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T Follicular Helper Cell Development and Functionality in Immune Aging

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Abstract

By 2050, there will be over 1.6 billion adults aged 65 years and older, making age-related diseases and conditions a growing public health concern. One of the leading causes of death in the aging population is pathogenic infections (e.g. influenza, S. *pneumoniae*). This age-dependent susceptibility to infection has been linked to a reduced ability of the aging immune system to mount protective responses against infectious pathogens, as well as to vaccines against these pathogens. The primary immune response that promotes protection is the production of antibodies by B cells – a response that is directly mediated by T follicular helper (T_{FH}) cells within germinal centers in secondary lymphoid tissues. In this review, we will summarize the current knowledge on the development and functionality of T_{FH} cells, the use of circulating T_{FH} cells as vaccine biomarkers and the influence of age on these processes. Moreover, we will discuss the strategies for overcoming T_{FH} cell dysfunction to improve protective antibody responses in the aging human population.

Keywords

Immunosenescence; T follicular regulatory cell; vaccine response; T cell differentiation, B cell antibody production, germinal center

Introduction.

Globally, human lifespan has been significantly increased – in part by medical advancement, improved sanitation and easier access to clean water. Indeed, it is predicted that by 2050, there will be over 1.6 billion (17% of the global population) adults over the age of 65 years. In the US alone, the older population is expected to double over the next 30 years – to 88 million people. As the population becomes older, age-related diseases and conditions also become a growing public health concern. A significant amount of aging research has shifted focus from extending lifespan to extending the length of disease-free living (termed “healthspan”). One of the major contributors to a reduced healthspan is increasing immune dysfunction with age. This immune aging phenomena results in a higher susceptibility to

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and mortality from pathogenic infections in older adults. Although vaccines have been developed to protect against many of these pathogens, older adults display diminished protective vaccine responses compared with younger adults. Thus, understanding why older adults have reduced protective immune responses to infection and vaccination is essential for designing more effective interventions to prevent infection-related morbidity and mortality in the older population.

The primary read-out for almost all vaccinations is the induction of protective antigen-specific antibodies. The induction of vaccine-specific antibodies can be mediated by follicular or extrafollicular B cell responses, which provide long-term or short-term protection, respectively. Although short-term responses provide rapid antigen-specific antibody production, the cells generated from these interactions display poor survival. Thus, the generation of long-lived antibody-producing cells is essential for an effective vaccine response.(1) In order to achieve long-lived protective antibody responses, B cells must undergo class switch recombination, somatic hypermutation and plasma cell differentiation, all of which require the help of a specialized T cell subset termed T follicular helper cells (T_{FH} cells). Here, we discuss current understanding of T_{FH} cell development, functionality and association with vaccine responses, how these processes are affected by aging and the clinical implications of age-dependent changes in T_{FH} cells for immune modulation.

A specialized T cell subset to help B cell responses.

T_{FH} cells are a subset of $CD4^+$ T cells that are specialized in providing help to follicular B cells within germinal centers of secondary lymphoid tissues (i.e. lymph nodes, tonsils, spleen, Peyer's patches). Discovered more than 18 years ago, T_{FH} cells are uniquely delineated by the expression of CXC-chemokine receptor 5 (CXCR5).(2, 3) Functionally, CXCR5 binds to CXC-chemokine ligand 13 (CXCL13) secreted by follicular stromal cells present within the secondary lymphoid tissues and allows for the homing of T_{FH} cells into follicles. Mature T_{FH} cells within tissues are further distinguished by high co-expression of programmed death receptor 1 (PD-1).(4) Genetic mutations causing reduced T_{FH} numbers, such as ICOS-deficient CVID (5, 6) and CD40 ligand-deficient hyper-IgM (7), lead to defects in humoral immunity; with major alterations in memory B cells and serum antibody levels.

The development of T_{FH} cells.

The development of T_{FH} cells is complex, involving multiple cell types and direct receptor and non-direct cytokine interactions.(8, 9) Classical differentiation of T_{FH} cells occurs in three main phases: 1) extrafollicular priming, 2) follicular maturation and 3) germinal center development. During extrafollicular priming, naïve CD4 T cells interact with local dendritic cells in the extrafollicular space of secondary lymphoid tissue. This interaction requires T cell receptor engagement with antigen-MHC II complex as well as specific cognate and soluble factors. In mice, T_{FH} cell priming is mediated by multiple cytokines including interleukin (IL)-6, IL-21 and IL-27.(10, 11) While TGF-β inhibits T_{FH} generation in mice (12), TGF-β or activin A in combination with IL-12 and several other cytokines promotes strong polarization of human naïve CD4 T cells towards a T_{FH} cell phenotype (13–15), demonstrating species-specific differences in T_{FH} development. However, the overall

outcome of naïve CD4 T cell priming in both species is the upregulation of the master transcription factor for T_{FH} cells, BCL-6.(14, 16) BCL-6 expression also depends upon the engagement of the co-stimulatory surface receptor ICOS on the developing T_{FH} cells by ICOS ligand.(17) Indeed, loss of ICOS in both mouse and man leads to significant reductions in T_{FH} cells and generation of germinal centers.(5, 18) The expression of BCL-6, in turn, drives the upregulation of CXCR5 on naïve CD4 T cells and allows for subsequent migration of "primed" precursor T_{FH} cells towards the B cell follicle border area.

The second phase of T_{FH} development occurs at the T-B border of the follicle, where precursor T_{FH} cells interact directly with antigen-specific B cells through their T cell receptor as well as via co-stimulatory (i.e. ICOS-ICOSL, OX40-OX40L) and co-inhibitory signals (i.e. PD-1-PD-L1). The intracellular adaptor protein, signal adaptor SLAM-associated protein (SAP), is critical for the development of a stable interaction between T and B cells during this second phase.(19) SAP-deficient mice and humans display normal frequencies of circulating memory T_{FH} cells, however mature T_{FH} cell frequencies and the formation of germinal centers is significantly reduced (20, 21), demonstrating that SAP is essential for transitioning from a precursor T_{FH} to a mature GC T_{FH}. During this second phase, B cells also receive the necessary help from maturing T_{FH} cells in the form of secreted IL-21 and CD40L-CD40 engagement that initiate germinal center reactions.

In the third phase of T_{FH} development, mature T_{FH} cells move from the T-B border area into the germinal center of the follicle, becoming germinal center (GC) T_{FH} cells. GC T_{FH} cells again engage with GC B cells via antigenic signals and co-stimulatory signals, providing the necessary help to promote antigen-specific B cell proliferation and plasma cells or memory B cell differentiation. After GC T_{FH} cells have provided help to GC B cells, they can exit the GC and migrate to a new GC, re-enter the original GC or downregulate BCL-6 for transition into a circulating memory T_{FH} cell. Alternatively, GC T_{FH} cells may stay within the germinal center until they encounter a secondary response.(22) Moreover, upon secondary antigen-exposure, circulating memory T_{FH} cells are rapidly re-recruited to germinal centers to produce effector antibody responses, thereby providing better and more robust immune protection against antigenic re-challenges.

T_{FH} cell functionality.

The main function of T_{FH} cells is to provide help to antigen-specific B cells to promote proliferation, antibody class switching and somatic hypermutation for the generation of long-lived plasma cells and memory B cells. Within the follicles, T_{FH} cells interact with B cells by secretion of soluble factors and direct cell-to-cell contact. IL-21 is the primary cytokine secreted by T_{FH} cells and promotes B cell class switching and differentiation into antibody secreting cells.(23) Moreover, the development of memory B cells within the germinal center requires T_{FH}-produced IL-9 secretion.(24) T_{FH} cells also secrete other cytokines including, but not limited to, IL-10, IL-4, IL-17 and IFN-γ, which can alter the quality and quantity of subsequent B cell responses. Expression of CD40 ligand on the surface of T_{FH} cells provides cognate signals to B cells required for B cell class switching and differentiation. A number of other co-stimulatory (ICOS, OX40) and co-inhibitory

receptors (PD-1) also play important roles in T-B cell interactions and T_{FH} development, which can affect downstream B cell responses.

Heterogeneity of T_{FH} cells.

T_{FH} cells are classically defined by the expression CXCR5. However, it is now clear that the T_{FH} compartment is highly heterogeneous, consisting of different phenotypic and functional populations similar to T_H1, T_H2, T_H17 and T regulatory CD4 T cells.(4) These subsets are distinguished by distinct patterns of surface receptor expression (e.g. CXCR3, CCR6, CCR4) that closely correlate with cytokine secretion profiles.(25) Moreover, these subsets can be further divided based on expression of CCR7, ICOS and PD-1, in which $ICOS^-PD\text{-}1^-CCR7^+$ cells within the $CXCR5^+$ compartment are most abundant in the circulation and consider to be quiescent T_{FH} precursor or memory T_{FH} subsets. $ICOS^+$ T_{FH} cells are a more activated T_{FH} subset and $PD\text{-}1^{low/+}$ T_{FH} cells display features of an intermediate effector-like subset.(4, 26)

T_{FH} cell subsets not only display different patterns of surface receptor expression and cytokine secretion, they also vary in their ability to provide help to B cells. T_H2- and T_H17-like T_{FH} cells have the functional ability to help B cells produce antibodies whereas T_H1-like T_{FH} cells do not.(27, 28) Moreover, the secretion of different cytokines by these subsets can affect B cell class switching and thus the effectiveness of antibody responses. The specific requirements for T_{FH} subset generation and tissue localization are currently unknown and warrant further investigation.

In addition to T_{FH} cells, a subset of CXCR5-expressing regulatory $CD4^+$ T cells can be found within secondary lymphoid tissues. These cells, termed T follicular regulatory cells (T_{FR} cells), are related to thymus-derived Treg cells and are classically defined by the co-expression of FOXP3 and CD25.(29–31) These cells are further characterized by the expression of CTLA-4 (32) and surface receptors shared by T_{FH} cells, such as CXCR5, ICOS and PD-1. T_{FR} cells are most prevalent at the T-B borders and within B cell follicles with few T_{FR} cells directly within the germinal centers in human lymph nodes.(33) However, recent studies have also shown a subset of $CD25^-$ T_{FR} cells specially localize to germinal centers in mice and humans.(34, 35) Functionally, both $CD25^+$ and $CD25^-$ T_{FR} cells inhibit follicular B cell responses – most likely through direct suppression of T_{FH} cell function.(31, 35, 36) Moreover, T_{FR} cells are preferentially induced by exposure to self-antigen, however foreign antigens, such as those in vaccinations, can also induce their development.(37) Consistently, alterations in T_{FR} to T_{FH} cell ratios within secondary lymph nodes have been found in autoimmune diseases and chronic infections, such as rheumatoid arthritis, malaria and HIV (38–40), and can significantly influence antibody responses and subsequent humoral immune protection.

Circulating T_{FH} cells in vaccine responses.

The induction of protective antibodies against infectious pathogens is the hallmark of almost all successful vaccines. With the discovery that T_{FH} cells guide these responses, researchers have started to address whether this cellular subset could be used as a predictive marker of vaccine efficacy. As mentioned above, after the engagement in a germinal center response,

T_{FH} cells can exit the germinal center and become circulating memory T_{FH} cells, thus the circulating subset potentially reflects the induction of antigen-specific immune responses and may be an accessible biomarker for determining the success of vaccinations. Indeed, many groups have now shown that the frequencies of cT_{FH} cells, in particular with an activated (i.e. ICOS-expressing) phenotype, positively predicts the levels of antigen-specific responses to vaccination, including vaccines against influenza and S. *pneumonia*.(41–46) Activated cT_{FH} frequencies are also predictive of mucosal antibody responses to oral vaccines (47) and recent functional studies show a dependence on ICOS, BCL-6 and IL-21 for effective T_{FH} function in vaccine-specific mucosal antibody responses.(48) Moreover, mouse models demonstrate that activated cT_{FH} cells elicit robust recall responses and antibody-mediated protection upon secondary exposure.(49) Thus, the frequency and activation status of cT_{FH} cells may be useful biomarkers in blood to predict effectiveness of multiple types of vaccinations.

cT_{FH} responses to vaccination in older individuals.

Older adults display diminished vaccine-specific antibody responses, including to vaccination against influenza, varicella zoster virus (VZV) and S. *pneumonia*. Thus, one could speculate that this reduction is linked with alterations in the cT_{FH} compartment – in which the association between activated cT_{FH} cells and vaccine-specific antibody titers would be lost with age. Indeed, studies have found that older adults fail to increase activated cT_{FH} cells after vaccination with the influenza vaccine, whereas young adults have significant increases in this subset that directly correlates with the production of influenza-specific antibodies.(45) This was due to the fact that older individuals displayed higher frequencies of $ICOS^+$ cT_{FH} cells pre-vaccination compared with younger adults. Similarly, HIV-infected individuals, who display characteristics similar to that of immune aging within the CD4 T cell compartment, also had no upregulation of activated T_{FH} cells after vaccination with the pneumococcal vaccine, in association with reduced titers of antigen-specific antibodies.(41) Notably, pre-vaccination levels of $CD38^+HLA\text{-}DR^+$ cT_{FH} cells negatively correlated with influenza vaccine responses, suggesting that high baseline frequencies of activated cT_{FH} cells may actually be inhibitory.(50) Thus, the magnitude of change in the activated cT_{FH} compartment may be a more robust biomarker for monitoring vaccine responsiveness in the aging population. Moreover, the high basal frequencies of activated cT_{FH} cells and the lack of expansion of activated cT_{FH} populations post-vaccination in older individuals suggests that T_{FH} development in the follicle or T_{FH} activation within the germinal center is compromised during aging.

T_{FH} cells dysfunction with age.

The diminished vaccine response in older individuals correlates with the loss of cT_{FH} activation, suggesting declining functionality of memory T_{FH} cells with age. Because there is limited information of T_{FH} cells during human aging, we will discuss the current available knowledge of T_{FH} cell aging from animal studies and how this is related to our current understanding of human T_{FH} cells in the context of the aging CD4 T cell compartment. An overview of these concepts is provided in Figure 1.

Aging mice display many similar features of human immune aging - including reduced humoral immune responses to vaccination. Thus, mouse studies can provide some mechanistic insight into the role of T_{FH} cells during aging. Humoral immune responses are recovered in old mice upon transfer of young T cells but not B cells, which demonstrates that the aging defects are specific to the T cell compartment.(51) Notably, studies on influenza vaccination in mice found that the ability of CD4 T cells to differentiate into precursor T_{FH} cell was unaffected by age.(52) Instead, aged T_{FH} cells demonstrate reduced activation, an inability to fully differentiate into bona fide GC T_{FH} cells and a more regulatory phenotype. Moreover, although circulating T_{FH} increase with age, the numbers and activation of T_{FH} cells within germinal centers are reduced; leading to defective antigen-specific responses.(53) Defective T_{FH} responses are also, in part, contributed to direct suppression by increased frequencies of T_{FR} cells in older mice.(53)

Similar to mouse studies, the total frequency of cT_{FH} cells increases with age in humans.(54) This phenomenon is also seen in HIV-infected individuals.(55) One possible explanation for the increase in cT_{FH} cells in aged individuals is the loss of the naïve compartment during aging, which indirectly inflates the relative frequency of the memory compartment. As cT_{FH} cells are composed primarily of memory cells, they would be indirectly expanded. However, the expansion of memory cT_{FH} cells would, in theory, provide more immune protection, not less. Thus, these findings do not explain reduced humoral immunity during aging. An alternative hypothesis is that T_{FH} cells lose functionality – such as observed in mouse models. It is still unclear how the findings in mice translate into T_{FH} dysfunction in older humans and further studies of human T_{FH} subsets and T_{FH} cells within secondary lymphoid tissues during aging are required. Below, we detail how changes within the naïve and memory CD4 T cell compartments could affect T_{FH} development and functionality during human aging.

Effect of aging on T_{FH} development and memory recall responses.

In the context of T_{FH} cells, there are two main possibilities for loss of functionality with age; defective T_{FH} development or defective memory T_{FH} recall responses. Immune protection from vaccination in older individuals relies mainly on recall responses by targeting and expanding already present memory T cells. However, naïve T cell responses play an important role in defense against new or forgotten pathogens and may also be affected by age. Indeed, our group has recently show that even recall responses in older individuals, as in the case of zoster vaccination, involves the recruitment of naïve T cells.(56) Thus, dysfunctions in both the naïve and memory CD4 T cell compartments may contribute to reductions in effective T_{FH} responses during aging.

Naïve CD4 T cell priming during aging.—The naïve CD4 T cell compartment undergoes many cell-intrinsic changes that could affect T_{FH} differentiation as well as functionality during aging. In particular, one hallmark of CD4 T cell aging is a reduction in T cell receptor signaling in naïve CD4 T cells caused by diminished expression of miR-181a in these cells with age.(57) Consistently, naïve CD4 T cells from older individuals show less activation than young adults after T cell receptor stimulation - exhibiting reduced expression of ICOS and CD40L on activated CD4 T cells.(58) Preliminary data from our group also

demonstrates a bias of naïve CD4 T cells from older individuals to favor development into inflammatory effector T cells rather than into T_{FH} cells upon T cell receptor stimulation under non-polarizing conditions, i.e. without adding T cell lineage determining cytokines. Similar shifts in naïve CD4 T cell differentiation, away from T_{FH} development, have been found in mice and are linked with alterations in the aged tissue environment.(59) Thus, alterations in naïve CD4 T cell receptor signaling and local T_{FH} priming may play an important role in the generation of T_{FH} responses to new pathogenic infections or vaccines during aging.

Memory CD4 T cell recall responses during aging.—Most of the T cell responses in older individuals derive from memory recall responses. In particular, vaccine responses are highly dependent on pre-existing immunological memory. The link between decreased vaccine responses and poor upregulation of activated cT_{FH} cells in older individuals is also indicative of a poor recall capacity of memory CD4 T cells. Such recall responses are classically derived from the central memory compartment, in which antigen-specific central memory CD4 T cells are recruited into secondary lymphoid organs and develop into CXCR5-expressing cells upon T cell receptor engagement. Although the repertoire diversity of the memory CD4 T cell compartment remains relatively unchanged with age(60), we do find distinct changes that may affect T_{FH} cell function. Memory CD4 T cells from older individuals preferentially differentiate into DUSP4- and CD39-expressing cells upon T cell receptor stimulation, which lack the ability to provide help to B cells.(58, 61) Instead, they produce inflammatory cytokines, in particular IFN-γ and have an increased propensity to undergo apoptosis. A genetic polymorphism determining the ability to express CD39 directly correlates with influenza and VZV vaccine responses.(61) DUSP4 expression also inversely correlated with CD40L and ICOS expression after influenza vaccination. Together, altered recall responses of memory CD4 T cells with age include defects that specifically influence T_{FH} functional ability to be activated and interact with B cells to promote humoral immune responses.

Targeting T_{FH} cells to improve vaccine responses with older individuals.

Designing vaccines to specifically overcome age-related dysfunctions in T_{FH} cells could provide a clinical intervention for improving immune protection in older individuals. Although more basic studies on T_{FH} and T_{FR} cells during human aging are needed, there are three main strategies one could employ for manipulating T_{FH} cell responses (62); altering the frequency of T_{FH} cells, changing the functionality of T_{FH} cells or adjusting T_{FR} cell suppression (outlined in Figure 2). The potential mechanisms and their caveats are detailed below.

Alter the frequency of T_{FH} cells.—In most vaccine studies, increasing frequencies of cT_{FH} cells correlate with the induction of protective humoral immunity.(41, 45, 47) Determining mechanisms for increasing cT_{FH} cells is therefore thought to be an effective way to enhance humoral immune responses. Indeed, addition of liposome adjuvant and toll-like receptor 4 (TLR4) agonist to a malaria vaccine significantly enhanced T_{FH} responses and subsequent antibody responses in mice.(63) Moreover, Ugolini et. al. recently discovered that T_{FH} differentiation is driven by TLR8 engagement and the addition of TLR8

agonists enhanced T_{FH} development and humoral immune responses in pigs.(64) These data suggest that the addition of specific adjuvants could increase T_{FH} responses to vaccination and may be of utility for enhancing humoral immunity in older individuals.

The addition of adjuvants to enhance immunity in the elderly population is an interesting and relatively new area of study. The specific effects of adjuvants on immune responses in the elderly is nicely reviewed in Del Giudice et. al.(65) For example, an influenza vaccine adjuvanted with MF59, an oil-in-water emulsion of squalene oil, was recently approved by the FDA for individuals older than 65 years. While there is not much evidence for improved antibody responses, it appears to be more protective in the elderly. Moreover, a zoster vaccine using the AS01 adjuvant has also been proven to be highly efficacious in protecting against herpes zoster in older individuals and induces long-term increases in vaccine-specific antibodies and CD4 T cells. It is currently unclear whether either of these vaccines function by inducing T_{FH} cells, however it highlights the idea that age-specific adjuvants may indeed be useful for enhancing T_{FH} frequencies and subsequent antibody responses in the elderly population.

The idea of enhancing T_{FH} frequencies is somewhat counterintuitive in the context of human aging, where elevated levels of cT_{FH} cells but still significant reduction in humoral immunity are observed. However, it is important to note that in influenza vaccine trials, although older individuals had higher levels of cT_{FH} cells prior to vaccination compared with young adults, there was no change in this frequency post-vaccination.(66) Thus, it is possible that current vaccines are not able to elicit antigen-specific T_{FH} responses and the elevated levels of cT_{FH} observed may simply be reflective of general accumulation of memory T cells with age. Indeed, a follow-up study revealed that increasing the antigen dose in the influenza vaccine elicited higher levels of activated cT_{FH} cells compared with the standard vaccine and correlated with increased seroconversion in older individuals.(66) As T cell receptor stimulation thresholds in both naïve and memory CD4 T cells change with age, these data suggest that increasing antigenic stimulation of precursor or memory T_{FH} cells may be an effective way to overcome age-dependent T_{FH} dysfunctions and elicit more robust humoral immune response in the older population - an interesting new concept for age-specific vaccine design. Consistently, increasing antigen dose has been successfully used to improve efficacy to vaccines for trivalent influenza vaccine and live-attenuated VZV.(67, 68)

Change the functionality of T_{FH} cells.—Besides altering the overall frequencies of T_{FH} cells, another (not exclusive) strategy is to change T_{FH} functionality by driving the development of specific T_{FH} subsets. The importance of appropriate T_{FH} subset development is clearly highlighted in the case of autoimmunity. Changes in T_{FH} subset distribution are found in numerous autoimmune diseases, including rheumatoid arthritis (69) and juvenile dermatomyositis.(28) Moreover, in psoriasis vulgaris (70) and systemic lupus erthematosus (71), increased levels of T_H17-like and T_H2-like T_{FH} cells, respectively, directly correlate with disease severity. In classical T helper cell differentiation, skewing of subsets is driven by cytokine exposure in the local environment.(72) Although currently unknown, T_{FH} subsets may develop in a similar fashion, skewed by the local cytokine milieu. Better understanding of requirements for the development of individual subsets and the distribution of T_{FH} subsets with aging are needed to better explore this strategy.

Reduce T_{FR} cell suppression.—In the context of aging, T_{FR} cells increase, at least in mouse models. Thus, decreasing the number of T_{FR} cells could be an avenue to enhance T_{FH} responses. Specific vaccine adjuvants can favor the development of T_{FH} cells over T_{FR} cells in an immune response. Immunization with TLR9 adjuvants significantly enhances the number of T_{FH} cells, reduces the number of T_{FR} cells and increases antigen-specific IgG2 production in mice.(73) TLR9 adjuvants also induce GC T_{FH} cells with increased ICOS expression and IL-21 secretion in neonatal mice.(74) In addition to making less T_{FR} cells during an immune response, the suppressive capacity of T_{FR} cell can be blocked or diminished by targeting the inhibitory molecules on T_{FR} cells. Inhibition of the inhibitory molecule cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) significantly increases T_{FH} function.(32, 75) Although the CTLA-4 inhibitor ipilmumab was the first immune checkpoint inhibitor approved for use in cancer patients and has been used in clinical studies, CTLA-4 blockade can cause significant side effect in patients including the development of autoimmunity. Likewise, recent evidence demonstrates that T_{FR} cells are critical to prevent autoimmune responses, where diminished T_{FR} responses cause high induction of auto-antibodies.(76) Of note, the T cell receptor repertoires of T_{FR} cells differs from that of T_{FH} cells,(77) suggesting that these cells may actually be blocking off-target (i.e. self) responses during the development of germinal center responses to foreign antigen. Thus, strategies to block the development or function of T_{FR} cells in older individuals could potentially drive the development of autoimmunity – of which older individuals are already at higher risk of developing. Although the risk of autoimmunity in young children is unacceptable, the trade-off between immune protection and development of autoimmunity in older individuals needs to be better assessed to determine whether the benefit outweighs the risk.

Concluding remarks.

Mounting evidence suggests that T_{FH} dysfunction causes, at least in part, reductions in protective antibody responses against infection and to vaccination during aging. Although we have a good understanding of T_{FH} development and function from mouse models, these processes differ in humans. Moreover, we have limited knowledge on the cellular and molecular effect of age, and the aging tissue environments, on T_{FH} and T_{FR} subsets. Understanding these changes will be crucial for developing clinical interventions that will improve protective immunity, in particular vaccine responses, in older individuals.

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Abbreviations:

CTLA	cytotoxic T-lymphocyte-associated protein
CVID	common variable immunodeficiency
CXCR	CXC receptor

CXCL	CXC ligand
GC	germinal center
ICOS	inducible T cell co-stimulator
IFNγ	interferon-gamma
IL	interleukin
MHC	major histocompatibility complex
SAP	signal adaptor SLAM-associated protein
T_{FH} cell	T follicular helper cell
cT_{FH}	circulating T_{FH}
T_{FR} cell	T follicular regulatory cell
TLR	toll-like receptor
VZV	varicella zoster virus

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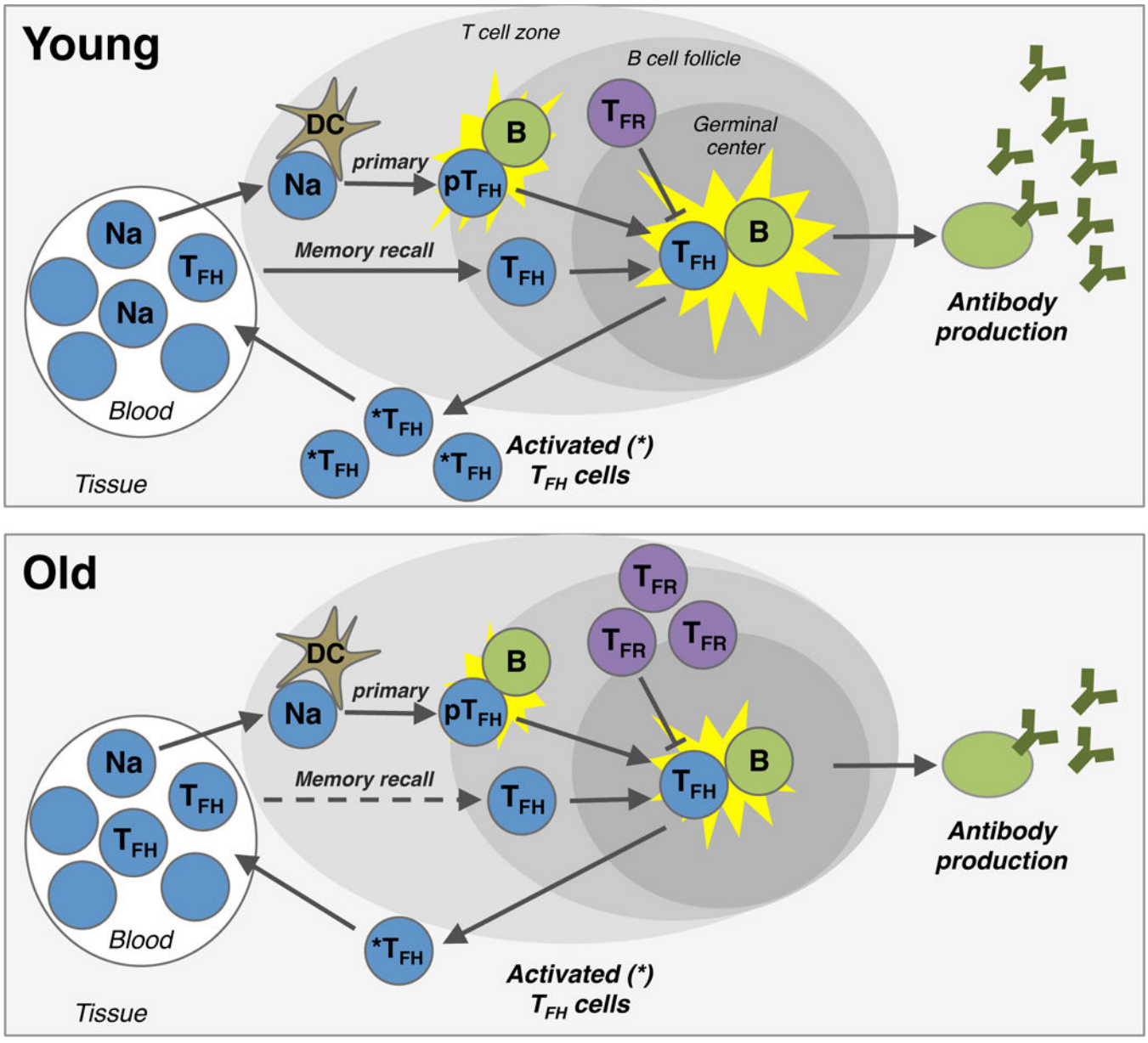

Figure 1. Alterations in T_{FH} cells during aging.

During a primary immune response, naïve CD4 T cells (Na) are recruited from the blood into the tissue, where they interaction with dendritic cells (DC). If activated via their T cell receptor in conjugation with the appropriate co-stimulation, naïve CD4 T cells upregulate CXCR5 and move into the B cell follicle. These precursor T_{FH} cells (pT_{FH}) interact with local B cells to undergo full maturation into bona fide T_{FH} cells, which again interact with B cells within germinal centers. This germinal center interaction induces the production of high affinity antibodies as well as the release of activated memory T_{FH} cells ($*T_{FH}$) from the tissue back into the blood. Memory T_{FH} cells in the blood can also be re-recruited into the follicle upon secondary exposure (i.e. memory recall) to rapidly promote the production of antibodies. T_{FH} responses can be inhibited by T follicular regulatory cells (T_{FR}) within follicles. During aging, multiple changes in this pathway occur, including alterations of

naïve CD4 and T_{FH} cell frequencies within the blood, reductions in T_{FH} -B cell interactions and increases in T_{FR} cells - which in turn lead to lower production of antigen-specific antibodies and activated T_{FH} cells.

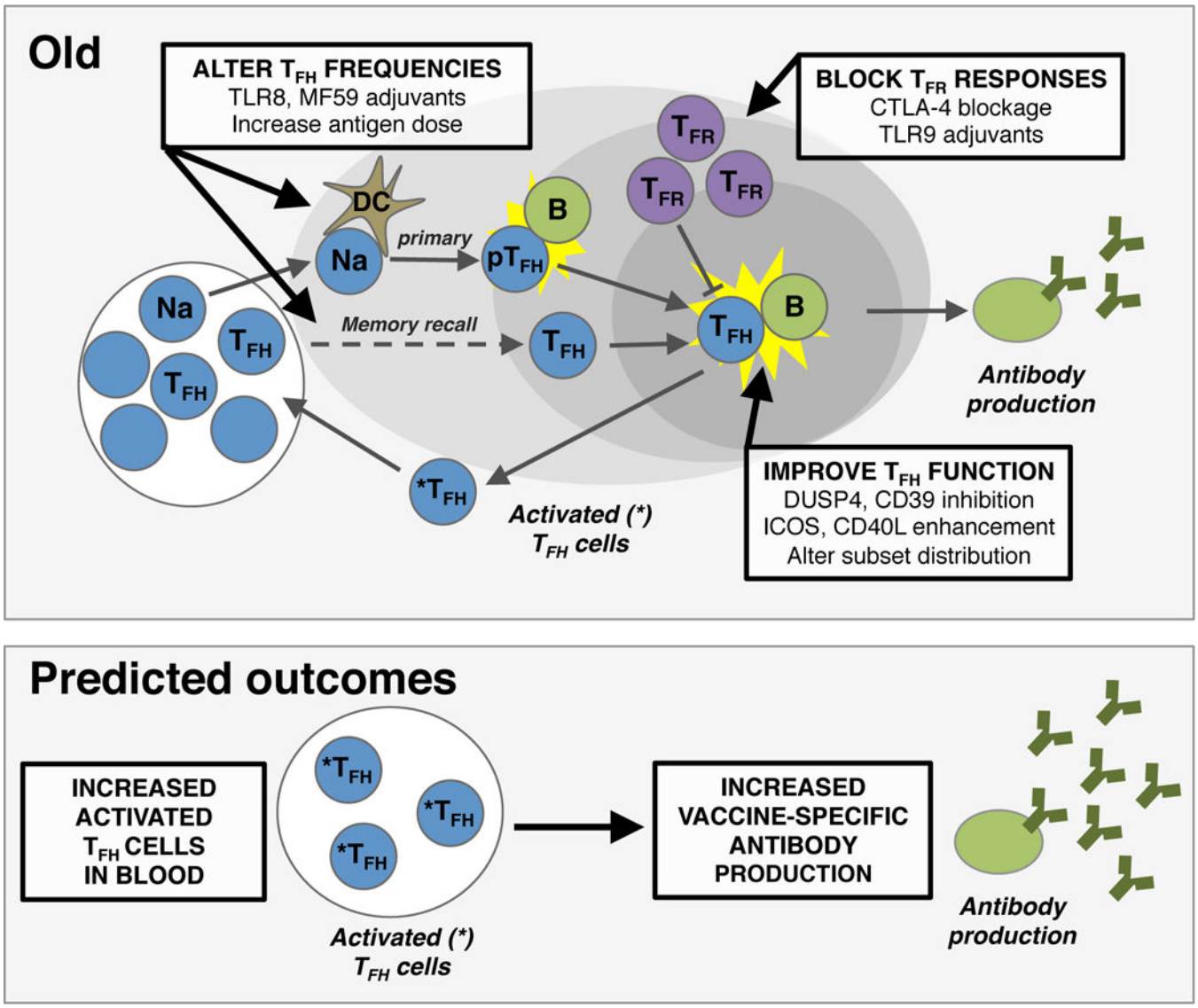

Figure 2. Interventions for enhancing T_{FH}-mediated vaccine responses during aging.

Multiple steps in the development of T_{FH} responses with age are possible targets for therapeutic interventions. These targets include 1) altering the frequencies of naïve CD4 T cells (Na), precursor T follicular helper cells (pT_{FH}) and T follicular helper cells (T_{FH}) that participate in a vaccine response, 2) inhibition of T follicular regulatory cell (T_{FR}) numbers and/or suppressive capacity, and 3) improving overall T_{FH} functionality. The ultimate outcome of these interventions would be an increase in functional T_{FH} cells indicated by higher frequencies of activated T_{FH} (*T_{FH}) within circulation and higher levels of vaccine-specific antibody production by B cells. Dendritic cell, DC.