CCR7 and L-selectin (CD62L), lack immediate effector function, efficiently stimulate dendritic cells, secrete IL2 but not IFNγ or IL4, have limited effector function but high proliferative capacity and differentiate into CCR7- effector cells upon secondary stimulation (27–29).

More recently, in analogy with other cellular systems, a population of memory CD8 T cells with stem-like properties have also been identified in human blood (30). The human memory stem cells express the CD45RA phenotype of naive T cells and others markers of naive T cells like CCR7, CD62L and interleukin 7 receptor α. However, unlike naive T cells, the memory stem cells express CD95, IL-2Rb, CXCR3, high levels of LFA-1, have undergone several round of division and show rapid cytokine production in response to TCR stimuli.

As in the case of T cells, expression of surface markers can allow the identification of subsets, of memory B cells and plasma cells. In particular, CD27 has been used as a marker for memory B cells (31). However there is also a fraction of memory B cells that lack the expression of CD27 (32). Memory B cells express TLR, whereas naive B cells do not. In contrast, the ABCB1 transporter is expressed exclusively on human mature naive B cells but not on immature activated or memory B cells (32). Also circulating plasma blasts and plasma cells can be distincted on the basis of surface markers. In fact a large fraction of circulating plasma blast and plasma cells express IgA, CCR10 and β7-integrin. Newly formed plasma blasts express CD62L, HLA-DR and Ki67, whereas plasma cells displaced from the bone marrow lack these markers (33). In humans, another population of circulating B cells is represented by marginal zone B cells. These cells express IgM and carry somatic mutated Ig genes. They respond to bacterial polysaccharide and are distinct from IgM memory B cells generated trough T-dependent responses (34). At present, a B memory stem cell population has not been identified.

Induction of immunological memory through vaccination

The absolute numbers of memory CD8$^+$ T cells is important for vaccine-induced protection, therefore there is great interest in the development of vaccination protocols that optimize that memory CD8 T cell development (35).

After vaccination, the superior protective capacity of memory CD8 T cells is closely linked to their increased abundance in both lymphoid and non-lymphoid organs and, as a consequence, much effort has been devoted to identifying strategies that increase the absolute numbers of memory CD8$^+$ T cells (35, 36). Among these strategies, prime-boost regimens are often used due to their ability to elicit large numbers of memory CD8$^+$ T cells (37, 38). The impact of this repeated antigen exposure on memory CD8$^+$ T cell differentiation has not been addressed in detail, and it is unclear whether repeatedly stimulated memory CD8$^+$ T cells are similar to primary memory CD8$^+$ T cells in terms of phenotype and function. A few recent studies have attempted to close this knowledge gap by stimulating memory CD8$^+$ T cells multiple times with heterologous infections expressing the same antigen (39–41). These studies show that multiple antigen encounters markedly impact memory CD8$^+$ T cell lineage, phenotype and function.

More recently, it has been reported that co-immunization strategies using DNA and virus-like particles induce sustained cellular and humoral memory immune response (42). Simultaneous co-administration of this multimeric protein and DNA resulted in a long-term sustained immunity that was of greater magnitude than administering the individual components alone or in a sequential DNA prime/protein-boost regimen (42).

Memory cell differentiation may occur in a non-linear fashion. Therefore, it would be important to establish which is the source of memory cells and the pathway of differentiation. Antigen-driven affinity maturation is certainly crucial for the establishment of memory B cells, whereas, especially for T cells, memory induction is further influenced by the context of antigen stimulation (cytokine milieu, chemokine signals and costimulation-as determined by the nature and activation of antigen presenting cells (APC) [reviewed in (3), (43), (44)]. In this context, the role of the innate immune system is critical. Recent reports indicate that different subsets of APC, by sensing microbes via pattern recognition receptors, become activated and modulate the strength, quality and persistence of adaptive immune response (45, 46). It is also well established that CD4 T cell help is important for the induction of memory B and CD8 T cells and crucial for their maintenance. Overall antigen specific T-B cell interaction is a highly orchestrated process that is initiated in primary lymphoid organs at the boundary between T and B cell areas, where T cells are primed by DC and macrophages lining the subcapsular sinus leading to rapid expansion and differentiation of B cells.

Finally, an important issue concerns the duration of memory. It is well documented that memory T and B cells as antibody levels in the serum persist for extended periods. In contrast, the duration of mucosal immunity is short lived. Costant numbers of circulating memory T and B cells are maintaned for virtually a lifetime in the absence of antigens through the help of cytokines. The survival cytokines for CD4 and CD8 T cells are IL7 and IL15 (47). For memory B cells, a survival cytokine has not yet been defined. However, it is known that an intact BCR and phospholipase Cγ2 are required for long-term maintenance of memory B cells (48). However, long-term plasma cells, which continually produce antibodies, survive without dividing in bone marrow niches formed by stromal cells where survival cytokines are provided (22).

Early correlates of immune memory

An analysis of the early features of the immune response that correlate with the long-term outcome of vaccination was

performed in humans receiving H5N1 avian flu vaccine (49). For avian influenza, microneutralization titers ≥80 have been proposed as a correlate of efficacy (50).

A priming protocol consisting of two injections of the vaccine, in adjuvant MF59, induced protective titers of neutralizing antibodies (51–53). The duration of the antibody response was limited, but a booster dose could quickly evoke protective titers if memory was succesfully induced (51–53). These observations would support a prime-boost strategy for the prevention of pandemic flu outbreaks, based on two immunizations for 'prepandemic vaccination' followed by a third 'booster dose' at the start of a pandemic outbreak. However, early markers would be needed to determine the proportion of the population that develops a memory response after priming. A clinical trial on healthy volunteers that received three doses of vaccine, at days 1, 22 and 202, and were monitored with respect to T cell responses and antibody titers up to day 382, reported a correlation between the increase in the frequency of antigen specific T cells after the first dose and a titer of neutralizing antibodies after the booster dose (49). In particular, a single dose of MF59-adjuvanted vaccine induced a 3-fold increase in the frequency of total antigen-specific-$H5^-$ $CD4^+$ T lymphocytes at day 22, with a minor increase after the second dose. The booster immunization at day 202 induced a 'memory' response, increasing the total $H5^-$ $CD4^+$ T cells to values 2-fold above the frequency observed after the first two doses. The number of H5-$CD4^+$ cells remained above baseline 6 months after the booster dose. In individual subjects, a ≥3-fold increase in the frequency of total cytokine + $H5^-CD4^+$ T cells after the first dose (day 22) correlated with the rise of MN titers ≥80 after booster vaccination and their maintenance 6 months later with 75% and 85% accuracy, respectively (49). In this immunization protocol, the adjuvant is essential to obtain a successful 'priming', as the plain vaccine, without adjuvant, never leads to protection. The administration of the vaccine without adjuvant caused only a 1.4-fold increase in the frequency of $H5^-$ $CD4^+$ T lymphocytes after the first and second dose, with no further increase after booster vaccination, and a contraction to values indistinguishable from baseline 6 months following booster immunization (49).

Importantly, the correlation between the size of the $CD4^+$ T cell population that responds to the vaccine and the titer of the humoral responses may reflect the role of $CD4^+$ T cells in the activation and proliferation of B cells, in the germinal center reaction and in the development of long-lived plasma and memory B cells (54–57). In a similar way, a correlation between protection and the frequency of antigen-specific CD4 T cells has been observed in a clinical trial of malaria vaccine RTS, S/AS, a subunit vaccine that consists of the repeat and C terminal region of the *P. falciparum* major circumsporozoite protein fused to the surface Ag of Hepatitis B virus and co-expressed with free surface antigen Ag (58).

To identify innate immunity signatures that correlate with the long-term immune response to vaccination with yellow fever vaccine YF-17D, gene expression profiling, multiplex analysis of cytokines and chemokines and flow cytometry data were integrated with computational modeling in a systems biology study (59, 60). YF-17D is a very effective vaccine, consisting of an attenuated viral strain (61). A single injection is able to induce a long-lasting neutralizing antibody response, as well a cytotoxic T cell response, that may play a role in protection (61).

Gene expression in peripheral blood mononuclear cells was analyzed by 'Affymetrix' microarrays at different timepoints, in particular 0, 1, 3, 7 and 21 days after vaccination (59). Genes modulated by vaccination were identified and doubly confirmed in another cohort (59). An enrichment of some transcription factor binding sites was observed, namely, the interferon-stimulated response element (ISRE), the binding site for the interferon regulatory factor 7 (IRF7) and the binding site for sterol regulatory element-binding protein 1 (SREBF1) (59). The network of regulated genes included interferon genes, genes involved in viral recognition, genes mediating antiviral immunity and complement genes (59). Regulated genes also included IP-10 and IL1α, and upregulation of CD86 on dendritic cells and monocytes (59). A similar immune signature was also observed in PBMCs stimulated *in vitro* with YF-17D for 3 and 12 h, which indicated that the vaccine is able to modulate the expression of these genes (59).

In the response to YF-17D, the peak of the expansion of CD4 and CD8 T cells occurs at 2 weeks. Activated CD8 T cells transiently upregulate HLA-DR and CD38, and the number of antigen-specific CD8 T cells is directly proportional to the size of the $HLA\text{-}DR^+CD38^+$ population (59). Immune responses, i.e., number of activated T cells and neutralizing antibody titers, varied among individuals by more than 10-fold. Although there was no correlation between the magnitude of the CD8 T cell response and the expression of IP-10, IL1α and CD86, the authors identified predictive rules that allowed the correct classification of vaccinees in high responders and low responders based on data from gene expression analysis performed at early timepoints of the immunization process, mainly at day 7 post immunization (59). The analysis suggested that gene EIF2AK, an integrated stress response gene, which regulates translation in response to environmental stress signals, could have a key function in mediating the $CD8^+$ T cell response to YF-17D (59). Similarly, gene expression signatures that predict the magnitude of the neutralizing antibody response at day 60 were identified. The analysis of the correlates of the antibody response suggested a key role for TNFRSF17, a receptor for the B cell growth factor BLyS-BAFF. Thus, the YF-17D study demonstrated the utility of systems biology approaches to predict the magnitude of adaptive immune responses (59, 60, 62).

Self-renewal of memory T and B cells

A further layer of understanding of the complexity of the immune response has been achieved in recent years, by total genome analysis of transcription, by analysis of the epigenetic state of the nucleus and by proteome analysis, allowing the definition of lymphocyte subsets based on unbiased molecular signatures (63). The search for correlates between

Table 3 Correlates of immune memory.

Early correlates:
• Increase in frequency of antigen specific T cells after the first vaccine dose (49)
• Changes in the gene expression profile of peripheral blood lymphocytes (59)
• In the case of the Yellow Fever vaccination (59), upregulation of:
– Interferon genes
–Genes involved in viral recognition and genes mediating antiviral immunity
–Complement genes
CD86 on dendritic cells and monocytes
Genes containing interferon-stimulated response element (ISRE), interferon regulatory factor 7 (IRF7), sterol regulatory element-binding protein 1 (SREBF1)
Late correlates:
• Significant increase of antibody titer after booster dose (49)
• Persistence of memory CD4 T cells above baseline 6 months after boosting (49)
• Long-term protection

patterns of gene expression and phenotypes allows the identification of genes and pathways not previously known to be involved in the immune response.

Analyses of lymphocyte transcriptome based on microarrays have demonstrated that different subsets of CD4 T cells are characterized by specific transcriptional signatures, and 'predictor genes' (64). The core signature of CD8 T cell memory differentiation that is conserved between mouse and human includes a common transcriptional program that is a general feature of memory differentiation in both B and T lymphocytes (65). A common feature of memory lymphocytes in all lineages is the elevated expression of transcription factors that could serve to enforce quiescence, e.g., KLF10 and BHLHB2 (65). Other transcripts shared by memory cells of different lineages, such as S100 family members, MYO1F and chemokine receptors, may be related to the ability of memory lymphocytes to migrate to sites of inflammation (65). Measuring the integrity of a defined gene expression signature corresponding to memory differentiation might be a useful surrogate marker for interrogating the human immune response and recognizing cells with the greatest potential to confer immunologic protection (65).

In the hematopoietic system, apart from memory T and B cells, the only cells that undergo self-renewal for the lifetime of the organism while retaining the ability to further differentiate when called on are long-term hematopoietic stem cells (66). Interestingly, memory T and memory B cells share a transcriptional program with long-term hematopoietic stem cells (Lt-HSC), a common signature of self-renewal including both up- and down-regulated transcripts (66). Transcriptional profiles suggest that the signaling molecules mitogen-activated protein kinase 12 and PKC-ζ and the transcription factor Pou6f1 may represent convergent nodes in the network of self-renewal pathways (66). Although nearly all of the transcripts shared between memory B and T cells were also found in Lt-HSC, many transcripts are shared between only one memory population and Lt-HSC, which supports the hypothesis that a given memory cell lineage reactivates only a subset of the redundant pathways expressed in HSC. For instance, the polycomb complex that includes Bmi-1 is likely to function in memory B cell self-renewal (66).

Finally, epigenetic studies, performed by gene expression profiling and analysis of histone-tail modifications in nucleosomes by chromatin immunoprecipitation followed by next-generation sequencing have provided an insight into the epigenetic mechanisms that allow effector genes in memory CD8 T cells to manifest transcription so much faster than in naive cells. Rapidly induced genes in memory CTLs were found to harbour histone modifications characteristic of active genes or those that are 'poised' to be transcribed, whereas in naive CD8 T cells they have modifications indicating chromatin remodeling is necessary for them to become transcriptionally competent (67).

Conclusions

Insights into the regulation of long-lived immune responses will have a profound impact on vaccine development strategies. Many of the factors governing the induction of optimal immunity are still incompletely understood and, in vaccine design and development, the numerous variables that intervene, including antigen-delivery systems, administration protocols, regimens, doses and matrices of prime-boost combinations, make the optimization of vaccination protocols a complex experimental problem. This area of research has seen in the past few years a rapidly expanding body of knowledge and impressive biotechnological achievements. Recent advances in the identification of memory cell subsets and early correlates of immune memory (Table 3) represents important advances in the field, and systems biology appears a feasible approach towards the definition of correlates of vaccine efficacy and the identification of protective immune memory ahead of time.

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