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REVIEW

Heterogeneity in the Differentiation and Function of CD8$^+$ T Cells

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Abstract It is well established that CD8$^+$ T cells constitute an important branch of adaptive immunity contributing to clearance of intracellular pathogens and providing long-term protection. These functions are mostly fulfilled by the best characterized subpopulation of CD8$^+$ T cells, the cytotoxic T lymphocytes (also called Tc1 cells), owing to their ability to kill infected cells and to secrete cytokines such as interferon-γ and tumor necrosis factor-α. However, there is growing evidence for alternative CD8$^+$ T cell fates influencing CD4$^+$ T-cell-mediated responses in the context of allergy, autoimmunity and infections. Thus, like subpopulations of CD4$^+$ T cells, also CD8$^+$ T cells under particular conditions acquire the expression of interleukin (IL)-4, IL-5, IL-9, IL-13, IL-17 or suppressive activity and thereby influence immune responses. The process of CD8$^+$ T-cell differentiation is dictated by antigen strength, co-stimulatory molecules and cytokines. These environmental cues induce transcription factors further specifying CD8$^+$ T-cell decision into Tc1, Tc2, Tc9, Tc17 or CD8$^+$ T regulatory fate. Here, we discuss our current understanding about functional diversity of effector CD8$^+$ T cells and contribution of transcription factors to this process.

Keywords CD8$^+$ T cells · Tc1 · Tc2 · Tc9 · Tc17 · CD8$^+$ Treg cells

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Introduction

CD8$^+$ T cells, a subpopulation of adaptive lymphocytes, play an important role in immunity to intracellular pathogens and tumors (Gattinoni et al. 2012; Klenerman and Hill 2005; Kuang et al. 2010; Lu et al. 2014). They also contribute to the regulation of pathologic processes such as autoimmune and allergic disorders (Huber et al. 2009; Kim and Cantor 2011; Loser et al. 2010; Tang et al. 2012; Visekruna et al. 2013). Naïve CD8$^+$ T cells are activated by recognition of specific peptides presented by MHC class I on antigen-presenting cells (APCs) in peripheral lymphatic organs. Additionally, co-stimulatory signals and skewing cytokines provided by APCs and/or CD4$^+$ T cells influence the differentiation of CD8$^+$ T cells. Thereafter, CD8$^+$ T cells undergo differentiation process and massive expansion to generate large numbers of effector cells which are able to migrate into the periphery. As MHC class I molecules are expressed on most nucleated cells, effector CD8$^+$ T cells can recognize their target antigen presented by almost all cells of our body except erythrocytes. Upon antigen re-encounter in the periphery, effector CD8$^+$ T cells of different subpopulations are able to fulfill their distinct functions. At the end of the primary response, the majority of responding CD8$^+$ T cells dies by apoptosis; however, a small fraction remains as long-lived memory T cells. These memory CD8$^+$ T cells respond with strong proliferation and rapid conversion into effector cells upon re-exposure to the cognate antigen (Kaech and Cui 2012; Shrikant et al. 2010). The models for generation of different subpopulations of memory Tc1 cells have been reviewed in detail recently (Buchholz et al. 2012; Kaech and Cui 2012; Restifo and Gattinoni 2013).

Here, we mainly focus on current understanding of diversity in the functions and differentiation programs of Tc1, Tc2, Tc9, Tc17 and $CD8^+$ T regulatory (Treg) cells.

Cytotoxic T Lymphocytes (Tc1 cells)

The Function of Tc1 Cells

The best characterized effector $CD8^+$ T-cell subpopulation, cytotoxic T lymphocytes (also named Tc1 cells), plays a crucial role in clearance of intracellular pathogens. Tc1 cells are capable of killing cells bearing the target antigen by releasing cytotoxic molecules, such as granzymes and perforin, into the immunological synapse and to secrete cytokines, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α. These cytokines further accelerate the innate and adaptive immune response against intracellular pathogens (Kaech and Cui 2012).

Phenotype of Effector and Memory Tc1 Cells

The differentiation of naïve $CD8^+$ T cells into effector Tc1 cells is strongly enhanced by cytokines such as interleukin (IL)-2 and IL-12 (Joshi et al. 2007; Kalia et al. 2010; Pipkin et al. 2010), and is accompanied by phenotypic changes which have been closely described in mouse models of infection such as with lymphocytic choriomeningitis virus (LCMV) or *Listeria monocytogenes*. The initial activation of $CD8^+$ T cells is associated with the up-regulation of surface markers, including CD44 and CD69. Differentiating effector cells acquire high expression of killer cell lectin-like receptor G1 (KLRG1) and IL-2 receptor subunit-α (CD25), while the L-selectin (CD62L), the IL-7 receptor subunit-α (CD127) and CD27 are down-regulated as compared to naïve cells. The majority of effector cells undergo apoptosis after pathogen clearance. However, a small fraction of activated cells persists for long-time establishing a memory-cell population. These memory precursor cells can be distinguished from effector cells already at early steps of immune responses by high expression of CD44 and maintenance of CD127 and CD27. Furthermore, memory precursor cells do not up-regulate KLRG1 and display low expression of CD25. Taken together, effector $CD8^+$ T cells are characterized by a $CD44^{hi}CD62L^{lo}CD27^{lo}KLRG1^{hi}IL7\text{-}R\alpha^{lo}$ phenotype and memory precursor can be defined as $CD44^{hi}CD27^{hi}KLRG1^{lo}IL7\text{-}R\alpha^{hi}$ cells (Kaech and Cui 2012).

Transcriptional Regulation of Effector and Memory Tc1 Cells

The phenotypic and functional changes in differentiating Tc1 cells are dictated by a transcriptional network. Whereas T-bet (Intlekofer et al. 2005; Joshi et al. 2007), Id2 (Cannarile et al. 2006), Blimp-1 (Kallies et al. 2009; Rutishauser et al. 2009) and interferon regulatory factor (IRF)4 (Man et al. 2013; Raczkowski et al. 2013; Yao et al. 2013) promote effector development, BCL-6 (Cui et al. 2011; Ichii et al. 2002), Eomesodermin (Eomes) (Intlekofer et al. 2005), Id3 (Ji et al. 2011; Yang et al. 2011), TCF-7 (Zhou et al. 2010) and Foxo1 (Hess Michelini et al. 2013; Kim et al. 2013; Tejera et al. 2013) are associated with memory-cell differentiation. Several signaling pathways induced by environmental cues regulate the expression of these transcriptional regulators. Thus, in accordance with the enhancement of effector Tc1 differentiation, the cytokine IL-12 promotes expression of T-bet and Id2 (Joshi et al. 2007; Takemoto et al. 2006; Yang et al. 2011), while IL-2 upregulates Id2 and suppresses memory-cell fate by controlling Id3 as well as BCL-6 (Pipkin et al. 2010; Yang et al. 2011). Downstream signaling molecules of IL-2 and IL-12, STAT5 and STAT4, respectively, drive Tc1 effector development probably by direct regulation of Id2 expression (Yang et al. 2011). IL-12 via phosphoinositide 3-kinase (PI3K)-AKT and STAT4 signaling also promotes nutrient-sensing serine/threonine protein kinase mammalian target of rapamycin (mTOR) activity, which has been demonstrated to influences the effector- versus memory-cell decision (Araki et al. 2009; Rao et al. 2010). Mechanistically, mTOR supports effector differentiation by inactivating the transcription factor Foxo1 which otherwise triggers memory development by mediating switch from T-bet to Eomes (Rao et al. 2012) through direct promotion of TCF-7 expression (Hess Michelini et al. 2013; Kim et al. 2013; Tejera et al. 2013). The transcription factor TCF-7 also known as T-cell factor 1 functions downstream of WNT-β-catenin pathway and enhances memory formation at least partially by induction of Eomes (Jeannet et al. 2010; Zhou et al. 2010). Furthermore, effector Tc1 differentiation is enhanced by the Hippo pathway, which is activated by cell–cell contact signals via CTLA4 and its ligand CD80, probably by suppression of Eomes and induction of Blimp-1 (Thaventhiran et al. 2012).

In contrast to STAT4 and STAT5, STAT3 signaling, which is induced by cytokines IL-6, IL-10 and IL-21, favors memory Tc1 development by up-regulation of Eomes, BCL-6 and Socs3. Socs3 in this setting dampens the enhancing effect of IL-12 on the effector development (Cui et al. 2011).

Finally, the strength of T cell receptor (TCR) signaling plays pivotal role for differentiation of effector Tc1 cells

and the transcription factor IRF4 was recently shown to be the central sensor translating signal strength into a transcriptional program (Man et al. 2013; Raczkowski et al. 2013; Yao et al. 2013). Strong TCR signaling causes high expression of IRF4, while weak signals induce lower amounts of this transcription factor. This effect seems to be mediated cooperatively by mTOR and IL-2 inducible T cells kinase-dependent pathways (Nayar et al. 2012; Yao et al. 2013). Although IRF4 is not important for early activation of $CD8^+$ T cells, it is crucial for the sustained proliferation, survival and effector differentiation of Tc1 cells (Man et al. 2013; Raczkowski et al. 2013; Yao et al. 2013). IRF4 fulfills these multiple effects by several means. On the one hand, IRF4 seems to regulate proliferation and apoptosis of $CD8^+$ T cells by direct inhibition of cyclin-dependent kinase inhibitors, including Cdkn2a, as well as of the proapoptotic protein Bim (Yao et al. 2013). However, the regulation of Bim expression by IRF4 is not solely responsible for the protection from apoptosis, because the double-deficiency in IRF4 and Bim does not improve the survival of IRF4-deficient $CD8^+$ T cells. On the other hand, IRF4 affects the effector differentiation by influencing the expression of key transcription factors Blimp-1 and T-bet as well as by contribution to the metabolic reprogramming of activated cells (Man et al. 2013; Raczkowski et al. 2013; Yao et al. 2013). To provide energy and biosynthetic precursors for rapid proliferation and production of effector molecules, after activation, naïve T cells switch the metabolic program from catabolic oxidative phosphorylation to aerobic glycolysis. This process is controlled by several transcription factors, including c-Myc, HIF-1α and Foxo1 (Wang and Green 2012). IRF4 seems not to be important for the initial activation controlled by c-Myc, but sustains this activation which is then characterized by high glycolytic turnover. On a molecular level, IRF4 controls the expression of transcription factors regulating this process, HIF-1α and Foxo1, but also directly promotes expression of proteins involved in this process such as the glucose transporters Glut1 and Glut3 (Man et al. 2013). For transcriptional control of some of these pathways, IRF4 cooperates with its known partner the B-cell activating transcription factor (BATF) (Grusdat et al. 2014; Kurachi et al. 2014; Man et al. 2013; Yao et al. 2013). Similar to deficiency in IRF4, deficiency in BATF also disturbs energy metabolism in $CD8^+$ T cells and influences their effector differentiation (Kurachi et al. 2014; Kuroda et al. 2011). On the other hand, inhibition of glycolytic metabolism has been shown to enhance memory $CD8^+$ T cell differentiation (MacIver et al. 2013; Sukumar et al. 2013).

Taken together, several signaling pathways responding to signals from environment, such as cytokines (STAT, AKT/mTOR), Wnt-proteins (β-catenin, mTOR), cell–cell contact (CTLA-4/CD80, Hippo) and the strength of MHC–TCR interaction, influence the expression of key transcription factors Eomes, T-bet, Blimp-1, BCL-6, Id2, Id3, TCF-7 and Foxo1, and the balance of these factors is decisive for the effector versus memory Tc1 fate. Moreover, for sustained effector differentiation, the metabolic switch into aerobic glycolysis is necessary and this process is maintained at least partially by IRF4 (Fig. 1; Table 1).

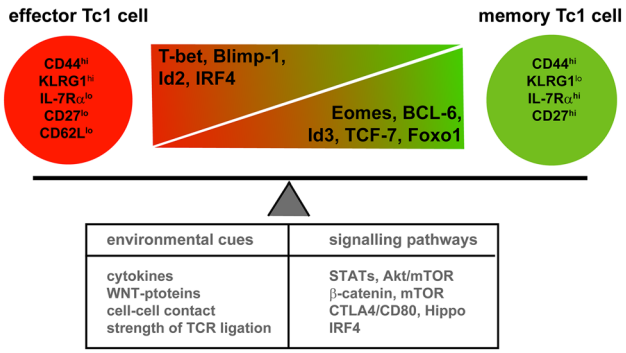

Fig. 1 Transcription factors, signaling pathways and environmental cues influencing effector and memory Tc1 fate. Effector and memory Tc1 cells can be discriminated by the expression of phenotypic markers (*shown inside the cells*). The differentiation of Tc1 cells into effector versus memory fates is dictated by several transcription factors (*shown inside of triangles*), which are regulated by environmental cues (*listed in the bottom of the figure*). For details see the section "Cytotoxic T Lymphocytes (Tc1 cells)"

Alternative $CD8^+$ T-Cell Subsets

Tc2 Cells

Tc2 cells can be induced in vitro in the presence of IL-4 (Croft et al. 1994). Their cytokine profile almost completely overlaps with that of Th2 cells; they produce IL-5 and IL-13; however, only to a limited extent IL-4. Furthermore, Tc2 cells express the lineage-specific transcription factor GATA3 but at lower levels than Th2 cells (Croft et al. 1994; Omori et al. 2003). Tc2 cells functionally differ from Tc1 cells as shown during influenza infection, in autoimmunity and allergic disorders (Cerwenka et al. 1999; Tang et al. 2012; Vizler et al. 2000). Whereas Tc1 cells are beneficial in allergic airway inflammation, Tc2 cells show only low level of cytotoxicity and aggravate disease. This enhancement of inflammation is at least partially dependent on the capacity of Tc2 cells to produce IL-13 (Tang et al. 2012).

Tc2 cells contribute probably to the development and progression of rheumatoid arthritis, because there was selective enrichment of IL-4 producing $CD8^+$ T cells with low perforin and granzyme B expression in the synovial fluid as compared to peripheral blood of patients (Cho et al.

Table 1 Overview of effector $CD8^+$ T-cell subpopulations, the conditions for their differentiation in vitro, transcription factors controlling their development and their known functions

Type	Polarizing cytokines in vitro	Important transcription factors	Effector molecules	Function	References
Tc1	IL-2, IL-12	T-bet, Blimp-1, Id2, IRF4	IFN-γ, TNF-α, granzymes, perforin	Immunity against intracellular pathogens and tumors	(Kaech and Cui 2012; Kim et al. 2013; Man et al. 2013)
Tc2	IL-4	GATA3	IL-5, IL-13, IL-4, granzymes, perforin	Propagation of Th2-mediated allergy, contribution to arthritis	(Cho et al. 2012; Omori et al. 2003; Tang et al. 2012)
Tc9	TGF-β, IL-4	?/IRF4	IL-9, IL-10	Inhibition of $CD4^+$ T-cell-mediated colitis, propagation of Th2-mediated allergy, anti-tumor response	(Chang et al. 2013; Lu et al. 2014; Visekruna et al. 2013)
Tc17	TGF-β, IL-6, IL-21	RORγt, RORα, IRF4	IL-17, IL-21	Propagation of autoimmunity, immunity to viral infections, contribution to anti-tumor response	(Hamada et al. 2009; Hinrichs et al. 2009; Huber et al. 2013)
$CD8^+$ Treg	TGF-β	?/Foxp3	TGF-β, IL-10, granzymes, perforin	Regulation of T-cell-mediated responses	(Kim and Cantor 2011; Robb et al. 2012; Tsai et al. 2010)

2012). In contrast, during influenza infection and in autoimmune diabetes, Tc2 cells seem to display high cytotoxic activity (Cerwenka et al. 1999; Vizler et al. 2000). However, despite cytotoxicity, Tc2 cells were less protective as compared to Tc1 cells during influenza infection, probably because of different homing capacities (Cerwenka et al. 1999). Likewise, in an autoimmune diabetes model, pancreas-specific homing, expansion and diabetogenic potential of Tc2 cells were lower as compared to Tc1 cells (Vizler et al. 2000). Thus, depending on the type of immune response, Tc2 cells can acquire high or low cytotoxicity and their functional properties strongly differ from those of Tc1. Taken together, Tc2 cells can be functionally associated with enhancement of allergic airway inflammation, impaired protective efficiency during influenza infection as well as lower diabetogenicity as compared to Tc1, and probably these cells contribute to rheumatoid arthritis.

Tc9 Cells

In the intestinal epithelium, CD8αβ intraepithelial lymphocytes (IEL), which produce IL-9, IL-10 and low levels of granzyme B, have been detected. The differentiation of $CD8^+$ T cells into IL-9 producers (Tc9 cells) could be induced in vitro by $CX3CR1^+$ dendritic cells isolated from lamina propria of the small intestine, which cross-presented cognate antigens. In vivo, probably these $CX3CR1^+$ dendritic cells process antigens from circulation and induce differentiation of IL-9-producing $CD8^+$ T cells, which display the markers PD-1 and chemokine receptor CCR6. These cells migrate then from lamina propria into the intestinal epithelium. Functionally, these $CD8^+$ T cells inhibit antigen-specific $CD4^+$ T-cell activation in an IL-10-dependent manner and prevent $CD4^+$ T-cell-mediated inflammation in the small intestine (Chang et al. 2013).

Another study describes that, similar to the induction of Th9 cells, the presence of IL-4 plus transforming growth factor (TGF)-β causes IL-9 production in $CD8^+$ T cells in vitro. These cells express less Tc1-associated transcription factors T-bet and Eomes as well as the cytotoxic molecule granzyme B, and therefore phenotypically resemble cells induced by $CX3CR1^+$ dendritic cells. In agreement with low expression of granzyme B, Tc9 cells display diminished cytotoxic activity in vitro. The molecular requirements for the differentiation of Th9 and Tc9 cells are similar, in both cell types the transcription factors STAT6 and IRF4 are important for IL-9 production and the regulatory T cell-specific transcription factor Foxp3 inhibits IL-9 induction. Functionally, in an allergic airway disease mouse model, Tc9 cells promoted the onset of airway inflammation, mediated by sub-pathogenic numbers of Th2 cells. Adoptively transferred Tc9 cells lost their capability to produce IL-9 in favor of IL-13. However, they retained reduced IFN-γ production revealing that their phenotype differed from Tc1 cells. Furthermore, increased frequencies of Tc9 cells were detected in the periphery of mice and humans with atopic dermatitis, a Th2-associated skin disease that often precedes asthma, suggesting that Tc9 cells contribute to propagation of Th2-mediated allergic inflammation (Visekruna et al. 2013).

Finally, low cytotoxic, IL-9-producing Tc9 cells have been shown to display greater anti-tumor activity against B16 melanoma as compared to Tc1 cells. This strong anti-

tumor activity was dependent on the marker cytokine of Tc9 cells, IL-9, but not on IFN-γ. In this setting, adoptively transferred Tc9 cells converted after 3 weeks to IFN-γ and IL-2 producers and displayed a phenotype similar to Tc1 memory cells characterized by KLRG1^{lo} and IL-7Rα expression (Lu et al. 2014). Thus, it is conceivable that dependent on the inflammatory conditions, Tc9 cells suppress Th1-mediated responses in lamina propria, enhance Th2-associated immunity in allergy and finely, like Th9 cells, provide strong IL-9-dependent anti-tumor response.

Tc17 Cells

Similar to Th17 cells, the cytokines IL-6 or IL-21 along with TGF-β determine the differentiation of IL-17-producing CD8$^+$ T (Tc17) cells. In addition, IL-23 stabilizes their phenotype. Tc17 cells produce the cytokines IL-17 and IL-21, express the receptor for IL-23 and the lineage-specific transcription factors RORγt and RORα (Hamada et al. 2009; Huber et al. 2009; Yen et al. 2009). The transcription factor IRF4 is also important for Tc17 differentiation. IRF4 coordinates Tc17 differentiation as positive regulator of RORγt and RORα expression as well as a suppressor of transcription factors contributing to Tc1 and Treg development, Eomes and Foxp3, respectively (Huber et al. 2013). In comparison to Tc1 cells, Tc17 cells express the transcription factors T-bet and Eomes at diminished levels and probably therefore their properties differ from those of Tc1 cells. Tc17 cells produce fewer proteins characteristic for Tc1 cells such as IFN-γ, granzyme B and perforin. Consequently, Tc17 cells exert impaired cytotoxic function (Hamada et al. 2009; Huber et al. 2009; Yen et al. 2009).

CD8$^+$ T cells lacking both, T-bet and Eomes, fail to differentiate into functional Tc1 cells. Upon LCMV infection, T-bet and Eomes-deficient CD8$^+$ T cells develop a phenotype similar to Tc17 cells with low cytotoxic activity causing progressive inflammation and wasting syndrome characterized by multi-organ infiltration by neutrophils (Intlekofer et al. 2008). However, these T-bet and Eomes double-deficient cells differ from genuine Tc17 cells, since several studies show a protective function of Tc17 cells in viral infection in mice and humans. In two different mouse models Tc17 cells are protective (1) against lethal influenza infection and provoke a strong neutrophil influx into the lungs (Hamada et al. 2009) and (2) against vaccinia virus using cytotoxic mechanisms partially dependent on FasL-expression (Yeh et al. 2010). Finally, increased Tc17 frequencies correlate with control of disease progression in human hepatitis C virus infection, suggesting a beneficial role for these cells (Billerbeck et al. 2010).

Tc17 cells are detectable in human hepatocellular carcinomas, and tumor-associated monocytes produce cytokines which induce proliferation of these cells. In this setting, Tc17 cells seem to promote tumor progression (Kuang et al. 2010). In contrast, in a mouse melanoma model, Tc17 cells enhance anti-tumor immunity, suggesting different functions of Tc17 cells depending on the tumor microenvironment (Hinrichs et al. 2009).

Pro-inflammatory properties of Tc17 cells have been further demonstrated during transplantation and autoimmunity. In T-bet-deficient mice, they cause allograft rejection (Burrell et al. 2008) and experimental autoimmune myocarditis (Rangachari et al. 2006). They can provoke autoimmune colitis after transfer into RAG1-deficient mice (Tajima et al. 2008) and are detected in skin lesions of patients with psoriasis (Kryczek et al. 2008) as well as in children with recent onset of type 1 diabetes (T1D) (Marwaha et al. 2010). Dependent on the mouse model, Tc17 cells are cytotoxic and diabetogenic (Ciric et al. 2009), or they display low cytotoxicity and are non-pathogenic, but they potentiate Th1-mediated diseases (Saxena et al. 2012).

In a mouse model for autoimmunity of the central nervous system (CNS), Tc17 cells alone are also not pathogenic, but promote Th17-mediated experimental autoimmune encephalomyelitis (EAE) (Huber et al. 2013). The "reverse help" of Tc17 cells towards enhanced pathogenicity of Th17 cells requires IL-17 expression by Tc17 cells. Tc17 cells induce development of a type 17 transcriptional program and IL-17 production by CD4$^+$ T cells via direct cell–cell contact. Probably, surface IL-17 expressed by Tc17 cells contributes to the IL-17-induction in CD4$^+$ T cells. Accordingly, patients with early-stage multiple sclerosis (MS) have a selective enrichment of Tc17 cells in the cerebrospinal fluid (CSF) and harbor significantly higher percentages of Tc17 cells in CSF as compared to the control group. These results reveal that Tc17 cells contribute to CNS autoimmunity in mice and humans by supporting Th17-cell pathogenicity (Huber et al. 2013).

Autoreactive, polyclonal Tc17 cells are also crucial for the onset of systemic autoimmunity including dermatitis, nephritis and increased antibody titer in transgenic mice overexpressing CD40L in basal keratinocytes. Myeloid-related proteins (Mrp)8 and Mrp14, which belong to damage-associated molecular pattern molecules, are strongly upregulated in diseased mice, and these proteins via Toll-like receptor 4 and in combination with CD40-CD40L signaling promote IL-17 production in CD8$^+$ T cells. Likewise, in human cutaneous lupus erythematosus, the Mrp8 and Mrp14 proteins are upregulated and strongly induce IL-17 production in CD8$^+$ T cells from patients, thus linking the expression of Mrp8 and Mrp14 proteins to

the induction of pathogenic Tc17 cells and to the development of systemic autoimmunity in mice and humans (Loser et al. 2010).

Taken together, there is strong evidence for a pathogenic function of Tc17 cells in autoimmune diseases. They are detectable in these disorders and their presence strongly correlates with the disease progression. Moreover, in mouse models they accelerate autoimmunity by promoting the $CD4^+$ T-cell responses as demonstrated for autoimmune encephalomyelitis and diabetes. For anti-viral and anti-tumor responses, the function of Tc17 cells is unclear and results are in part contradictory. Depending on the virus or the type of tumor, Tc17 cells can either promote clearance of infection or tumor, or they fail to control viral eradication and even promote tumor growth.

Mucosal associated invariant T (MAIT) cells have also been described as IL-17 secreting $CD8^+$ T cells in humans (Dusseaux et al. 2011). MAIT cells can be found in the liver and mucosal tissue, and are involved in protection against microbial infection. However, MAIT cells differ substantially from Tc17 cells. MAIT cells express only intermediary levels of the CD8αβ heterodimer or are even CD8-negative. These cells use an invariant TCRα chain (Vα19 in mice and Vα7.2 in humans, combined with the Jα33 element) associated with a limited number of Vβ elements and are restricted by the MHC class Ib molecule MR1. MAIT cells can be activated by vitamin B2 metabolites presented in the context of MR1 and produce not only IL-17, but also other cytokines such as IFN-γ and TNF-α. Thus, MAIT cells represent an unconventional T cell subset that share many features with other innate T cells such as NKT cells or γδT cells (Le Bourhis et al. 2013; Walker et al. 2012).

$CD8^+$ Treg Cells

$CD8^+$ suppressor T cell-mediated regulation of $CD4^+$ T cell responses was originally described in the early 1970s by Gershon and Kondo (1970). The suppressor $CD8^+$ T cells are now termed $CD8^+$ Tregs and have been associated with disease protection and recovery from EAE in mice. In humans, dysfunction of $CD8^+$ Tregs has been implicated in the development of autoimmune diseases including inflammatory bowel disease, MS and T1D (Jiang et al. 2010; Smith and Kumar 2008).

$CD8^+$ Treg cells restricted by the non-classical MHC class Ib molecules Qa-1 (mouse) or HLA-E (human) represent a relatively well-defined $CD8^+$ Treg-cell subset. They specifically recognize peptides in complex with Qa-1 expressed by activated $CD4^+$ T cells and then eliminate these cells in a perforin-dependent manner. Two interactions with Qa-1 control their activity: (1) triggering of CD94/NKG2A by Qa-1 in association with Qdm peptides, which are derived from the signal sequence of MHC class Ia molecules, inhibits their activity, while (2) engagement of the TCR by Qa-1 loaded with other peptides leads to activation and proliferation of these cells. Consequently, specific genetic disruption of the Qa-1-dependent $CD8^+$ Treg activation pathway with preserved CD94/NKG2A-mediated inhibition causes severe autoimmune disease in mice characterized by unrestricted activity of $CD4^+$ T cells expressing high levels of Qa-1. In this system, Qa-1-restricted $CD8^+$ Tregs have been shown to prevent autoimmunity including lupus-like syndrome, EAE and arthritis by eliminating follicular T helper (Tfh) cells and/or Th17 cells (Hu et al. 2004; Kim et al. 2010; Leavenworth et al. 2013). Qa-1-restricted $CD8^+$ Treg cells arise late during immune responses and become functional after antigen re-encounter, suggesting that the acquisition of suppressor activity resembles that of development of cytotoxic activity by Tc1 cells. Qa-1 restricted $CD8^+$ Treg cells show a $CD44^{hi}$ $CD122^+$ $Ly49^+$ phenotype and IL-15 is important for the formation and activity of these cells (Kim et al. 2010, 2011). They represent 3–5 % of all $CD8^+$ T cells (Kim and Cantor 2011).

There is also evidence for other $CD8^+$ Treg-cell subpopulations, including MHC class Ia restricted $CD8^+$ Tregs, which suppress IFN-γ production by T cells via IL-10 in a non-cytolytic manner (Endharti et al. 2005). These cells can suppress vaccine-induced anti-tumor responses (Wang et al. 2010).

In an autoimmune diabetes model, memory-like, autoregulatory $CD8^+$ Treg cells can be identified, which arise from non-pathogenic precursors which recognize autoantigens with low avidity. These cells inhibit diabetes onset and can even revert the established disease by down-regulation of autoreactive T-cell responses via suppression of antigen presentation. For suppression, these $CD8^+$ Treg cells rely on diverse mechanisms including perforin, indoleamine 2,3-dioxygenase (IDO) and IFN-γ (Tsai et al. 2010).

Finally, after allogeneic bone marrow transplantation the expansion of a population of highly suppressive $CD8^+$ $Foxp3^+$ Treg cells with preferential tropism for the gastrointestinal tract can be detected. These cells prevent graft versus host disease (GvHD) by inhibition of MHC class I-restricted T-cell responses and the suppressive T-cell population can be expanded by co-administration of rapamycin and IL-2/anti-IL-2 antibody complexes (Robb et al. 2012). Thus, similar to $CD4^+$ Treg cells, there is heterogeneity in $CD8^+$ Treg subpopulations and their mechanisms of suppression.

Memory Formation by Alternative CD8$^+$ T Cells

In contrast to Tc1 cells, there is only limited information on memory formation of alternative CD8$^+$ T-cell subsets. Tc2 cells with a memory phenotype are found in the synovial fluids of patients with rheumatoid arthritis (Cho et al. 2012) and human Tc17 cells predominantly belong to memory subsets (Kondo et al. 2009), suggesting that at least in humans both subpopulations are able to establish memory cells. In a mouse tumor model, transferred Tc9 cells acquired a Tc1 memory phenotype, indicating that memory formation was associated with the transition into Tc1 cells (Lu et al. 2014). Whether such transition can be generalized to IL-9-producing IELs or Tc9 cells involved in allergy is currently unknown.

For CD8$^+$ Treg cells, subpopulations with a memory phenotype have been described. Memory-like autoregulatory CD8$^+$ T cells that suppress diabetes are detected after treatment of mice with nanoparticles coated with disease-relevant peptide–MHC complexes (Tsai et al. 2010), and CD8$^+$CD122$^+$ Treg cells with a memory phenotype are observed in humans and mice (Kim and Cantor 2011). In fact, several reports describe alternative CD8$^+$ T cells with a memory phenotype, but more work is necessary to elucidate the requirements and mechanisms involved in memory formation of these cells.

Plasticity of CD8$^+$ T-Cell Subsets

Similar to CD4$^+$ Th cells, CD8$^+$ Tc cells also show some lineage plasticity. CD8$^+$ T-cell subsets distinctly form Tc1 cells, can acquire the capability to produce IFN-γ in vivo. Expression of IFN-γ is not necessarily connected with the loss of the original cytokines; thus, Tc2 cells producing IFN-γ and IL-13 or Tc17 cells positive for IFN-γ and IL-17 can be detected. In a diabetes model, Tc2 cells continue to produce IL-4 and IL-10 after transfer but additionally acquire IFN-γ production, although at lower level as compared to Tc1 cells (Vizler et al. 2000).

Likewise, Tc17 cells maintain IL-17 production but start to produce IFN-γ in EAE (Huber et al. 2013), in a diabetes model (Saxena et al. 2012), in tumor models (Hinrichs et al. 2009; Yu et al. 2013), during GvHD of mice (Beres et al. 2012) and upon viral infection of mice (Yen et al. 2009). The cytokine IL-12 has been shown to promote the switch of Tc17 toward Tc1 via epigenetic suppression of Socs3, which on the one hand promotes Tc17 generation (Satoh et al. 2012; Yu et al. 2013) and on the other dampens Tc1 effector development (Cui et al. 2011). Interestingly, in allergic airway disease IFN-γ-deficient CD8$^+$ T cells develop a Tc17/Tc2 hybrid phenotype, revealing the suppressive function for IFN-γ for Tc2 and Tc17 development, and the potential of CD8$^+$ T cells to produce IL-17 and IL-13 simultaneously (Tang et al. 2012). Moreover, Foxp3$^+$ CD8$^+$ Treg cells have been shown to produce IL-17 (Robb et al. 2012).

In contrast to Tc2 and Tc17 cells, Tc9 cells fail to maintain their marker cytokine IL-9 in two disease models. In a model of allergic airway disease, Tc9 cells acquire a Tc1/Tc2 hybrid phenotype characterized by simultaneous IL-13 and IFN-γ production (Visekruna et al. 2013), and in a melanoma model, Tc9 with IL-9 dependent anti-tumor reactivity transform to IFN-γ and IL-2 producing Tc1 cells with a memory cell phenotype (Lu et al. 2014).

Finally, fully differentiated Tc1 cells can acquire the ability to produce IL-10 in a Blimp-1-dependent manner to limit local inflammation in response to viral infections (Zhang and Bevan 2011). However, these IL-10-producing Tc1 cells represent a transient state of effector Tc1 cells, because after transfer into infected hosts both IL-10$^+$ and IL-10$^-$ cells develop into populations with similar fractions of IL-10 producers (Sun et al. 2009, 2011; Trandem et al. 2011). On the other hand, Qa-1-restricted CD8$^+$ Treg cells resemble Tc1 cells in the production of IFN-γ and strong cytotoxicity (Kim and Cantor 2011).

In summary, Tc1 and CD8$^+$ Treg cells seem to possess relatively stable fates while Tc2, Tc9 and Tc17 cells tend to acquire qualities of other subpopulations. Tc2 and Tc17 cells maintain their cytokine profile, but acquire additionally characteristics of Tc1 cells. Tc9 cells appear to be relatively unstable in vivo with plasticity toward the Tc1 or

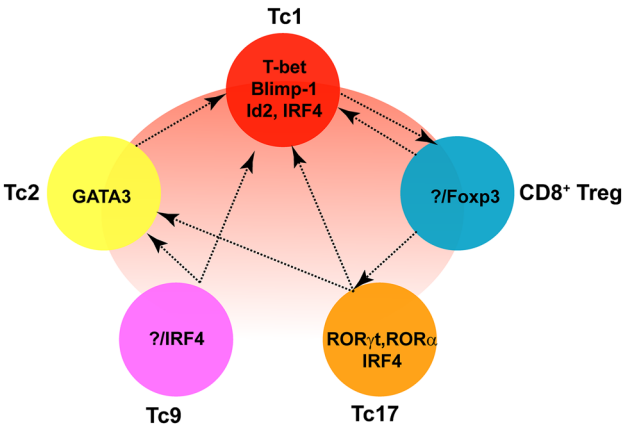

Fig. 2 Plasticity of CD8$^+$ T-cell subsets. CD8$^+$ T cells acquire different phenotypes described as Tc1, Tc2, Tc9, Tc17 and CD8$^+$ Treg. These subpopulations express specific transcription factors shown *inside the cells*. So far not identified master regulators are indicated with *question marks*. The *arrows* depict the capacity of cells to acquire qualities of the other Tc subsets. The *color intensity inside the oval* denotes the strength of cytotoxic activity displayed by the CD8$^+$ T-cell subpopulations. For details see the section "Plasticity of CD8$^+$ T-Cell Subsets"

Tc1/Tc2 fates. Figure 2 summarizes the level of plasticity for different $CD8^+$ T cell subsets.

Concluding Remarks

In addition to the well-characterized subpopulation of $CD8^+$ T cells, the IFN-γ and TNF-α producing and highly cytotoxic Tc1 cells, there is strong evidence for "alternative" $CD8^+$ T-cell subpopulations. $CD8^+$ T cells which produce IL-4, IL-9 and IL-17 as well as $CD8^+$ T cells with suppressive properties are detectable in mice and humans during physiological and pathological immune responses. These alternative $CD8^+$ T cells, although displaying considerable plasticity, differ in their function substantially from Tc1 cells, and many of them strongly influence $CD4^+$ T-cell-mediated immunity. For example, the Qa-1-restricted $CD8^+$ Tregs constrain Tfh- and Th17-mediated responses as demonstrated in lupus-like syndrome, EAE and arthritis, and Tc9 cells display inhibitory activity towards $CD4^+$ T-cell-mediated colitis. On the other hand, alternative $CD8^+$ T cells can also support $CD4^+$ T-cell-mediated responses. This has been demonstrated in the context of allergy for Tc2 and Tc9 cells, which promote Th2-mediated pathology in this disease. Similarly, Tc17 cells accelerated Th17-mediated autoimmune encephalomyelitis and promote Th1-mediated autoimmune diabetes. In summary, these results strongly suggest a "reciprocal cross-talk" during immune response between subpopulations of $CD4^+$ and $CD8^+$ T cells, in which not only $CD4^+$ T cells provide help for $CD8^+$ T-cell responses, but also in turn, $CD8^+$ T cells strongly influence $CD4^+$ T-cell responses.

Several transcription factors regulate the generation of $CD8^+$ T-cell subsets. For Tc1 differentiation, the expression of BCL-6, Blimp-1, Eomes, Id2, Id3, TCF-7, Foxo1 and T-bet is decisive for the effector versus memory fate. Additionally, IRF4 has been recently shown to be crucial for effector and memory Tc1 differentiation. IRF4 controls the transcription factors important for effector differentiation and influences the metabolisms of cells. Similar to its function in $CD4^+$ T cells, IRF4 is essential for the differentiation of $CD8^+$ T cells to Tc9 and Tc17 cells. IRF4 coordinates Tc17 maturation by up-regulation of the type 17-specific transcription factors RORγt and RORα and suppression of the Tc1-specific factor Eomes and Treg-specific factor Foxp3. In Tc9 cells, IRF4 directly influences IL-9 production by binding to the *Il9* promoter (own unpublished results) and indirectly by inhibition of Foxp3 expression. Like for Th9 cells, Tc9-specific transcription factors have so far not been identified. Only a minority of $CD8^+$ Treg cells express the lineage-specific factor Foxp3. Future studies characterizing the functions and the mechanisms controlling the differentiation, plasticity and memory formation of alternative $CD8^+$ T cells as well as their interactions with other cells could pave the way for new therapeutic options in the modulation of immune responses.

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