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Novel therapies for memory cells in autoimmune diseases

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Summary

Autoimmune diseases are a major cause of morbidity, and their incidence and prevalence continue to rise. Treatments for these diseases are non-specific and result in significant adverse effects. Targeted therapies may help in improving the risk : benefit ratio associated with treatment. Immunological memory is an important feature of the vertebrate immune system that results in the production of cells that are long-lived and able to respond to antigens in a more robust manner. In the setting of autoimmunity this characteristic becomes detrimental due to the ongoing response to a self-antigen(s). These memory cells have been shown to play key roles in various autoimmune diseases such as type 1 diabetes, multiple sclerosis and psoriasis. Memory T cells and B cells can be identified based on various molecules expressed on their surface. Memory T cells can be divided into three main categories – central memory, effector memory and resident memory cells. These subsets have different proliferative potential and cytokine-producing abilities. Utilizing differentially expressed surface molecules or downstream signalling pathway proteins in these cells it is now possible to target memory cells while sparing naive cells. We will discuss the various available options for such a strategy and several potential strategies that may yield successful therapies in the future.

Keywords: autoimmune disease, Immunological memory, memory T cell, memory B cell, targeted therapy

Introduction

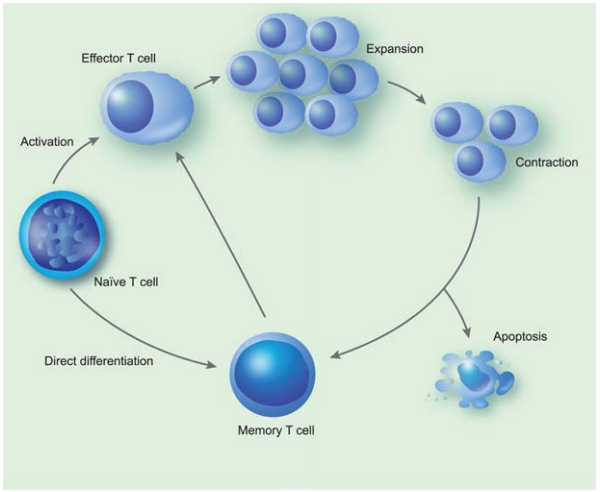
The prevalence and incidence of autoimmune disease continues to rise across the globe [1–3]. Several of these diseases affect individuals in young or middle age, and thus have major societal costs in addition to the high level of individual morbidity [4]. Treatments for autoimmune disorders have largely been non-specific and involved immunosuppression targeting the adaptive immune system. While effective, these broad-spectrum approaches led to significant adverse effects, including increased risk of infections and toxicity to non-immune cells. More specific therapies targeting individual cell populations could lead potentially to reductions in these adverse effects. Refining the targets to include cells that are pathogenic, while sparing other components of the adaptive immune system, could lead to a more acceptable risk : benefit ratio.

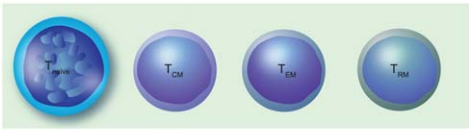
Immunological memory is an important feature of the adaptive immune system that allows it to mount an intensified immune response to a previously recognized antigen, and plays an important role in the defence against infectious pathogens [5]. This particular attribute may, however, be an effective target in autoimmune disorders, in which the ability of the immune system to recognize an autoantigen more readily would be detrimental. We will explore briefly the generation and characteristics of memory cells and the importance of memory cells in autoimmune disease and will then address the current and possible future methods of targeting these cells.

T cell memory

Generation of memory T cells

There are two leading theories regarding the generation of memory cells: linear and divergent [6]. In the linear model, the encounter of an antigen-specific naive $CD4^+$ or $CD8^+$ T cell (T_{naive}) can lead to activation followed by proliferation and differentiation into cytokine-producing effector T





CD45RA	+	-	-	-
CD45RO	-	+	+	+
CCR7	+	+	-	-
CD69	-	-	-	+
Kv1.3	lo	lo	hi	
S1PR1	hi	hi	lo	lo

Fig. 1. Generation of memory T cells and common surface markers of various subtypes of memory T cells. (a) The process of generation of memory T cells. Naive T cells undergo activation following engagement of the T cell receptor (TCR) and appropriate co-stimulatory signals, subsequently undergoing proliferation and differentiation into effector T cells. Later in the immune response effector T cells undergo a contraction phase resulting in either apoptosis or differentiation into long-lived memory T cells. Additional pathways for generation of memory cells include direct differentiation of memory T cells from naïve cells and production of effector and memory T cells from naive cells by asymmetric cell division. (b) The common surface markers in tabular form used to identify the naive and memory T cells such as CD45RA, CD45RO, CCR7 and CD69. In addition, it lists some other markers that are expressed differentially on these cell populations and could potentially be used to target specific memory T cell populations.

cells (T_{eff}) [7]. Following the acute response, the majority of these cells undergo apoptosis in a contraction phase with a small proportion persisting and differentiating into memory T cells (T_{mem}). In the divergent model, activated T_{naive} cells can differentiate directly into the memory phenotype bypassing the T_{eff} phase [8]. While the production of both effector and memory cells from the asymmetrical division of T cells has been demonstrated unequivocally, the extent to which this process leads to the production of the memory cell population is uncertain (Fig. 1) [9]. Recent studies provide evidence in favour of a model in which T_{naive} cells can heterogeneously produce different T_{mem} cell subsets [10,11]. This may depend upon different factors, such as the strength of T cell receptor (TCR) stimulation, dendritic cell (DC) interactions and cytokine signalling [12–14]. These memory cell subsets serve as precursors for T_{eff} cells. The precise mechanisms governing differentiation into a particular memory cell subset are unknown.

Subsets of memory T cells

Memory T cells are identified by the expression of the marker CD45RO and absence of CD45RA (found on T_{naive} cells) [15,16]. In addition, compared to T_{naive} cells they also have increased expression of CD2, CD11a and CD44 [15]. They are long-lived and proliferate in a more rapid fashion when exposed to antigen, differentiating to give rise to cytokine-producing T_{eff} cells. Three major subtypes of T_{mem} cells are now recognized: central memory cells (T_{CM}), effector memory cells (T_{EM}) and resident memory cells (T_{RM}) [17,18].

T_{CM} cells are $CCR7^+$ and $CD62L^{hi}$ and retain their ability to circulate to secondary lymphoid tissues [18]. These cells have a greater proliferative capacity and are longer-lived. They are thought to be important for production of T_{eff} cells following antigen recall [19,20]. By virtue of being $CCR7^-$ and $CD62L^{lo}$, T_{EM} cells circulate to peripheral non-lymphoid tissues and provide immediate effector functions. They are thought to be shorter-lived than T_{CM} cells, have lower proliferate capacity but greater cytokine production [19,20]. A more recently described class of memory cells is the T_{RM} subset. Similar to T_{EM}, these cells are $CCR7^-$, but express additional markers CD69 with or without CD103 [21]. T_{RM} subsets of $CD4^+$ and $CD8^+$ T cells were described initially in mice and were identified subsequently in humans [17,22–25]. These cells are localized within tissues and do not circulate to the bloodstream. Their functions are highly dependent upon the tissue in which they are found [12]. The role that these cells might play in organ-specific autoimmune disorders is being gradually clarified.

Cytokines important for memory cell production and survival

Studies of the generation of $CD4^+$ memory cells have revealed that interleukin (IL)-7 plays an important role in the formation of memory $CD4^+$ cells [14]. Resting T cells express IL-7R and down-regulate this when they are activated. T_{eff} cells that are destined to become memory cells will up-regulate IL-7R. The role of IL-7 was clarified by the lack of a memory response in $IL7^{-/-}$ hosts and in mice with mutations of the IL-7R alpha gene [26,27]. IL-15 has been shown to be important for the production of T_{mem} cells [28–30]. Both IL-7 and IL-15 play an important role in the survival of $CD4^+$ and $CD8^+$ memory cells, with

IL-7 being more important for $CD4^+$ cells [31,32]. In addition to these cytokines, transforming growth factor (TGF)-β is another cytokine that has been found to play an important role in the development of $CD8^+$ T_{RM} in various tissues [23,33]. TGF-β increases the expression of CD103, a marker that is characteristic for T_{RM} cells, and blockade of TGF signalling can lead to reduced production of T_{RM} cells. These various cytokines may serve as therapeutic targets for autoimmune memory cells.

Metabolism and T cell phenotype

In recent years, differences in the metabolism of T cells based on their function have been noted. T_{eff} cells utilize glycolysis as a means of production of adenosine triphosphate (ATP) even in the presence of sufficient oxygen, and one potential role of this metabolic-switch in facilitating cytokine production was elucidated recently [34]. Conversely, $CD8^+$ and $CD4^+$ T_{mem} cells have been demonstrated to prefer fatty acid oxidation (FAO) as their means of ATP production while suppressing glycolysis [35,36]. These distinct metabolic profiles of T_{eff} and T_{mem} cells may enable targeting of specific metabolic pathways that are important for the survival and function of memory cells.

Memory cells are important in autoimmune disease

The role of memory cells in various autoimmune diseases has been explored extensively. We will briefly discuss the role as studied in multiple sclerosis (MS), an inflammatory demyelinating disease involving the central nervous system [37].

Studies have shown that memory cells are important in the pathogenesis of MS. A study in paediatric MS showed that patients had a higher percentage of memory T cells similar to that in 20–30-year-older healthy controls [38]. Studies in adult MS subjects have demonstrated increased frequencies of T_{mem} cells, especially T_{EM} cells [39–42]. Evidence for the importance of these cells also comes from studies demonstrating that memory cells are enriched in the cerebrospinal fluid (CSF) of patients with MS, and the majority of T cells found in parenchymal MS lesions are T_{EM} cells [43–45].

Similarly, other diseases have been shown to demonstrate changes in the proportion of memory cells in the peripheral circulation as well as the target tissues [46,47].

Markers for pathogenic memory T cells

Because autoimmune disorders are often marked by an ongoing exposure of autoimmune memory cells to the offending antigen, Niesner *et al.* studied the transcriptomes of repeatedly activated T helper type 1 (Th1) cells and found that the expression of the Twist1 gene was upregulated and increased incrementally with each restimulation [48]. Twist1 has been shown to be a regulator of Th1 cell cytokine production and inhibition of Twist1 function leads to exaggeration of Th1-mediated inflammation. T cells isolated from tissues with rheumatoid arthritis and IBD patients showed extremely high levels of Twist1 expression, providing further support for this as a biomarker for pathogenic memory T cells [49]. The identification of other markers defining pathogenic memory cells will help in developing more targeted therapeutic approaches.

Strategies to target memory T cells

Targeting memory T cell surface markers. (a) Alefacept: alefacept is a dimeric fusion protein, consisting of the CD2 binding portion of the leucocyte function-associated antigen-3 (LFA-3) and the Fc portion of human immunoglobulin G, which was initially approved by the Food and Drug Administration (FDA) for treatment of psoriasis [50]. CD58 or LFA3 is expressed on antigen-presenting cells (APCs) and is the endogenous ligand for CD2 leading to T cell stimulation [51]. As CD2 is expressed highly on T_{mem} cells, with levels being highest on T_{EM} cells and slightly lower on T_{CM} cells, it was felt that Alefacept would target these cells selectively. Alefacept disrupts the CD2–CD58 interaction and results in depletion of T_{EM} cells and, to a lesser extent, T_{CM} cells in trials in psoriasis and type 1 DM [52,53]. In patients with psoriasis alefacept reduced T_{EM} cells numbers in diseased skin as well as in peripheral blood [54]. Studies in non-human primates have shown that alefacept can target co-stimulatory blockade resistant T_{EM} cells, which are an important player in autoimmunity [55].

(b) Cytokine signalling blockade: as IL-15 and IL-7 are important in the production and survival of T_{EM} and T_{CM} cells, blockade of signalling though their cytokine receptors could serve as an effective strategy to target memory cells. Janus kinases (Jak) are cytoplasmic tyrosine kinases that play a role in intracellular signalling downstream of type I cytokines such as IL-2, IL-7 and IL-15 [56].

Tofacitinib is a potent inhibitor of Jak 1and Jak 3 that has shown efficacy in the treatment of rheumatoid arthritis [57]. Tofacitinib has shown efficacy in preventing rejection of transplants and its effect may be related to blocking IL-15 signalling [58]. Further studies are required to determine the effect on T_{mem} cell subsets in subjects treated with tofacitinib.

Ruxolitinib is an inhibitor of Jak 1 and 2 and has been proposed as a possible means of disrupting IL-15 signalling in T_{mem} cells [59]. In a study by Xing *et al.*, the importance of cytotoxic $CD8^+$ T_{EM} phenotype cells in the pathogenesis of alopecia areata was demonstrated [60]. The authors then demonstrated the efficacy of Jak 1 and 2 inhibition in an animal model of alopecia areata, and finally the improvement of alopecia areata in patients who were treated with ruxolitinib. Further studies would be required to clearly define changes in the memory cell population in subjects treated with this medication.

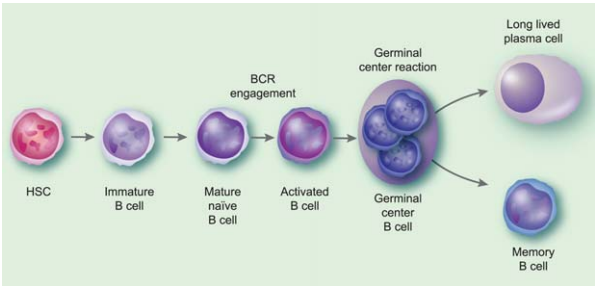


Fig. 2. B cell differentiation and generation of memory B cells and long-lived plasma cells. This figure depicts the process of production of memory B cells and long-lived plasma cells. While the majority of memory B cells and long-lived plasma cells are derived from the germinal centre reaction in secondary lymphoid tissues, subsets of each of these types of cells that have extra-follicular origins have been described.

(c) S1P receptor modulators: S1P signalling plays a major role in the egress of T cells from lymphoid tissue in concert with other cellular surface molecules such as CCR7, CD69 and CD62L [61]. Initial studies demonstrated marked depletion of central memory cells as well as naive cells from the peripheral circulation in patients treated with fingolimod (S1P receptor modulator) [62]. T_{EM} cells, which have low receptor $S1P_1$ expression, were not reduced significantly. However, the drug resulted in a marked reduction in Th17 effector cells, and this led to the assumption that T_{CM} cells were the precursors for the majority of Th17 effectors [63]. Nevertheless, actions of fingolimod extend beyond lymphocyte trapping in the lymph nodes and can have direct effects on signal transducer and activator of transcription-1 (STAT-3) signalling, which is instrumental for the development of Th17 responses [64].

Also of interest are the effects of S1P signalling in the production and retention of T_{RM} cells. T_{RM} cells express CD69 and have KLF2 decreased activation and low $S1P_1R$ expression [65]. Forced expression of KLF2 or $S1P_1R$ on the T_{RM} cells leads to reduced establishment of a T_{RM} pool. This suggests that modulation of S1P signalling may also work by altering T_{RM} pools; however, further studies are required to confirm this possible mechanism of action.

(d) Kv1.3 inhibition: Kv1.3 is an outward rectifying potassium channel that is up-regulated specifically on T_{EM} cells and appears to be essential for the effector function of these cells' channels by allowing the countercurrent influx of calcium [66]. T_{naive} cells and T_{CM} cells have a higher expression of KCa3.1 channels and are relatively less dependent on Kv1.3 [67]. In MS, previous studies have demonstrated an increased presence of $CD45RA^{-}CCR7^{-}$ T_{EM} cells in perivenular infiltrates and MS lesions [44]. These cells have an abundance of Kv1.3 channels. Blockade of Kv1.3 channels has been shown to ameliorate experimental autoimmune encephalitis (EAE), a mouse model of MS, and suppress effector memory cell function of human myelin reactive T cells [41,68,69].

Psoriatic skin lesions also show evidence of accumulation of T cells with up-regulation of Kv1.3 channels [70]. A study of a Kv1.3 channel blocker ameliorated disease in skin grafts of psoriatic skin in severe compromised immunodeficient (SCID) mice [70]. Thus blockade of Kv1.3 channels may serve as an effective treatment targeting autoimmune T_{EM} cells.

(e) Tumour necrosis factor (TNF) family receptor FAS/CD95 targeting: the TNF family receptor FAS plays an important role in maintaining immunological self-tolerance [71]. Interestingly, it has been shown that T_{EM} cells are highly susceptible to FAS-mediated apoptosis, while T_{CM} and T_{naive} cells are relatively resistant. Administration of FAS ligand led to apoptosis of T_{EM} cells selectively while sparing T_{naive} and T_{CM} cells [72]. This is thought to be due to more efficient assembly and activation of the FAS-associated death-inducing signalling complex (DISC) in T_{EM} cells. Thus, utilizing FAS ligands may help to eliminate T_{EM} cells in autoimmune diseases.

Targeting memory cell metabolism

Because T_{mem} cells are long-lived and utilize FAO rather than glycolysis, targeting FAO in these cells may result in reduction in the numbers and function of T_{mem} cells [36]. A recent study demonstrated that, unlike T_{eff} cells, T_{mem} cells did not utilize extrinsic fatty acids but rather produce fatty acids required for FAO within the cell [35]. Lipolysis due to lysosomal acid lipase (LAL) in lysosomes was imperative for the survival of $CD8^{+}$ T_{mem} cells. LAL knock-out led to a lack of production of T_{mem} cells when T_{eff} cells were deprived of antigen and hence went through a contraction phase, underlining the importance of metabolism in the development of T_{mem} cells. In another study the suppression of FAO in $CD4^{+}$ T_{mem} cells led to a reduction in the functional capacity and survival of these cells [36]. These studies suggest that disruption of specific metabolic pathways in T_{mem} cells may be an approach for the specific targeting of this cell population.

Humoral memory

Immunological memory in the humoral arm of the adaptive immune system is mediated through long-lived memory B cells and sustained antibody titres produced from long-lived plasma cells [73]. These cells are produced primarily in the germinal centres of secondary lymphoid organs; however, the precise mechanisms leading to differentiation from naive B cells to memory B cells or long-lived plasma cells are unclear (Fig. 2) [74].

Memory B cells provide enhanced antibody production when restimulated and are characterized by isotype switching and affinity maturation [75]. Memory B cells

in humans were identified originally as class-switched immunoglobulin D negative cells and have been identified more recently by the expression of CD27. Subsets of B cells that are $CD27^{-}$ but display the characteristics of memory B cells have also been described.

As well as the production of antibodies, memory B cells also play important roles in autoimmunity through cytokine production and antigen presentation to T cells [76,77]. Additionally, memory B cells may not require certain survival signals, such as B cell activating factor (BAFF)/BAFF-R interaction, making them resistant to certain drugs targeting these pathways (Belimumab) [78].

Long-lived plasma cells also provide humoral immunological memory and could serve as a source of pathogenic antibodies in autoimmune disease. Long-lived plasma cells can persist for several years and have high expression of CXCR4, which helps them to home to specialized niches high in CXCL12 such as the bone marrow [79]. They require several different growth factors for survival, such as IL-6, ligands for CD44 and CD28–B7 interactions [80,81].

Strategies for targeting humoral memory

B cell depletion

In MS, treatment with B cell-depleting agents leads to significant reductions in disease activity [82,83]. The basis for this effect appears to be independent of B cell antibody production and may be related to a reduced production of proinflammatory cytokines such as IL-6 or reduced antigen presentation by B cells, which by their sheer numbers are an important APC pool [84]. Studies with normal human B cells demonstrated that memory B cells are the major producers of proinflammatory cytokines such as lymphotoxin and TNF-α [77]. In patients with MS, B cells produce lower amounts of the anti-inflammatory cytokine IL-10 [77]. Following B cell depletion, a repopulation with naive B cells that produce larger amounts of IL-10 and lower amounts of proinflammatory cytokines was seen, and could explain the long-term efficacy of this strategy [77,85].

In subjects with immune thrombocytopenic purpura, it was noted that B cell depletion with rituximab led to an increase in the number of splenic long-lived plasma cells. This was thought to be secondary to a change in the splenic micro-environment and could potentially explain the lack of efficacy of B cell depletion in certain autoimmune diseases. In such disorders, a combined strategy that targets both B cells as well as long-lived plasma cells may be required.

Targeted B cell therapies

(a) Atacicept: the importance of memory B cells in the pathogenesis of autoimmune disorders was also demonstrated by the lack of efficacy of atacicept [86,87]. Atacicept is a fusion protein consisting of the extracellular domain of the transmembrane activator and CAML interactor (TACI) receptor, bound to the Fc portion of human immunoglobulin [88]. This receptor binds B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), which are cytokines involved in B cell proliferation and survival [89]. Atacicept was shown to target mature B cells and short-lived plasma cells while sparing memory cells, as well as B cell progenitors [88]. In a trial of atacicept in patients with rheumatoid arthritis a transient increase in memory B cells was noted [90]. This lack of removal of memory B cells may explain the inefficacy of this approach, given the previous evidence of the role of memory B cells in autoimmunity [76,77].

(b) Tocilizumab: tocilizumab is a humanized monoclonal antibody to the IL-6 receptor that binds both soluble and membrane-bound forms of the receptor. It is approved for use in patients with RA who have had an inadequate response to other therapies [91]. IL-6 is a pleiotropic cytokine secreted by several different cell types including T cells, macrophages, fibroblasts, osteoblasts and endothelial cells. It plays an important role in B cell activation and the development of antibody-producing plasma cells. In patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), tocilizumab treatment resulted in a reduction in memory B cells [92,93]. Tocilizumab also reduced immunoglobulin levels in patients with SLE and RA, suggesting a reduction in plasma cell numbers [92,94].

The efficacy of tocilizumab suggests that targeting memory B cells may be an effective strategy to treat autoimmune disease.

Future directions

Cautions

Experience with previous 'targeted' approaches that were found subsequently to have other off-target effects, leading to serious adverse effects, must make us cautious when testing new putative therapies targeting immune memory. Anti-inflammatory medications such as anti-TNF-α agents, that were effective in certain autoimmune disorders, led to the development of inflammatory demyelinating lesions of the CNS [95].

Additionally, although memory cells may play an important role in autoimmunity, they continue to be important for other functions, such as protection against infections and anti-tumour effects. A balanced approach targeting the subsets of cells likely to be the most pathogenic would yield the best balance of risk and benefit.

Better targets for pathogenic memory cells

Targets to define more clearly the factors that cause the generation of different subsets of memory cells would help to develop novel therapies. GWAS studies have now identified several different loci that are associated with autoimmune disease [96,97]. Studies are now beginning

to link these genes with gene expression data from different cell subtypes to define which memory cell-associated genes are implicated in autoimmune disease [98]. Targeting of these gene products may lead to more efficient pathogenic memory cell targeting while preserving helpful immunological memory.

With advances in the understanding of the generation and survival of different memory subsets, insight into the identification of pathogenic memory cells and new approaches to identify cell-specific gene variants in autoimmune disease that may reveal new therapeutic targets, it is likely that memory cell-specific therapies may become a reality in the near future. These could be effective and safe for treating a variety of autoimmune diseases.

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Disclosure

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REFERENCES

1 Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 2010; **9**:520–32.
2 Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof?. Diabetes Metab Res Rev 2011; **27**:3–13.
3 Logan I, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. Autoimmun Rev 2010; **9**:A372–8.
4 Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997; **84**:223–43.
5 Amsen D, Backer RA, Helbig C. Decisions on the road to memory. Adv Exp Med Biol 2013; **785**:107–20.
6 Van Leeuwen EMM, Sprent J, Surh CD. Generation and maintenance of memory CD4($^+$) T cells. Curr Opin Immunol 2009; **21**:167–72.
7 Gerlach C, van Heijst JWJ, Schumacher TNM. The descent of memory T cells. Ann NY Acad Sci 2011; **1217**:139–53.
8 Ahmed R, Bevan MJ, Reiner SL, Fearon DT. The precursors of memory: models and controversies. Nat Rev Immunol 2009; **9**: 662–8.
9 Chang JT, Palanivel VR, Kinjyo I et al. Asymmetric T lymphocyte division in the initiation of adaptive immune responses. Science 2007; **315**:1687–91.
10 Buchholz VR, Flossdorf M, Hensel I et al. Disparate individual fates compose robust CD8$^+$ T cell immunity. Science 2013; **340**: 630–5.
11 Gerlach C, Rohr JC, Perié L et al. Heterogeneous differentiation patterns of individual CD8$^+$ T cells. Science 2013; **340**: 635–9.
12 Hu W, Pasare C. Location, location, location: tissue-specific regulation of immune responses. J Leukoc Biol 2013; **94**: 409–21.
13 Blair DA, Lefrançois L. Increased competition for antigen during priming negatively impacts the generation of memory CD4 T cells. Proc Natl Acad Sci USA 2007; **104**:15045–50.
14 Dooms H, Wolslegel K, Lin P, Abbas AK. Interleukin-2 enhances CD4$^+$ T cell memory by promoting the generation of IL-7R alpha-expressing cells. J Exp Med 2007; **204**:547–57.
15 Sanders ME, Makgoba MW, Sharrow SO et al. Human memory T lymphocytes express increased levels of three cell adhesion molecules (LFA-3, CD2, and LFA-1) and three other molecules (UCHL1, CDw29, and Pgp-1) and have enhanced IFN-gamma production. J Immunol 1988; **140**:1401–7.
16 Smith SH, Brown MH, Rowe D et al. Functional subsets of human helper-inducer cells defined by a new monoclonal antibody, UCHL1. Immunology 1986; **58**:63–70.
17 Teijaro JR, Turner D, Pham Q et al. Cutting edge: tissue-retentive lung memory CD4 T cells mediate optimal protection to respiratory virus infection. J Immunol 2011; **187**: 5510–4.
18 Sallusto F, Lenig D, Förster R et al. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature 1999; **401**:708–12.
19 Champagne P, Ogg GS, King AS et al. Skewed maturation of memory HIV-specific CD8 T lymphocytes. Nature 2001; **410**: 106–11.
20 Ellefsen K, Harari A, Champagne P et al. Distribution and functional analysis of memory antiviral CD8 T cell responses in HIV-1 and cytomegalovirus infections. Eur J Immunol 2002; **32**: 3756–64.
21 Farber DL, Yudanin NA, Restifo NP. Human memory T cells: generation, compartmentalization and homeostasis. Nat Rev Immunol 2014; **14**:24–35.
22 Turner DL, Farber DL. Mucosal resident memory CD4 T cells in protection and immunopathology. Front Immunol 2014; **5**: 331.
23 Mackay LK, Rahimpour A, Ma JZ et al. The developmental pathway for CD103($^+$)CD8$^+$ tissue-resident memory T cells of skin. Nat Immunol 2013; **14**:1294–301.
24 Clark RA, Watanabe R, Teague JE et al. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. Sci Transl Med 2012; **4**: 117ra7.
25 Booth JS, Toapanta FR, Salerno-Goncalves R et al. Characterization and functional properties of gastric tissue-resident memory T cells from children, adults, and the elderly. Front Immunol 2014; **5**:294.
26 Kondrack RM, Harbertson J, Tan JT et al. Interleukin 7 regulates the survival and generation of memory CD4 cells. J Exp Med 2003; **198**:1797–806.
27 Osborne LC, Dhanji S, Snow JW et al. Impaired CD8 T cell memory and CD4 T cell primary responses in IL-7R alpha mutant mice. J Exp Med 2007; **204**:619–31.
28 Itsumi M, Yoshikai Y, Yamada H. IL-15 is critical for the maintenance and innate functions of self-specific CD8($^+$) T cells. Eur J Immunol 2009; **39**:1784–93.

29 Schluns KS, Williams K, Ma A et al. Cutting edge: requirement for IL-15 in the generation of primary and memory antigen-specific CD8 T cells. J Immunol 2002; **168**:4827–31.

30 Waldmann TA. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. J Invest Dermatol Symp Proc 2013; **16**:S28–30.

31 Klonowski KD, Williams KJ, Marzo AL, Lefrançois L. Cutting edge: IL-7-independent regulation of IL-7 receptor alpha expression and memory CD8 T cell development. J Immunol 2006; **177**:4247–51.

32 Devarajan P, Chen Z. Autoimmune effector memory T cells: the bad and the good. Immunol Res 2013; **57**:12–22.

33 Zhang N, Bevan MJ. Transforming growth factor-β signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. Immunity 2013; **39**:687–96.

34 Chang C-H, Curtis JD, Maggi LB et al. Posttranscriptional control of T cell effector function by aerobic glycolysis. Cell 2013; **153**:1239–51.

35 O'Sullivan D, van der Windt GJW, Huang SC-C et al. Memory CD8($^+$) T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development. Immunity 2014; **41**:75–88.

36 Taub DD, Hesdorffer CS, Ferrucci L et al. Distinct energy requirements for human memory CD4 T-cell homeostatic functions. FASEB J 2013; **27**:342–9.

37 Compston A, Coles A. Multiple sclerosis. Lancet 2008; **372**: 1502–17.

38 Balint B, Haas J, Schwarz A et al. T-cell homeostasis in pediatric multiple sclerosis: old cells in young patients. Neurology 2013; **81**:784–92.

39 Haegele KF, Stueckle CA, Malin J-P, Sindern E. Increase of CD8$^+$ T-effector memory cells in peripheral blood of patients with relapsing-remitting multiple sclerosis compared to healthy controls. J Neuroimmunol 2007; **183**:168–74.

40 Lovett-Racke AE, Trotter JL, Lauber J et al. Decreased dependence of myelin basic protein-reactive T cells on CD28-mediated costimulation in multiple sclerosis patients. A marker of activated/memory T cells. J Clin Invest 1998; **101**: 725–30.

41 Wulff H, Calabresi PA, Allie R et al. The voltage-gated Kv1.3 K($^+$) channel in effector memory T cells as new target for MS. J Clin Invest 2003; **111**:1703–13.

42 Allegretta M, Nicklas JA, Sriram S, Albertini RJ. T cells responsive to myelin basic protein in patients with multiple sclerosis. Science 1990; **247**:718–21.

43 Kivisäkk P, Mahad DJ, Callahan MK et al. Expression of CCR7 in multiple sclerosis: implications for CNS immunity. Ann Neurol 2004; **55**:627–38.

44 Rus H, Pardo CA, Hu L et al. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proc Natl Acad Sci USA 2005; **102**: 11094–9.

45 Mullen KM, Gocke AR, Allie R et al. Expression of CCR7 and CD45RA in CD4$^+$ and CD8$^+$ subsets in cerebrospinal fluid of 134 patients with inflammatory and non-inflammatory neurological diseases. J Neuroimmunol 2012; **249**:86–92.

46 Hayashi M, Furuhashi T, Nishida E et al. Increased population of central memory T cells in circulating peripheral blood of psoriasis patients. J Dermatol Sci 2013; **70**:61–4.

47 Matteucci E, Ghimenti M, Di Beo S, Giampietro O. Altered proportions of naïve, central memory and terminally differentiated central memory subsets among CD4$^+$ and CD8 $^+$ T cells expressing CD26 in patients with type 1 diabetes. J Clin Immunol 2011; **31**:977–84.

48 Niesner U, Albrecht I, Janke M et al. Autoregulation of Th1-mediated inflammation by twist1. J Exp Med 2008; **205**:1889–901.

49 Chang H-D, Radbruch A. Targeting pathogenic T helper cell memory. Ann Rheum Dis 2011; **70** (Suppl. 1):i85–7.

50 Krueger GG, Papp KA, Stough DB et al. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002; **47**: 821–33.

51 Luo L, Sun Z, Cheng H, Luo G. Memory T-cell-specific therapeutics attenuate allograft rejection via mediation of alloreactivity in memory cells. Immunol Lett 2012; **148**:53–8.

52 Rigby MR, DiMeglio LA, Rendell MS et al. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol 2013; **1**:284–94.

53 Chamian F, Lin S-L, Lee E et al. Alefacept (anti-CD2) causes a selective reduction in circulating effector memory T cells (Tem) and relative preservation of central memory T cells (Tcm) in psoriasis. J Transl Med 2007; **5**:27.

54 Vissers WHPM, van Duijnhoven M, van Erp PEJ et al. The effect of alefacept on T-cell subsets and cells expressing NK receptors in lesional psoriatic skin: the effects of monotherapy and combination treatment with calcipotriol. J Dermatol Treat 2008; **19**:344–50.

55 Weaver TA, Charafeddine AH, Agarwal A et al. Alefacept promotes co-stimulation blockade based allograft survival in nonhuman primates. Nat Med 2009; **15**:746–9.

56 Rochman Y, Spolski R, Leonard WJ. New insights into the regulation of T cells by gamma(c) family cytokines. Nat Rev Immunol 2009; **9**:480–90.

57 Fleischmann R, Kremer J, Cush J et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012; **367**:495–507.

58 Wojciechowski D, Vincenti F. Tofacitinib in kidney transplantation. Expert Opin Invest Drugs 2013; **22**:1193–9.

59 Mesa RA, Yasothan U, Kirkpatrick P. Ruxolitinib. Nat Rev Drug Discov 2012; **11**:103–4.

60 Xing L, Dai Z, Jabbari A et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med 2014; **20**:1043–9.

61 Garris CS, Blaho VA, Hla T, Han MH. Sphingosine-1-phosphate receptor 1 signalling in T cells: trafficking and beyond. Immunology 2014; **142**:347–53.

62 Mehling M, Brinkmann V, Antel J et al. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. Neurology 2008; **71**:1261–7.

63 Mehling M, Lindberg R, Raulf F et al. Th17 central memory T cells are reduced by FTY720 in patients with multiple sclerosis. Neurology 2010; **75**:403–10.

64 Liao J-J, Huang M-C, Goetzl EJ. Cutting edge: alternative signaling of Th17 cell development by sphingosine 1-phosphate. J Immunol 2007; **178**:5425–8.

65 Skon CN, Lee J-Y, Anderson KG et al. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory $CD8^+$ T cells. Nat Immunol 2013; **14**:1285–93.
66 Cahalan MD, Chandy KG. Ion channels in the immune system as targets for immunosuppression. Curr Opin Biotechnol 1997; **8**:749–56.
67 Rangaraju S, Chi V, Pennington MW, Chandy KG. Kv1.3 potassium channels as a therapeutic target in multiple sclerosis. Expert Opin Ther Targets 2009; **13**:909–24.
68 Beeton C, Wulff H, Barbaria J et al. Selective blockade of T lymphocyte $K(^+)$ channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. Proc Natl Acad Sci USA 2001; **98**:13942–7.
69 Hu L, Pennington M, Jiang Q et al. Characterization of the functional properties of the voltage-gated potassium channel Kv1.3 in human $CD4^+$ T lymphocytes. J Immunol 2007; **179**:4563–70.
70 Gilhar A, Bergman R, Assay B et al. The beneficial effect of blocking Kv1.3 in the psoriasiform SCID mouse model. J Invest Dermatol 2011; **131**:118–24.
71 Straus SE, Sneller M, Lenardo MJ et al. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. Ann Intern Med 1999; **130**:591–601.
72 Ramaswamy M, Cruz AC, Cleland SY et al. Specific elimination of effector memory $CD4^+$ T cells due to enhanced Fas signaling complex formation and association with lipid raft microdomains. Cell Death Differ 2011; **18**:712–20.
73 Shlomchik MJ, Weisel F. Germinal center selection and the development of memory B and plasma cells. Immunol Rev 2012; **247**:52–63.
74 Pieper K, Grimbacher B, Eibel H. B-cell biology and development. J Allergy Clin Immunol 2013; **131**:959–71.
75 Yoshida T, Mei H, Dörner T et al. Memory B and memory plasma cells. Immunol Rev 2010; **237**:117–39.
76 Harp CT, Ireland S, Davis LS et al. Memory B cells from a subset of treatment-naïve relapsing-remitting multiple sclerosis patients elicit $CD4(^+)$ T-cell proliferation and IFN-γ production in response to myelin basic protein and myelin oligodendrocyte glycoprotein. Eur J Immunol 2010; **40**:2942–56.
77 Duddy M, Niino M, Adatia F et al. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. J Immunol 2007; **178**:6092–9.
78 Stohl W, Hiepe F, Latinis KM et al. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with systemic lupus erythematosus. Arthritis Rheum 2012; **64**:2328–37.
79 Nie Y, Waite J, Brewer F et al. The role of CXCR4 in maintaining peripheral B cell compartments and humoral immunity. J Exp Med 2004; **200**:1145–56.
80 Cassese G, Arce S, Hauser AE et al. Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. J Immunol 2003; **171**:1684–90.
81 Njau MN, Kim JH, Chappell CP et al. CD28-B7 interaction modulates short- and long-lived plasma cell function. J Immunol 2012; **189**:2758–67.
82 Hauser SL, Waubant E, Arnold DL et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008; **358**:676–88.
83 Kappos L, Li D, Calabresi PA et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011; **378**:1779–87.
84 Barr TA, Shen P, Brown S et al. B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells. J Exp Med 2012; **209**:1001–10.
85 Bar-Or A, Calabresi PA, Arnold D et al. Rituximab in relapsing–remitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol 2008; **63**:395–400.
86 Richez C, Truchetet M-E, Schaeverbeke T, Bannwarth B. Atacicept as an investigated therapy for rheumatoid arthritis. Expert Opin Invest Drugs 2014; **23**:1285–94.
87 Kappos L, Hartung H-P, Freedman MS et al. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Neurol 2014; **13**:353–63.
88 Hartung H-P, Kieseier BC. Atacicept: targeting B cells in multiple sclerosis. Ther Adv Neurol Disord 2010; **3**:205–16.
89 Dillon SR, Gross JA, Ansell SM, Novak AJ. An APRIL to remember: novel TNF ligands as therapeutic targets. Nat Rev Drug Discov 2006; **5**:235–46.
90 Van Vollenhoven RF, Kinnman N, Vincent E et al. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. Arthritis Rheum 2011; **63**:1782–92.
91 Kaly L, Rosner I. Tocilizumab-a novel therapy for non-organ-specific autoimmune diseases. Best Pract Res Clin Rheumatol 2012; **26**:157–65.
92 Roll P, Muhammad K, Schumann M et al. *In vivo* effects of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment. Arthritis Rheum 2011; **63**:1255–64.
93 Shirota Y, Yarboro C, Fischer R et al. Impact of anti-interleukin-6 receptor blockade on circulating T and B cell subsets in patients with systemic lupus erythematosus. Ann Rheum Dis 2013; **72**:118–28.
94 Illei GG, Shirota Y, Yarboro CH et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum 2010; **62**:542–52.
95 Solomon AJ, Spain RI, Kruer MC, Bourdette D. Inflammatory neurological disease in patients treated with tumor necrosis factor alpha inhibitors. Mult Scler 2011; **17**:1472–87.
96 The International Multiple Sclerosis Genetics Consortium (IMSGC). Evidence for polygenic susceptibility to multiple sclerosis-the shape of things to come. Am J Hum Genet 2010; **86**:621–5.
97 Beecham AH, Patsopoulos NA, Xifara DK et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet 2013; **45**:1353–60.
98 Baranzini SE, Khankhanian P, Patsopoulos NA et al. Network-based multiple sclerosis pathway analysis with GWAS data from 15,000 cases and 30,000 controls. Am J Hum Genet 2013; **92**: 854–65.