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Influence of immune aging on vaccine responses

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1. To understand the differences in vaccine responses based on age and how older adults respond to various types of vaccines.
2. To understand age-related defects in T cells and how that affects primary vaccine response.
3. To discuss ways in which aging affects the functionality of the B-cell compartment.
4. To understand different vaccination strategies that can be used to overcome deficiencies of vaccine responses in the aging immune system.

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Impaired vaccine responses in older individuals are associated with alterations in both the quantity and quality of the T-cell compartment with age. As reviewed herein, the T-cell response to vaccination requires a fine balance between the generation of inflammatory effector T cells versus follicular helper T (T_{FH}) cells that mediate high-affinity antibody production in tandem with the induction of long-lived memory cells for effective recall immunity. During aging, we find that this balance is tipped where T cells favor short-lived effector but not memory or T_{FH} responses. Consistently, vaccine-induced antibodies commonly display a lower protective capacity. Mechanistically, multiple, potentially targetable, changes in T cells have been identified that contribute to these age-related defects, including posttranscription regulation, T-cell receptor signaling, and metabolic function. Although research into the induction of tissue-specific immunity by vaccines and with age is still limited, current mechanistic insights provide a framework for improved design of age-specific vaccination strategies that require further evaluation in a clinical setting. (J Allergy Clin Immunol 2020;145:1309-21.)

Key words: *Vaccination, antibody, T cells, T-cell receptor, recall response, age*

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Abbreviations used
ABC: Age-associated B cell
AID: Activation-induced cytidine deaminase
BCR: B-cell receptor
JEV: Japanese encephalitis virus
miR: microRNA
mTORC: mTOR complex
SLT: Secondary lymphoid tissue
TCR: T-cell receptor
T_{FH}: T follicular helper cell
VZV: Varicella zoster virus
YF: Yellow fever

By 2050, there will be more than 1.6 billion adults 65 years and older worldwide, making age-related diseases and conditions growing public health concerns. One of the leading causes of hospitalization and death in the aging population is an increase in pathogenic infection (eg, influenza and pneumococcal disease). Moreover, newly emerging pathogens, such as the West Nile virus and severe acute respiratory syndrome coronavirus 2, responsible for the ongoing pandemic of coronavirus disease 2019 (COVID-19), show increased disease severity in the older population.[1,2] This age-related susceptibility to infection is further amplified by an impairment in protective vaccine responses in older individuals—both of which are linked to the erosion of adaptive immune function with age.[3-5] A major and consistent hallmark of immune aging is the significant alteration in both quantity and quality of the T-cell compartment. Here, we will review the current understanding of how an effective vaccine response is generated and how these responses change with age, discuss emerging mechanisms of T-cell aging that contribute to reduced vaccine responses in older individuals, and explore potential ways to manipulate T-cell responses to enhance overall vaccine efficacy and promote lasting immune protection in the older population. Although we focus primarily on human studies, we will indicate where animal studies are referenced for mechanistic insights.

FEATURES OF AN EFFECTIVE VACCINE RESPONSE

All modern vaccines work by tricking our immune system into developing "immunologic memory" against a specific infectious pathogen. This immunologic memory is mediated by B and T cells and typically manifests as the presence of antibodies in sufficient concentrations to neutralize the pathogen as well as the rapid effector cell generation when this pathogen is encountered in real life (ie, a "recall response"). Immunologic memory can last for decades[6-8] and thus provide lifelong protection against infection. To generate effective immunologic memory in response to vaccination, the specific orchestra of events must occur, starting from naive cell activation to memory cell formation and subsequent long-term memory cell homeostasis (overviewed in Fig 1). Any alteration in these events, both in quality and/or in quantity, can significantly influence the effectiveness of immune protection elicited by vaccines.

Most current vaccines rely on the generation of protective antibodies through B-cell and T follicular helper (T_{FH})-cell interactions. T_{FH} cells provide critical signals that are required for the development of long-lived memory B cells and plasma cells as well as high-affinity, class-switched antibodies. Indeed, the induction of T_{FH} cells correlates to higher avidity antibody responses after influenza vaccination.[9,10] In addition to optimizing antibody generation in recall responses, memory T cells can provide primary protection against infection. CD4 memory T cells are involved in preventing varicella zoster virus (VZV) reactivation in older individuals.[11,12] CD8 memory T cells, the induction of which largely depends on live vaccines, provide critical protection against viral pathogens such has influenza and respiratory syncytial virus, at least in part through the generation of tissue-resident memory CD8 T cells.[13-16] Understanding how functional T_{FH} and memory T cells are generated, as well as alterations in these processes with age, is essential to develop a successful vaccine.

Upon infection or vaccination, a small number of naive antigen-specific T cells undergo massive expansion, increasing up to 10,000- to 50,000-fold, while differentiating into effector T cells. After resolution of antigen, 90% to 95% of effector T cells die, with a small subset surviving as long-lived memory T cells.[17,18] Memory cells provide protection against repeat antigen exposure, due to higher frequency of antigen-specific T cells as well as their poised effector state. In mice, the precursors that eventually differentiate into antigen-specific memory CD8 T cells can be identified at the peak of primary responses by the expression of IL-7 receptor α, while the vast majority of effector CD8 T cells express KLRG1 and are short-lived.[19,20] Unlike CD8 T cells, definitive markers to identify memory precursors in the CD4 compartment have not been identified.[21] However, CD4 T_{FH} cells use a similar differentiation program as CD8 memory precursor T cells, which involves transcription factor networks of BCL6, TCF1, LEF1, and ID3. This is in contrast to the short-lived effector CD8 T-cell transcription factor network that involves BLIMP-1, RUNX3, and JUN.[22] Recent studies have also shown that decreased CD25 expression by early effector CD4 T cells predicts memory T-cell number in mice[23] and CD39 expression identifies short-lived effector CD4 T cells in humans.[24] Thus, these transcription factors and surface receptors are potential markers for delineating memory precursors and T_{FH} cells from effector T cells. Although the generation of short-lived effector cells is obviously critical for controlling pathogens in the context of infections, understanding signals favoring memory precursors or T_{FH} cells is relevant in the context of vaccination.

Several factors have been identified that are involved in the pathway decision to develop into short-lived effector versus memory or T_{FH} cells. Strong T-cell receptor (TCR) signal strengths (as measured by CD25 expression) favor terminal effector CD8 T cells, whereas memory precursor CD8 T cells are efficiently generated with relatively weaker TCR signals.[23,25] Similarly for CD4 T cells, stronger signals appear to favor T_H1 (ie, IFN-γ producing) cell development, whereas weaker signals are sufficient to induce T_{FH} and T_H2 cells,[23,25,26] although longer dwell times appear to be necessary to develop germinal center T_{FH} cells.[27] In general, the distinction between signal strength and duration of stimulation is difficult in most experimental systems, and at the extreme, sustained stimulation can lead to exhaustion. Costimulatory signals such as CD27 are also required for optimal memory T-cell development.[28,29] Equally importantly, inflammatory signals induced by the infection or adjuvanted vaccines determine memory T-cell fates.[30] Prolonged exposure to inflammatory cytokines such as IL-12 and IL-2 during priming favors short-lived effector cells through the

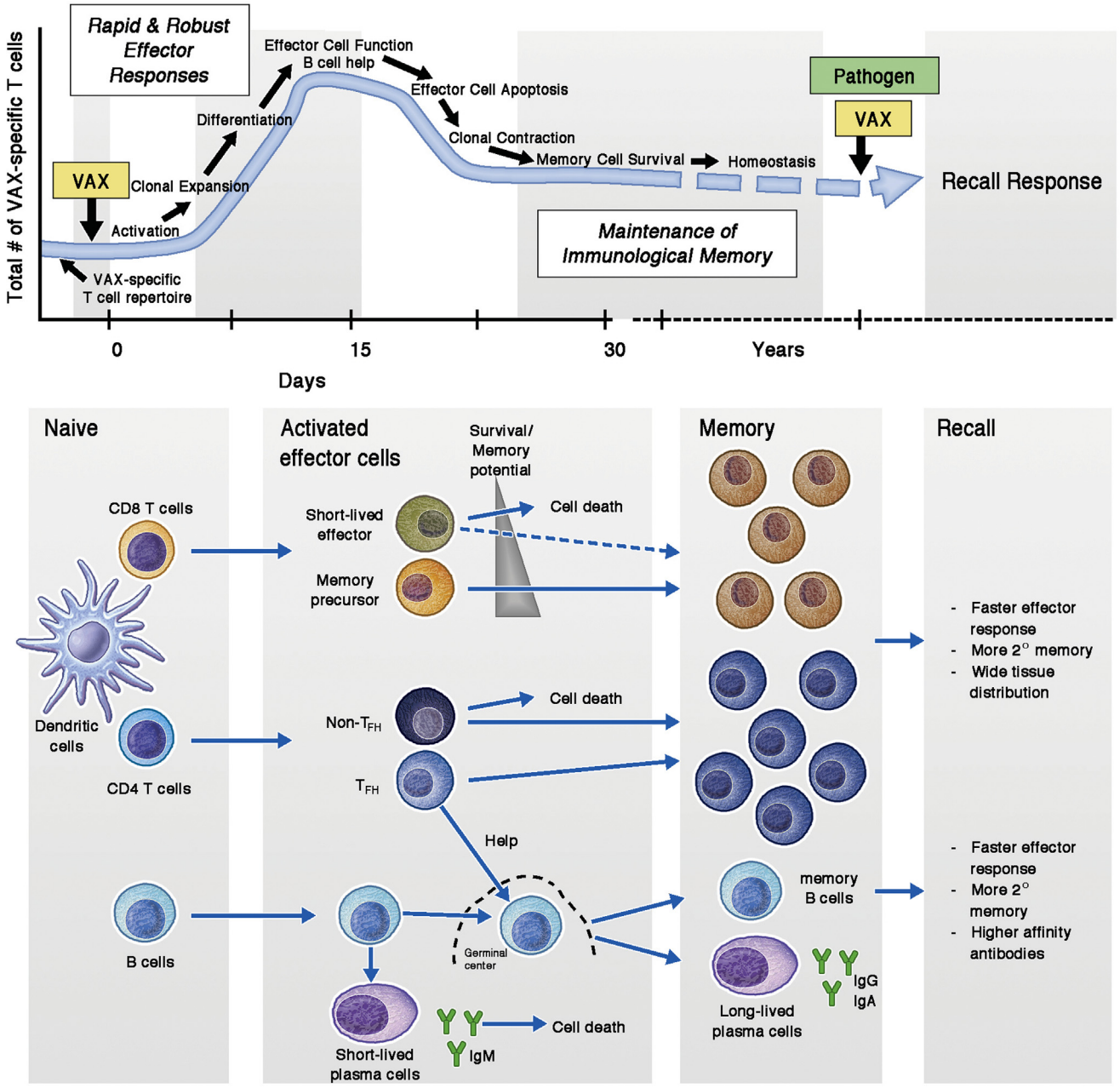

FIG 1. Key features of a primary T-cell response after vaccination. In the human T-cell repertoire, approximately 1 in every 10,000 naive cells will be a vaccine (VAX)-specific cell. Upon exposure to vaccination, these cells become activated through engagement of their TCR, and other costimulatory receptors, and undergo massive clonal expansion. During this expansion phase, activated naive cells differentiate into short-lived effector cells or memory precursor cells (MPECs). T_{FH} cells are generated, likely in a similar manner as MPECs, and provide critical help to B cells for the generation of high-affinity vaccine-specific antibodies. After resolution of vaccine antigen, most effector cells die. A small subset of MPECs survives to become long-lived memory T cells. These memory cells provide protection against subsequent infection or booster vaccination, possibly for decades, via a higher frequency of vaccine-specific cells, their poised effector state, and potential tissue localization. Recall responses after booster vaccination follow the same scheme, however, starting at higher initial frequency of VAX-specific T cells.

transcription factors T-bet and signal transducer and activator of transcription 5, whereas IL-10 and IL-21 improve memory precursor cell generation through signal transducer and activator of transcription 3 activation.[19,31-33] Metabolic programming is another critical determinant of T-cell fate. Upon activation, T cells activate an aerobic glycolysis program that, by providing precursor molecules through the pentose phosphate pathway, supports their massive expansion and their differentiation into short-lived effector T cells. In contrast, memory precursor cells depend on oxidative phosphorylation to generate ATP. Metabolic interference to switch from glycolysis to mitochondrial respiration is effective in redirecting T-cell differentiation. Improved memory

CD8 T-cell generation has been accomplished in mice by inhibiting glycolysis with 2-DG, inhibition of mTOR complex (mTORC) 1, and activation of adenosine monophosphate kinase.[34-36] Collectively, significant progress has been made to understand the molecular mechanisms that drive the generation of T_{FH} and memory cells versus short-lived effector T cells after infection and vaccinations. These insights from mice provide an excellent framework to examine how the vaccine response in humans is affected by age and design approaches that could improve vaccination efficacy.

VACCINE RESPONSES IN OLDER INDIVIDUALS

Interpreting vaccination studies is difficult in the older population, in particular due to the high heterogeneity of immune responses observed with age and the multitude of underlying comorbidities found within the aging population. Moreover, directly comparing the immune responses generated in vaccination studies is often challenging due to variations in the nature of individual vaccines (ie, live attenuated, protein subunit, adjuvant utilization, antigen dosing, etc) as well as the study group characteristics, including the exact definition of "older" adults ranging from older than 50 years to older than 80 years. In this review, we generally use the definition of 65 years or older for the "older" population.

Both in the clinical setting and in research, a response to vaccination is most commonly assessed by the levels of vaccine-specific antibodies within circulation. However, these levels do not always correlate directly with protection against infection. Antibody titers reflect the successful generation of activated B cells and short-lived plasma cells, if measured during the effector phase postvaccination, as well as long-lived plasma cells. Antibody functionality can additionally be determined by assessing the ability of antibodies to neutralize a pathogen, the antibody isotype (ie, IgG, IgA, IgM), and the levels of somatic hypermutation and antibody affinity. These data provide information not only on B-cell responses but also indirect insights into T_{FH} generation and functionality. Additional data are required to gain information on the generation of memory T cells or on tissue-resident T-cell formation that is critical for protective immunity at local tissue sites. Other techniques that are used to get a general idea of T-cell frequency and functionality postvaccination include delayed-type hypersensitivity testing, antigen-specific tetramer staining, *ex vivo* detection of surface activation markers (eg, HLA-DR, CD38, and inducible costimulator on circulating T_{FH} cells), and *in vitro* stimulation with vaccine antigens to determine cell proliferation and cytokine production. A marker for the quality of the vaccine-specific memory T-cell response is its polyfunctionality, that is, the ability to coproduce multiple cytokines such as IFN-γ, TNF-α, and IL-2.[37] Below we discuss the current literature on primary and recall vaccination responses during aging.

Impaired primary responses to vaccination in older individuals

In older individuals, most vaccinations are given to boost preexisting immunity. There are few studies on primary responses in humans, making it difficult to study these responses in aging. Early studies looking at primary vaccine responses in humans used a live, attenuated yellow fever (YF) virus vaccine, which is one of the most effective vaccines currently available. These studies demonstrated that older individuals have slower generation of antibodies as compared with young adults, coinciding with higher viremia at 5 days postvaccination.[38] However, by 28 days vaccine-specific antibody levels were similar between age groups and viremia was controlled. A large clinical study similarly found equal titers of YF-neutralizing antibodies 30 days postvaccination across ages.[39] These data suggest that the aging immune system has the potential to develop sufficient primary responses, albeit possibly at a slower rate. Additional YF vaccine studies, however, found that the neutralizing capacity of YF-specific antibodies at peak response (day 14) is lower in individuals older than 50 years, as was the effector response for CD8 T cells,[40] suggesting that although the immune system can respond to develop sufficient immunologic memory for B cells and CD8 T cells, the generation of the effector phase may be compromised in older individuals. Moreover, although CD4 T cells specific to YF had similar frequencies across age, these cells were qualitatively much less polyfunctional in older adults compared with young. YF-specific CD4 T cells also showed significantly less long-term survival with age, implying ineffective development of immunologic memory for CD4 T cells.

Similar to the above YF studies, 2 more recent studies using inactivated, adjuvanted vaccines, one for hepatitis B and the other for Japanese encephalitis virus (JEV), found that older individuals displayed delayed and overall reduced primary antibody responses compared with young adults.[41,42] For JEV, almost 50% of individuals older than 60 years did not reach antibody levels required for a protective response, compared with less than 15% in young adults.[42] In addition, JEV-specific memory T cells (day 35 postvaccination) were tested for their recall ability. The production of IFN-γ, a main effector cytokine, was significantly lower in the older cohort compared with the young, as was IL-10. IL-2 responses were similar between groups, together suggesting that memory T-cell polarization in response to vaccination is altered with age. Thus, from the limited data sets available, it appears that the ability of older individuals to mount primary vaccine responses fails in 3 distinct ways: impaired CD8 T-cell effector responses, reduced CD4 T-cell functionality, and possibly poor memory T-cell maintenance, although this last concept requires further, more detailed study.

Differential recall responses in older individuals

Most vaccinations that are recommended for older adults are given to boost preexisting immune memory from previous vaccination or infection. Although these booster vaccines reduce the disease burden to some extent, infections such as influenza and those caused by *Streptococcus pneumoniae* or herpes zoster reactivation are still highly prevalent in the older population, indicating ineffective recall responses. Because T cells more specifically mediate influenza and herpes zoster protection, we will examine these vaccine responses independently and attempt to integrate what we know about their B-cell and T-cell responses into a collective understanding of the capacity of the aging adaptive immune system to mount recall responses.

Influenza virus. Respiratory infection caused by the influenza virus is one of the major causes of morbidity and mortality in older adults. This increased susceptibility and predisposition to poorer outcome is attributed to immune aging.[43] Indeed, multiple vaccine studies find that older adults display significantly reduced

influenza-specific antibody responses compared with young adults[44,45] and/or fail to maintain durable antibody titers indicative of immune protection (termed "seroprotection").[46] In addition, the antibodies that are produced in older individuals have a lower ability to prevent, or "neutralize," infection, as well as display restricted repertoire diversity and fewer somatic hypermutations.[47,48] Although influenza-specific memory B-cell frequencies are similar across age, older individuals show significantly lower expression of activation-induced cytidine deaminase (AID) and BLIMP-1, a transcription factor involved in plasma cell differentiation.[49] These features are indicative of altered germinal center interactions, with an upstream dysfunction in T_{FH} cells and a downstream impairment in plasma cell differentiation, respectively. Indeed, although relatively similar in frequency, circulating influenza-specific T_{FH}-like cells demonstrate lower IL-21 and inducible costimulator expression in older adults compared with young adults after vaccination, which could significantly impact high-affinity antibody generation within secondary lymphoid tissues (SLTs).[50-52] However, because circulating T_{FH} populations are distinct from those in tissues,[53] further studies are required to truly determine the impact of aging on influenza-specific T_{FH} frequencies and functionality.

In mice, the CD8 T-cell responses to influenza are diminished with age[54]; however, whether the same defect holds true in humans is less clear. Before vaccination, CD8 T-cell immunity against influenza vaccination is reduced, with older adults having significantly lower basal frequencies of circulating influenza-specific memory CD8 T cells than young adults.[55,56] This reduction is in conjunction with TCR repertoire narrowing,[57,58] which is likely associated with the altered functionality of these cells with age. Indeed, CD8 responses to influenza antigen displayed reduced polyfunctionality and increased expression of senescence-associated markers CD57 and KLRG1 with age.[56,59] Moreover, influenza-specific memory T cells in older individuals are more effector-like (ie, higher T-bet),[59] which may suggest they are more short-lived with a potentially reduced proliferative capacity. Collectively, these data suggest overall impairment in the generation of effector cell function and immunologic memory upon influenza vaccination in older individuals and highlight the need for better understanding of vaccine-specific interactions both systemically and within local tissue sites.

Varicella zoster virus. Unlike influenza, VZV infection is a latent viral infection in which immunologic memory, in particular T-cell memory, is required to prevent viral reactivation presenting as shingles or herpes zoster. Unfortunately, immunity acquired naturally against this pathogen breaks down with age.[60] Zostavax (Merck & Co, Whitehouse Station, NJ), a live attenuated variant of VZV, was developed to mimic infection and bolster the waning immune memory in older adults. Although it reduces the incidence of herpes zoster by approximately 50% in adults older than 60 years, its efficacy dramatically declines with age, where adults older than 80 years show only 18% vaccine efficacy.[61,62] Moreover, the immune protection induced by the vaccine diminishes within 8 years after vaccination regardless of age.[63,64] Thus, Zostavax does not generate robust long-term immunologic memory in older individuals. Somewhat surprisingly, Zostavax is able to generate similar CD4 T-cell responses in young and older individuals. However, the T-cell response reached maximum levels slower with age,[65] in part because of a failure to expand preexisting large VZV-specific CD4 memory T-cell clones.[66] Instead, Zostavax vaccination mostly recruited VZV-specific T cells from the naive repertoire, which in the absence of a booster vaccination may not reach sufficient frequencies to be protective. Moreover, CD4 T cells lose polyfunctional cytokine production with age.[65] Most importantly, age is associated with an accelerated contraction of VZV-specific CD4 T cells immediately after vaccination-induced peak effector responses,[67] possibly due to a preferential generation of short-lived effector T cells. Thus, although Zostavax appears to induce sufficient effector levels, the quality of this response is compromised with age, as is its ability to generate or maintain effective long-term memory T cells. Although Zostavax elicits vaccine-specific antibody production,[68] little is known about how age affects the memory B-cell responses.

Recently, a new adjuvanted subunit vaccine for VZV, called Shingrix (GlaxoSmithKlein, Research Triangle Park, NC), was developed. Strikingly, this vaccine provides more than 97% efficacy across all ages.[69,70] Moreover, the immunologic memory developed by the vaccine lasts for at least 9 years, and potentially longer.[71,72] Although the underlying mechanisms for why this vaccine works significantly better than Zostavax in older individuals is currently unclear, Shingrix induces more vaccine-specific CD4 and CD8 memory T cells that persist much longer.[73] These cells also display higher IFN-γ responses. Thus, this new vaccine strategy appears to induce significantly better immunologic memory and suggests that aging memory T cells may require stimulation conditions distinct from that of young memory cells for sufficient recall responses. We will discuss this possibility in further detail below.

Streptococcus pneumoniae. Pneumococcal pneumonia is a highly prevalent bacterial infection in the aging population. There are 2 types of vaccines targeting *Streptococcus pneumoniae* currently available: a polysaccharide-based vaccine (PPSV23) and a polysaccharide-protein conjugate vaccine (PCV13).[74] As of June 2019, the Centers for Disease Control and Prevention recommends a single booster dose of PPSV23 for healthy adults 65 years or older; thus, we will focus primarily on PPSV23 responses with age. Although the overall effectiveness of PPSV23 in the older population is somewhat variable, a recent study found the overall efficacy of PPSV23 to be 25% in adults older than 65 years.[75] Other studies have found vaccine efficacies against invasive pneumococcal disease ranging from 45% to 73%.[76] The protection provided by the PPSV23 vaccine however consistently and rapidly wanes over time,[76,77] highlighting the hyporesponsiveness of polysaccharide antigens to booster immunologic memory.

Immunologically, PPSV23 vaccination induces similar levels of vaccine-specific IgG across age.[74,78,79] However, vaccine-specific antibodies produced in older individuals are significantly less functional than in young,[80] displaying a reduced capacity to opsonize pneumococcal bacteria. This loss of functionality has been linked with the reduced generation of vaccine-specific IgM and IgA in older individuals.[78,79,81] There is also evidence from mouse studies that CD4 T cells are required for effective antipolysaccharide antibody responses[82,83]; however, the responsiveness of T cells, particularly those within mucosal tissues, to PPSV23 in older adults is still unclear. In addition, the use of PCV13 (currently recommended in multiple European countries), which in theory should elicit higher T-cell responses and better mucosal immunity, only showed 65% efficacy in adults aged 65 years and rapidly dropped to 40% in adults aged 75 years.[84,85] Thus, there is significant room for improved understanding of

TABLE I. T-cell and B-cell responses to vaccination with age

Phase of dysfunction	Age-related changes	Vaccine response
Initial antigen-T-cell interactions	- **Decline in total vaccine-specific T-cell numbers** - **Reduced TCR diversity of naive cells** - **Impaired dendritic cell interactions** - **SLT breakdown**	- **Reduced generation of effector and memory T cells** - **Lower T_{FH} generation**
Activation/expansion	- **Reduced TCR signaling** - **Partial differentiation of naive T cells** - Cellular senescence	- **Reduced T-cell expansion** - **Altered functionality of effector and/or memory T-cell responses**
Differentiation	- **Aged naive T-cell bias toward effector not memory or T_{FH}** - **Naive T cells bias toward T_H9** - *Reduced Blimp-1 expression by B cells*	- **Reduced generation of memory T cells** - **Lower T_{FH} generation** - **Altered functionality of effector and/or memory T-cell responses** - *Reduced plasma cell generation*
Effector function	- *Lower antibody secretion by plasma cells*	- *Reduced levels of antibodies*
Germinal center interactions	- **Reduced T_{FH} function** - *Lower AID expression in B cells*	- *Reduced antibody affinity* - *Reduced antibody function*
Memory survival/ homeostasis	- **Increased frequencies of TEMRAs** - **Altered metabolic function in memory T cells** - **Increased CD39 expression on memory T cells** - *Increased frequencies of ABCs*	- **Reduced memory T-cell survival** - **Lower T-cell recall responses** - *Lower B-cell recall responses*

TEMRA, Terminally differentiated effector memory cells.
T-cell–specific changes in boldface. B-cell–specific changes in italics.

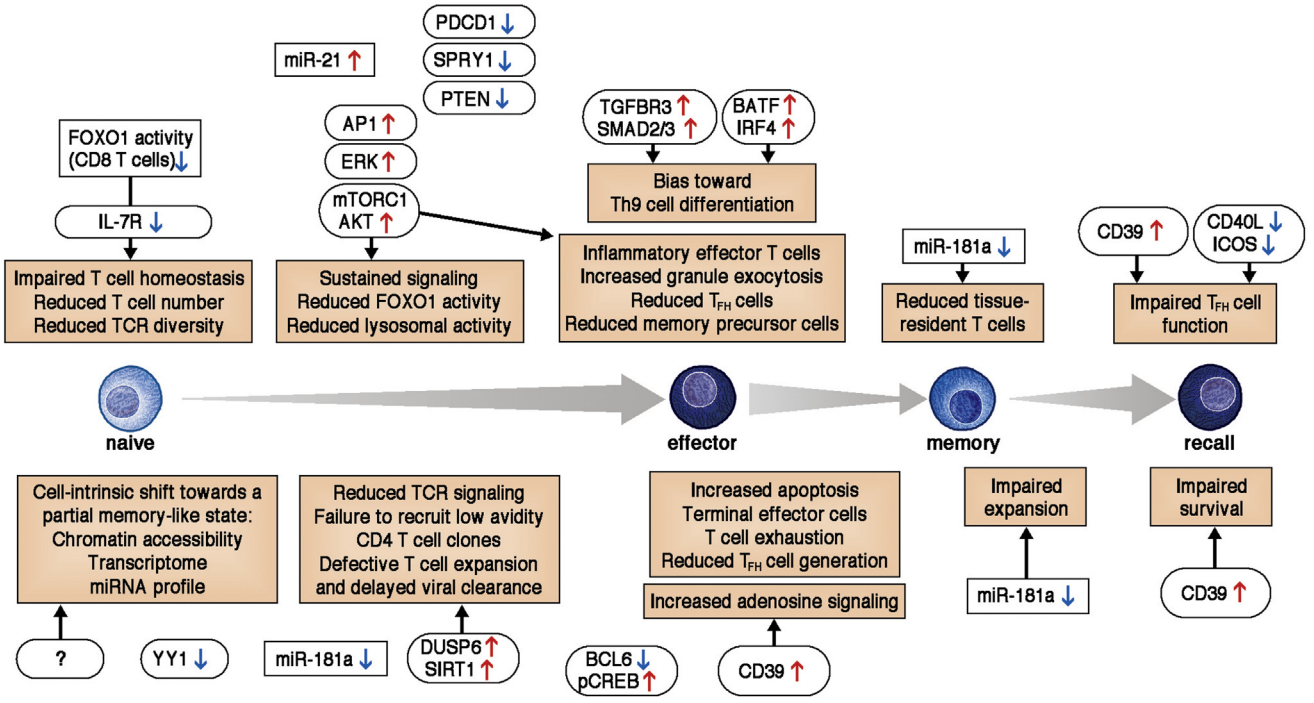

FIG 2. Molecular mechanisms of age-associated defects in T-cell responses to vaccines. A mechanistic overview of known age-related changes in key regulators of primary and recall T-cell responses to infections and vaccinations and their functional consequences (orange boxes). Red arrows indicate increases and blue arrows indicate decreases with age.

polysaccharide-based immunity, vaccine design, such as the addition of adjuvants,[86] and age.

Is it all that bad? Diphtheria versus tetanus. The differential ability of the aging immune system to induce an effective recall response is particularly highlighted in the case of diphtheria and tetanus, in which these 2 components (both toxoids), along with pertussis antigen, are delivered together in a single vaccine, Tdap. Here, both vaccine antigens induce robust effector responses, reaching similar antibody titers in both young and old adults.[87,88] However, 5 years after vaccination, more than half (54%) of older adults have lost protective levels of diphtheria-specific antibodies, versus a quarter (24%) of young adults.[87] Conversely, all individuals maintained high protective levels of tetanus-specific antibodies. Tetanus toxoid induces robust CD4 T-cell responses,[89] which could potentially explain differential antibody responses. However, frequencies and

functionality of circulating CD4 T-cell recall responses to both tetanus and diphtheria toxoid were similar across age groups.[87] Moreover, the neutralizing capacity of diphtheria-specific antibodies was maintained in older individuals, suggesting sufficient T_{FH} help. What allows tetanus antigen to maintain better immunologic memory than diphtheria antigen remains unclear but may provide an interesting basis to study age-related mediators of protective immunity.

MECHANISMS OF DECLINING VACCINE RESPONSES WITH AGE

Immune aging is commonly considered synonymous with "immuno-senescence." However, this term is misleading if implying that cellular senescence is the major driver of immune aging.[3] Senescence is a cellular state typically defined by an irreversible growth arrest, which impairs cellular proliferation. Immune cell senescence, for example, as a consequence of telomere shortening,[90] could cause poor vaccine responses, because these responses rely on the ability of T and B cells to proliferate. However, as described above and detailed below, T-cell dysfunction with age is not primarily based on an inability of T cells to proliferate in response to antigenic stimulation, but population changes in combination with cellular changes that affect individual steps in the vaccine response. Table I delineates critical steps in the vaccine response and how they could be affected by age-associated defects, starting from a reduced starting pool of vaccine-responsive cells to poor survival of vaccine-specific memory cells. These models are not mutually exclusive, but the defects act in concert, with differences depending on the individual and the vaccine. Below we detail current mechanistic understanding of age-related changes in T cells, as well as discuss those in B cells, that may account for these alterations in older individuals.

Age-related defects in naive T cells that affect primary vaccine responses

Primary vaccine responses in older individuals display features consistent with impaired effector T-cell development, altered effector functionality, and reduced generation of long-term immunologic memory. An overview of known mechanisms that contribute to dysfunctional development of effector and memory responses in naive T cells with age is provided in Fig 2.

Antigen-specific naive cell precursors typically range from approximately $1/10^6$ to $1/10^5$ cells within the T-cell population of adults.[91,92] Thus, an easy explanation for lower effector cell responses is simply a reduction in naive cells available to participate in vaccine-specific immune responses. Indeed, a key and highly reproducible feature of immune aging is the quantitative loss of naive T cells.[93-95] This loss is much more prevalent in the CD8 compartment than in the CD4 compartment, in which the starting pool of naive CD8 T cells is lower than that of CD4 in young adults and contraction rates with age are higher. For example, a recent study quantified absolute numbers of naive T cells across age where naive CD4 T cells contracted from approximately 300 to approximately 200 cells/μL in 20- to 70-year-olds, respectively, and naive CD8 T cells contracted from approximately 200 to approximately 50 cells/μL.[95] Whether this contraction alone is sufficient to alter the inherent ability of the naive T-cell repertoire to recognize specific antigens from new pathogens or vaccines as we age is unclear. However, this cellular contraction is in tandem with a significant loss of TCR diversity in both CD4 and CD8 naive compartments.[96,97] A 4-fold contraction in diversity has been estimated with age, from approximately 20×10^6 unique receptors in young to approximately 5×10^6 in healthy older individuals for both CD4 and CD8 naive T cells,[96] which implies a significant loss of unique antigen-specific naive T cells in older individuals. Consistently, diminished YF vaccine-specific CD8 and CD4 effector responses were found to be highly correlated with baseline frequencies of naive CD8 and $CD31^+$ naive CD4 T cells, respectively.[40] Collectively, an overall contraction of the naive T-cell repertoire together with lower cell numbers may account, at least in part, for reduced primary vaccine responses, although complete loss of recognition of specific antigens in the human repertoire is unlikely given the extensive diversity and cross-reactivity of the TCR.[98]

Although the loss of naive cells could be a potential causative factor in decreased effector responses, a quantitative decrease alone does not account for *functional* differences observed in effector and memory T-cell responses, as well as in B-cell responses. Consistently, recent studies reveal that naive CD8 T cells not only have decreased survival with age but that they also become phenotypically and functionally distinct from naive T cells in young adults —becoming more epigenetically, transcriptionally, and posttranscriptionally (ie, microRNA [miR]) similar to central memory T cells.[99,100] This partial differentiation appears to be naive cell–intrinsic and distinct from infiltration of the naive compartment with naive-like memory cells, a population that increases in frequencies in older individuals. As humans lose the ability to make new naive T cells via thymic output,[101,102] the cause of this partial differentiation phenotype could be 2-fold: selection of long-lived, more memory-like cells and/or adaptation of naive cells to an aging (and possibility inflamed) tissue environment. The first scenario is intriguing because recent fate mapping studies in mice have found that the naive CD8 T-cell compartment in adults is composed of multiple subsets that have distinct developmental pathways and unique responses to infection.[103,104] However, mathematically, an adaptation scenario is favored, where cells adapt to their environment, becoming more fit (ie, acquire a survival or proliferative advantage) with age.[105] It is also more consistent with the loss of stem-like features and reduced plasticity we observe in naive T cells in older individuals,[99,106] and in line with conversion of naive T cells to virtual memory–like cells observed in mice with age.[107,108] Virtual memory cells are a "naive" cell population that acquires features of memory T cells without prior antigenic stimulation, driven instead by cytokine-mediated signaling.

A specific feature that may account for reduced effector responses from naive T cells with age is impaired TCR signaling. In naive CD4 T cells from older individuals, reductions in the transcription factor YY1 mediate lower miR-181a expression, leading to reduced ERK signaling upon TCR engagement.[109,110] Similar reductions in miR-181a are found in naive CD8 T cells with age[100] and likely contribute to reduced TCR signaling in these cells as well. Reduced miR-181a with age is functionally important. In a mouse model of miR-181a deletion in peripheral T cells, the generation of antiviral CD8 T-cell responses is impaired, causing defective viral clearance and reduced generation of liver-residing memory CD8 T cells[111]—similar defects to those seen with vaccinations during aging.

Consistent with the reduction in frequencies of vaccine-induced memory T cells in older individuals, activation of naive T cells in older individuals favors short-lived effector T-cell

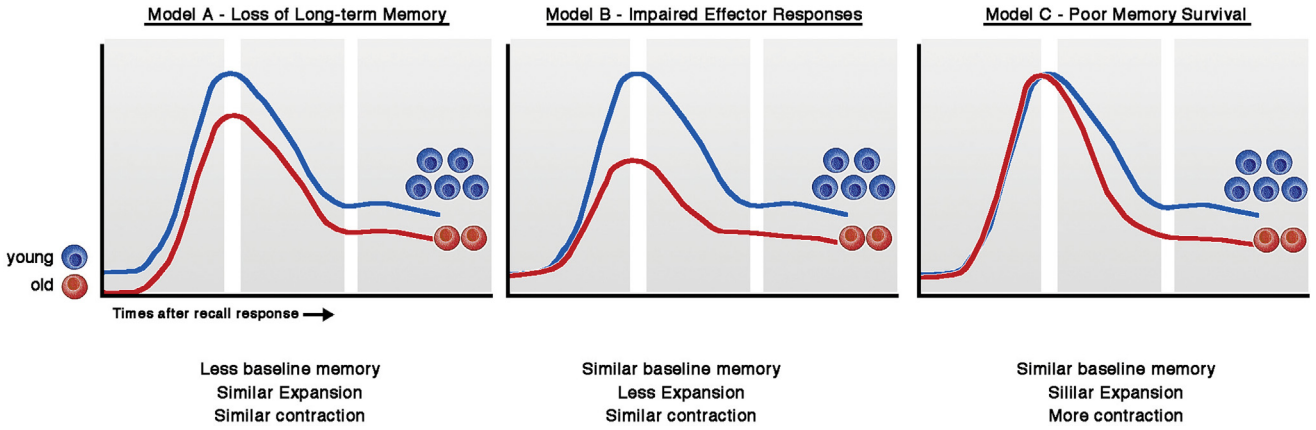

FIG 3. Potential models for reduced recall responses in aging. Loss of recall responses observed in older individuals could be contributed to 3, not mutually exclusive, scenarios: (Model A) reduced frequency of vaccine-specific memory cells for initial recall, (Model B) less expansion of vaccine-specific memory cells during recall, and (Model C) increased contraction, or poor survival, of vaccine-specific memory postrecall.

generation over memory precursor cells. Mechanistically, aged naive CD4 T cells demonstrate a basal shift in transcriptional factor profiles away from a T_{FH}-like signature of BCL6 and ID3.[106] This profile shift also skews naive CD4 subset polarization toward a T_H9 phenotype upon antigenic stimulation in older individuals and may also account for diminished CD4 T_{FH} functionality in response to vaccination with aging. Moreover, an age-associated increase in miR-21 expression in naive CD4 T cells sustains the activity of several signaling pathways including AKT-the mammalian target of rapamycin and mitogen-activated protein kinase by targeting their negative regulators, thereby promoting the generation of short-lived effector T cells.[112] In parallel, prolonged activation of AKT results in sustained FOXO1 degradation that impairs the functional activity of lysosomes resulting in impaired proteostasis and the production of B-cell–toxic exosomes.[113] In addition, effector-like T cells express higher levels of the ATPase CD39, and CD39 levels on activated CD4 T cells inversely correlate with the development of influenza-specific memory T-cell responses.[24] Moreover, adenosine generated by CD39 from secreted ATP inhibited TFH development, through negative regulation by BCL6.[114] As CD39 expression on activated CD4 T cells increases with age, it likely plays a role in the impairment of age-related T-memory and TFH responses to vaccination.

In addition, IL-2 signaling preferentially induces the formation of effector rather than memory cells.[31] The expression of CD25 (ie, IL-2 receptor alpha) inversely correlates with the development of memory CD4 T cells postantigenic exposure in mice, where $CD25^{low}$ cells more effectively develop into T_{FH} and memory CD4 T cells.[23] As CD25 expression increases on human naive CD4 T cells with age,[115] this may also influence the development of memory/TFH cells during aging. Overall, expanded system immunology-based studies may provide a larger, more cohesive picture of naive CD4 and CD8 T-cell dysfunctions with aging and their relationship to the development of memory responses to vaccinations.

Aging tissue microenvironment as a blockade to effective primary vaccine responses

In addition to T-cell–intrinsic changes with age, it is becoming more appreciated that cell-extrinsic alterations in tissue microenvironments can contribute to immune aging. In animal models, aging SLTs (eg, lymph nodes) exhibit a collapse of stromal networks, an increase in fibrosis (ie, collagen deposition), and reductions in homing chemokines levels,[116-120] suggesting that SLT aging may be associated with naive T-cell dysfunction and to poor vaccine responses in older individuals. Indeed, increased lymph node fibrosis has been recently linked with reduced primary CD4 T-cell responses to YF vaccination and to subsequent diminution in antibody production.[121] Within SLTs, naive T cells are maintained by secretion of the essential survival cytokine IL-7 from fibroblastic reticular cells.[122] However, studies on IL-7 and age have not supported the differential production of IL-7 by fibroblastic reticular cells as a cause of naive T-cell reduction with age.[120,123,124] Aged naive CD8 T cells do however express lower levels of IL-7 receptor caused by a reduction in FOXO1 activity, which may account for some age-related dysfunction.[100] Determining the role of aging SLTs, particularly fibrosis and mediators beyond IL-7, in naive T-cell function and its breakdown with human aging is a new active area of research.

Memory T-cell recall response with age—Inability to mount an effective recall response and/or maintain immunologic memory?

Booster vaccination given later in life, such as those for influenza and herpes zoster, rely on the ability of our adaptive immune system not only to maintain immunologic memory over the course of decades but also to retain a high functional capacity of memory cells during this time. Thus, the impaired vaccine responses observed with aging to some of these vaccines are potentially caused by different mechanisms. We discuss potential scenarios, not mutually exclusive, for possible loss of vaccine effectiveness in the context of T-cell memory recall below and overviewed in Fig 3.

Similar to primary vaccine responses, one explanation for ineffective vaccine recall responses is merely the quantitative loss of memory T cells over time. Indeed, although the relative frequencies of memory CD4 and CD8 T cells increase with age, there is still an overall numerical loss of memory T cells.[95,125] However, unlike the naive repertoire, memory T cells demonstrate little, if any, loss of TCR richness with age.[96] Instead, an

expansion of individual TCRs (ie, clonotypes) is observed. A similar finding is observed in response to the influenza vaccine, where older individuals generate multiple influenza-specific CD8 T-cell populations after vaccination but these populations displayed large clonal expansions and distinct TCR usage compared with younger adults.[55,57] These data demonstrate that memory contraction during aging is insufficient to completely wipe out antigen-specific clones. Moreover, long-lived stem-like memory T cells, which have reacquired a naive phenotype,[126,127] are relatively maintained across age.[95] However, aging may cause expansion of certain clonotypes that subsequently dominate the immune recall response. Although excessive clonal expansion does not affect the overall phenotype or functionality, which is in contrast to the functional defects of T-cell exhaustion during chronic viral infection, their proliferative potential appears to be compromised. Consistent with this concept, clonal expansion after Zostavax vaccination was inversely correlated with clonal size.[66]

Another possible scenario is that the recalled memory cells in older individuals cannot or do not generate functional effector responses. Strikingly, the overall ability of memory T cells to expand postrecall seems relatively similar in numbers to that of young adults across multiple booster vaccines. This is also observed *in vitro*, with memory T cells from young and old displaying similar levels of proliferation after TCR stimulation.[128] Moreover, aging memory T cells do not have an intrinsically altered ability to produce effector cytokines, including IFN-γ, TNF-α, and MIP-1α.[129] This is consistent with both effector memory and central memory CD8 T cells from older individuals displaying intact epigenetic signatures of effector T cells,[99] with recent unpublished data from our group (Hu, Jadhav, Weyand, and Goronzy, 2020) suggesting the same for memory CD4 T cells. If anything, binding motifs to bZIP family transcription factors such as AP-1 or basic leucine zipper ATF-like transcription factor that are important for effector cytokines transcription are more accessible with age. However, many vaccine responses in aging described above found reduced polyfunctional T-cell responses. Loss of polyfunctionality may be a consequence of more progressed or end-differentiation, as indicated by the chromatin state of old central memory T cells or the increased frequencies of terminally differentiated effector memory cells (TEMRAs).[130] An alternative explanation is that memory T cells in older individuals respond qualitatively differently to TCR stimulation than in young. Indeed, similar to naive T cells, memory CD8 T cells display reduced miR-181a, which likely reduces some TCR-mediated signals. Interestingly, miR-181a knockout CD4 memory T cells display a preferential selection for higher affinity clones during recall.[111] One could speculate that because TCR affinity has been shown to directly correlate with polyfunctionality,[131] the down-tuning of TCR signaling in aging memory cells may cause selection for high-affinity survival but not have sufficient signaling to maintain optimal, broad polyfunctionality. In addition, the local cytokine milieu may influence polyfunctional T-cell responses in aging.[132]

A third scenario is that memory cells demonstrate an effector response similar to young but do not generate or maintain the subsequent memory cells. This concept is similar to that observed in the aging naive compartment, in which naive T cells from older individuals preferentially become short-lived effector cells and not more long-lived memory precursor cells. Consistently, after Zostavax vaccination, VZV-specific CD4 memory cells expanded at a similar rate between young and old; however, there was a more significant contraction of vaccine-specific cells, leading to an overall reduction in VZV-specific memory.[67] CD4 T cells from older individuals also mount similar levels of effector responses against influenza vaccination but contract more, leaving less memory,[133] indicating that memory T cells share a common feature of poor memory development upon recall. This has been confirmed in a study demonstrating that the persistence of memory T_H1-type CD4 to VZV depended on age, whereas initial effector response did not.[134]

Mechanistically, effector CD4 T cells derived from the activation of memory T cells of older individuals exhibit altered metabolic function with higher oxidative phosphorylation and increased ATP secretion,[128] which, in conjunction with increased CD39 expression, may affect their long-term survival. Gene expression studies point to the importance of DNA damage responses and cell cycle regulation in the failure of older activated T cells to survive as long-lived memory T cells.[67] Collectively, a similar model emerges for memory recall responses as for primary memory T-cell response; that is, that T-cell aging is associated with a bias to differentiate into short-lived effector T cells rather than T_{FH} or memory precursor cells.

B CELLS, AGING, AND VACCINE RESPONSES

As described in Fig 1, the function of T_{FH} cells in vaccine responses is to regulate B-cell activation and differentiation. There is growing evidence that, much like T cells, B cells also become dysfunctional with age. The most common feature of the aging vaccine responses is lower induction of *functional* vaccine-specific antibodies. Antibody functionality in this context varies but is usually determined by hemagglutinin inhibition assays for influenza, viral neutralization assays for YF, bacterial opsonization for *Streptococcus pneumoniae*, and antigen-binding antibody levels for most other responses including JEV, VZV, and hepatitis B. The development of protective antibodies requires multiple sequential steps similar to that of T cells and includes naive B-cell activation, cell expansion, and differentiation into antibody-secreting plasma cells. Moreover, the generation of memory B cells is essential to establish effective protection against subsequent pathogenic exposure. However, the induction of protective antibodies also uniquely requires class switch recombination (eg, the conversion of the B-cell receptor [BCR] from IgM to IgG or IgA isotype) and affinity maturation driven by BCR somatic hypermutation (eg, mutations of the BCR that increase antigen binding). These 2 processes are mediated by the enzyme AID.

Age-related changes in the B-cell compartment are somewhat unique compared with those in T cells. Even with skewing of hematopoietic stem cell differentiation away from the lymphoid lineage, the peripheral B-cell compartment is relatively maintained in numbers across age. Vaccine-specific development of effector and memory B cells also appears somewhat intact, with influenza vaccination inducing similar frequencies of influenza-specific memory B cells and plasmablasts in young and older adults.[47,49] Although little quantitative differences are found with age, significant qualitative differences are observed. These included the reduced expression of AID, which mediates class switch recombination/somatic hypermutation in naive and memory B cells, and of BLIMP-1, which induces their differentiation into plasma cells.[49,135] Moreover, fewer mutations in the BCR

repertoire and an increased clonality is found in influenza-specific B cells from older adults.[47] These changes could potentially account for reduced antibody functionality caused by reduced affinity maturation, and are closely related with loss of T_{FH}-cell function with age.

The memory B-cell compartment shows additional qualitative changes with age, particularly highlighted by an expansion of a proinflammatory subset whose phenotype is thought to be driven by local tissue inflammation.[136-138] These proinflammatory cells in older individuals are similar to age-associated B cells (ABCs) first described in mice by the Cancro and Marrack groups.[139,140] ABCs are mainly characterized by their expression of CD11c and T-bet and the absence of CD21, although the exact definition of these cells varies widely between studies.[141,142] These cells produce antibodies in response to toll-like receptor, but not BCR, engagement and are elevated in various circumstances independent of biological age including chronic viral infections and multiple autoimmune diseases. In the context of vaccination, increased $CD27^+$ ABCs in the periphery of older adults associate with reduced titers of functional influenza-specific antibodies,[143] implying a relationship between ABCs, tissue aging, and vaccine responses. However, further studies in humans are required to gain insight into the functional role of this proinflammatory B-cell subset and antigen-specific antibody responses in older individuals.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

As described above, innovative vaccine development for VZV using a novel subunit plus adjuvant $AS01_B$ vaccination strategy has overcome age-related antibody reduction in response to this vaccination and provides similarly high protection regardless of age.[70] This vaccination also induced robust CD4 T-cell responses that persist for almost a decade.[71,144] Similarly, influenza vaccines with increased antigen dosage or the addition of the MF59 adjuvant have shown increased immunogenicity. More importantly, several studies of the adjuvanted vaccine found significant improvement in influenza-related outcomes in older individuals, such as hospitalization due to vascular events or pneumonia, and at least a trend toward reduced incidence of laboratory-confirmed influenza.[145,146] Thus, the defect in vaccine responses seen in older individuals may not be an absolute feature of the aging immune system but a limitation of specific vaccination strategies. Increasing the antigen dose or using adjuvants to delay the clearance of antigen, in conjunction with the increased expression of costimulatory molecules, can overcome defects in T-cell activation and also compensate for lower frequencies of antigen-specific T cells. Booster vaccinations may also be needed more regularly, because larger memory T-cell clones in older individuals have a lower propensity to expand, and recall responses therefore rely on the expansion of infrequent antigen-specific T cells, as in primary responses. Interestingly, Shingrix, a vaccine that is highly efficient in preventing VZV reactivation across age, includes a booster vaccination.

A more difficult task is to influence the differentiation of T cells to favor memory precursor cells and T_{FH} cells over short-lived effector T cells. The nature of the vaccine adjuvant is important in determining the fate of the differentiating T cells,[147] and newer adjuvants may overcome the bias in older individuals to generate short-lived effector T cells in primary as well as recall responses. In the context of HIV vaccination, Cirelli et al[148] have shown the superiority of slow delivery over conventional immunization in inducing more robust T_{FH}-cell responses and germinal center B cells in rhesus monkeys.[148] Moreover, although conventional bolus-immunized animals developed antibodies to nonneutralizing immunodominant epitopes of the envelope protein, slow delivery–immunized animals targeted a more diverse set of epitopes. Although the methods of slow delivery immunization used in this study are not practical for population-wide vaccination campaigns such as those for influenza virus protection, the insights from this study are spearheading new approaches to improve vaccination in the elderly.

It might also be possible to pharmacologically influence T-cell differentiation. Prolonged activation of the AKT-mTORC pathway favors the differentiation into effector T cells, which can be attenuated by mTORC inhibition.[35] Initial human studies have used the mammalian target of rapamycin inhibition via rapalogs in the setting of influenza vaccination, finding increased generation of influenza-specific antibodies postvaccination.[149] Sustained mTORC signaling as well as signaling of mitogen-activated protein kinase in older T cells is due to the overexpression of miR-21, raising the possibility that preventing the upregulation of miR-21 could be a promising avenue to skew T-cell differentiation pathways. Metabolic interference may also be successful to favor generation of memory T cells that rely on oxidative phosphorylation. Indeed, C1q has recently been shown as a mitochondrial activator that suppresses exuberant short-lived effector responses in CD8 T cells.[150,151] Finally, genetically predisposed, CD39-expressing older individuals suppress T_{FH} generation through the stimulation of the adenosine receptor $A2_AR$[24,114]; in these individuals, interventions to prevent CD39 upregulation or $A2_AR$ signaling in the first 2 weeks after vaccination may be beneficial to improve B- and T-cell memory.

Taken together, we have made great strides in understanding the mechanisms how immunologic memory after vaccination is induced and how it can be optimized. Defects in the aging immune system have been identified that appear to be surmountable. These insights should allow for a rationale design of vaccination strategies to improve protective immune responses in older individuals and need to be tested in clinical studies.

What do we know?

- **The development of immunologic memory is diminished with age for both primary and booster vaccination.**
- **Aged T cells favor the generation of short-lived effector over memory/T_{FH} cells.**
- **T-cell differentiation can be augmented to favor memory/T_{FH} development via inhibition of the mammalian target of rapamycin complex (mTORC) or $A2_AR$ signaling.**

What is still unknown?

- **Ability of vaccines to induce tissue-resident memory with age.**
- **Contribution of age-related tissue inflammation and/or fibrosis on vaccine-specific T-cell responses.**
- **Effectiveness of modulating T-cell differentiation to improve vaccine efficacy in older individuals.**

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