INTRODUCTION

Bone marrow (BM)-derived T cell precursors seed the thymus, where they differentiate into mature T cells. During this process, those T cells bearing appropriate α/β T cell receptors (TCR) are positively selected in order to ensure MHC restriction. In addition, those harmful T cells recognizing MHC/self-peptide complexes (referred to as self-MHC hereafter) with high affinity are mostly purged from the repertoire by negative selection. This process of T cell selection in the thymus warrants that peripheral T cells are MHC restricted, so they are able to recognize infected cells, but react only weakly to self-MHC and thus autoimmunity is minimized (Klein et al., 2009).

Once naive T cells exit the thymus, they recirculate between secondary lymphoid organs via blood or lymph. Upon encountering cognate antigen presented by MHC on dendritic cells (DCs), T cells are primed and differentiated into potent effector cells with the ability to localize the immune response to foreign antigen. This ability is due to their unique secondary lymphoid organ distribution, where they differentiate into mature T cells. During this process, memory T cells can be differentiated into naive T cells and the few DCs presenting the respective cognate antigen; (2) self-MHC recognition on DCs prior to an encounter with foreign antigen; (3) tonic signaling that augments the antigen sensitivity of T cells (Hirota et al., 2010). The latter is commonly accepted that the capacity of DCs to provide signals 1, 2, and 3 simultaneously makes them particularly suited to promote priming of naive T cells. In addition, DCs located in the T cell areas of lymphoid organs, or easily migrate into them upon activation, forming an extensive network of dendrites thus providing a topographical context in which DCs and T cells interact (Lindequist et al., 2004). This may be an important differential feature of DCs, since other professional APCs such as B cells also express high levels of costimulatory molecules and produce a variety of T cell growth factors, but are not located in the T cell area under normal conditions.

During the steady state, T cells frequently contact DCs in secondary lymphoid organs. There are at least two important consequences of these frequent contacts: (1) they increase the likelihood for encounters between extremely low frequencies of antigen-specific naive T cells and the few DCs presenting the respective cognate antigen; (2) self-MHC recognition on DCs in the absence of cognate antigen induces a basal, tonic TCR signaling that augments the antigen sensitivity of T cells (Box 1). This review focuses on recent developments by which self-MHC recognition on DCs prior to an encounter with foreign antigen induces tonic TCR signaling thereby increases the awareness of T cells for subsequent encounters with their cognate antigen. Finally,
lymph node (LN) which has been shown to significantly impact T cell clonality, technical issues, as well as the depth of imaging in the 2005). These variations may likely be due to differences in the T

We discuss some key questions in this field that remain to be answered.

**BOX 1 | Summary of self-MHC recognition, tonic TCR signaling and antigen sensitivity.**

Antigen sensitivity is the capacity of T cells to respond to TCR stimulation via cognate MHC/antigen recognition to become activated and undergo proliferation. The higher the sensitivity, the lower the amount of MHC/antigen recognition required to trigger full T cell activation. T cells can undergo different states of antigen sensitivity depending on the cues they integrate from the environment. A key cue is the recognition of MHC/self-peptide complexes (referred to as self-MHC), which induces a basal level of TCR activation resulting in increased sensitivity toward cognate antigen (Ebert et al., 2003; Hochweller et al., 2010). This basal activation of the TCR complex is also referred to as tonic TCR signaling and is exemplified by low levels of CD3ζ phosphorylation. Thus, self-MHC recognition increases the awareness of T cells and licenses them to respond to lower amounts of cognate antigen. When does self-MHC recognition increase the antigen sensitivity of T cells? There are two stages during which self-MHC recognition increases the T cell antigen sensitivity: prior to and concomitant to recognition of foreign antigen.

Self-MHC recognition in the absence of cognate antigen. DCs and T cells continuously interact in secondary lymphoid organs. Self-MHC recognition by T cells results in tonic TCR signaling and increased T cell responsiveness toward a subsequent encounter with cognate antigen. The nature of the self-peptide(s) is presently unknown. Concomitant recognition of self- and foreign-antigen bound to MHC. The sole recognition of MHC/self-peptide complexes is inefficient to trigger naive T cell activation. Concomitant recognition of self-MHC complexes dramatically increases T cell responsiveness (Coppoird et al., 2008). The same self-MHC complexes that drive positive selection in the thymus have been shown to increase the antigen sensitivity during concomitant recognition of foreign antigen (Ebert et al., 2003; Lo et al., 2009).

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minimizing autoimmunity (Kurt et al., 1997; Probst et al., 2003), and (2) recognition of self-MHC on DCs induces a tonic TCR signaling that promotes the survival of T cells toward their cognate antigen (Stefanova et al., 2002; Hochweller et al., 2010). These two major functions of steady-state DCs seem at first contradictory. We have proposed that the affinity of TCR-self-MHC recognition dictates the final T cell outcome: high-affinity interactions lead to T cell deletion, whereas those of weaker affinity promote T cell antigen sensitivity (Garbi et al., 2010).

**DENDRITIC CELLS ARE REQUIRED TO MAINTAIN THE ANTIGEN SENSITIVITY OF NAIVE T CELLS**

By analyzing CD3ε expression as a surrogate marker of TCR triggering, it has recently been shown that most of the tonic TCR signaling of naive T cells occurs in the secondary lymphoid organs (Mandl et al., 2012). Most contacts between T cells and DCs in the LN take place for about 5 min. For CD4 T cells, these contacts are highly dependent on MHC-II expression by the DC, because absence of MHC-II results in shorter interactions of about 2 min (Mandl et al., 2012). Pioneering work in Germain’s laboratory showed that self-MHC recognition by T cells in the absence of cognate antigen resulted in basal activation of the TCR complex and increased antigen sensitivity of T cells toward subsequent encounters with their cognate antigen (Stefanova et al., 2002). The requirement of DCs for tonic TCR signaling and maintenance of the antigen sensitivity in T cells was described in transgenic CD11c.DOG mice, in which DCs express the human diphtheria toxin receptor (DTR) and thus can be depleted by single or repetitive administrations of diphtheria toxin (DT; Hochweller et al., 2008). In these mice, naive CD4 and CD8 T cells isolated after DT application show a marked hypoproliferative response against a variety of antigens presented by professional APCs, including cognate peptide, superantigen (Hochweller et al., 2010), and anti-TCRβ antibody (Figure 1A). These results indicate that DC–T cell interactions in the steady state in the absence of cognate antigen are required to maintain the sensitivity of naive T cells for their cognate antigen. Similar results have been obtained in other transgenic mouse strains such as CD11c.DTR (Hochweller et al., 2010), and the recently described CD11c.LuciDTR (Figure 1B) that expresses luciferase and DTR under the CD11c promoter (Tittel et al., 2012). The proliferative response to anti-CD3ε antibody is, however, not compromised in T cells from DC-depleted mice (Birnberg et al., 2008; Figure 1C). Although at present we cannot explain why T cells from DC-depleted mice are able to respond normally to anti-CD3ε stimulation, but not to activation with MHC/antigen or anti-TCRβ antibody, differences in the binding affinities or in the ability of anti-TCRβ and anti-CD3ε antibodies to cross-link different TCR complexes may contribute to explain this paradox.

Tuning of the T cell antigen sensitivity is a dynamic process that depends on fast interactions with DCs. Antigen sensitivity is lost very quickly after disruption of cell–cell contacts (within 15 min; Stefanova et al., 2002), and it is regained also very promptly, within 30 min of reintroduced DC–T cell contacts (Hochweller et al., 2010). The loss of antigen sensitivity is not associated to decreased viability of T cells following DC depletion. Both the frequency and the numbers of viable T cells is not altered in DC-depleted mice (Hochweller et al., 2010), which is consistent with findings that mice constitutively lacking DCs do not present reduced T cell counts (Birnberg et al., 2008; Ohnmacht et al., 2009).

Studies using DC depletion have demonstrated that DCs are required to maintain the sensitivity of T cells for subsequent challenges with their cognate antigen. Both splenic CD8+ and CD4+ DCs are equally suited for tuning the T cell's antigen sensitivity (Hochweller et al., 2010). B cells are also able to maintain T cell responsiveness in vitro, although due to anatomical restrictions in vivo, naive T cells will only seldomly interact with B cells at the

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**FIGURE 1** CD4 T cell proliferation in mice lacking DCs. 3 × 10^4 MACS-purified CD4 T cells from the indicated mouse strain were activated for 4 days with the specified concentration of plate-bound anti-TCR (clone H57-597) or anti-CD3ε (145.2C11) antibodies. Proliferation was quantified by incorporation of 3[H]-thymidine for the last 9 h of the experiment (B,C). Results are expressed as mean ± SEM (n = 3 mice). Shown is one representative of three experiments. Similar results were obtained with BL6 mice treated with DT or with the respective transgenic mice treated with PBS.
borders between the T and B cell zones. However, not all APCs can do it; macrophages are not able to promote T cell antigen sensitiv-
ity (Hochweller et al., 2010), and whether this is due to differences in the expression level of self-MHC or other molecules is still an open question. A central question was how many DCs are required to maintain the T cell sensitivity? Using mixed BM chimeras in which a graded percentage of DCs expressed DTR, we showed that depletion of only half of the DC compartment already resulted in partial loss of antigen sensitivity. The activation status of the remaining DCs was not altered regarding expression of MHC-I and -II, and costimulatory molecules (N. Garbi, unpublished data), suggesting that the level of DC activation does not play a key role in the maintenance of T cell antigen sensitivity. Thus, minor alterations in the size of the DC compartment seem to have an impact on the T cell responsiveness. This is particularly important in view of the rapid turnover of DCs in the lymphoid organs of mice. Depending on the methodology used, the half-life of CD11c+ DCs in the spleen has been estimated to be between about 2 days (Kamath et al., 2002) and 7 days (Liu et al., 2007), the whole splenic DC compartment is replaced about 130 or 45 times, respectively, during the lifespan of a laboratory mouse.

**DEPENDENCE ON SELF-MHC RECOGNITION AND COSTIMULATORY MOLECULES**

Semenal work by the group of Germain, demonstrated that recognition of self-MHC class II by CD4 T cells promoted the sensitivity of naive CD4 T cells against a subsequent challenge with cognate antigen (Stefanova et al., 2002, 2003). This work demonstrated that in the steady state, the TCR is actively integrating cues from self-MHC recognition leading to a basal activation of proximal TCR signaling events, specifically CD3ξ phosphorylation (Stefanova et al., 2002). A subsequent study showed that self-MHC-II recognition was required to promote CD4 T cell antigen sensitivity also in vivo (Fischer et al., 2007). DCs were later identified as the cells providing self-MHC recognition to CD4 and CD8 T cells resulting in increased T cell antigen sensitivity toward subsequent challenges (Garbi et al., 2010; Hochweller et al., 2010). Therefore, the requirement of DCs to maintain T cell antigen sen-
sitivity is molecularly based on recognition of self-MHC. Indeed, interaction of DCs and T cells resulted in a specific increase in the basal phosphorylation of ZAP70-associated CD3ζ interaction of DCs and T cells resulted in a specific increase in the expression level of ZAP70, which is known to modulate the TCR antigen sensitivity (Roy et al., 2010).

The loss in antigen sensitivity is not accompanied by changes in the expression of molecules known to modulate TCR signaling such as TCRβ, CD3δ, CD3ε, CD4, and CD8α (Hochweller et al., 2000), or in global gene expression (Hochweller and Garbi, unpublished data), suggesting specific defects in signaling events rather than in expression patterns. This is supported by the rapid loss of antigen sensitivity after disruption of DC-T cell contacts (~15 min; Hochweller et al., 2010) and rapid reconstitution upon contact reintroduction (~30 min; Stefanova et al., 2002). In addition, T cells from DC-depleted mice proliferate normally in response to TCR-independent stimuli such as CostA or PMA/ionomycin stimulation, indicating that they do not have a global defect in cell cycle entry.

The requirement for self-MHC recognition on DCs to promote T cell responsiveness toward a subsequent antigenic challenge is reminiscent of recent data showing that self-MHC-II recognition at the time of foreign antigen recognition also increases the response of CD4 T cells to their cognate antigens (Ebert et al., 2009; Lo et al., 2009) in what has been defined as the pseudodimer model (Krogsgaard et al., 2005, 2007). The nature of the MHC class I/peptide complex required to maintain CD8 T cell antigen sensitivity is less clear. Our results show that CD8 T cells require prior self-MHC recognition on DCs to maximally respond to a sub-
sequent antigenic challenge (Hochweller et al., 2010). In analogy to the pseudodimer model for CD4 T cell activation, simultaneous recognition of MHC class I molecules loaded with foreign stimulating peptide and with endogenous non-stimulating pep-
tides strongly increases the sensitivity to the former (Purbhoo et al., 2014; Gebecauser et al., 2005; Yachi et al., 2005, 2007; Ani-
kereva et al., 2006). However, as opposed to CD4 T cells, all tested MHC class I-binding peptides served as coagonists (Yachi et al., 2005, 2007), suggesting that it is the interaction between CD8 coreceptor and MHC class I/endogenous peptide what is required to amplify responses against cognate antigens and not the specific TCR-MHC/self peptide recognition observed for CD4 T cells (Gascoigne, 2008). This hypothesis is supported by the finding that the CD8 coreceptor, but not CD4 is required to increase sensitivity of T cells at high density of peptide ligands (Purbhoo et al., 2004). However, as for the maintenance of CD4 T cell antigen sensitivity, it remains unknown whether specific MHC class I/endogenous peptide complexes need to be recognized prior to foreign antigen challenge for maximal responses.

Altered peptide ligands (APLs) bound to MHC have been shown to partially activate the TCR complex (Evavold et al., 1993). However, the outcome of these partial TCR activation dramatically differs from the tonic TCR signaling induced by self-MHC recognition discussed in this review. APLs often result in (1) partial T cell activation leading to functional T cell anergy in response to subsequent encounter with cognate antigen, or (2) TCR antagonism when recognized simultaneously with cognate antigen (Sloan-Lancaster and Allen, 1996). Although some endogenous self-peptides have been shown to function as APL for a given TCR clone (Evavold et al., 1993), self-MHC ligands induc-
ting tonic signaling do not induce T cell activation (as defined by the “quiescent” state of naive T cells in vivo) but increase their sensitivity toward subsequent encounters with cognate antigens. Although presently unknown, the biochemical basis for the differ-
ence between self-ligands inducing T cell anergy (APLs) and those inducing productive tonic TCR signaling may reside in the affinity for the TCR.

Thus, self-MHC recognition tunes T cell responsiveness toward foreign antigen in two different contexts: first, exclusive self-MHC recognition in the absence of foreign antigen results in tonic TCR signaling and enhanced T cell responsiveness to a subsequent chal-
genue with cognate antigen, second, as defined in the pseudodimer
model, concomitant recognition of MHC molecules loaded with self- and foreign-peptides leads to increased sensitivity to the later.

Interestingly, it is the same ligands driving positive selection in the thymus that increase the CD4 T cell responsiveness toward cognate antigen when recognized simultaneously in the periphery (Elbert et al., 2009; Lu et al., 2009). We proposed that a similar mechanism is in place to promote responsiveness to subsequent antigenic challenge, i.e., it is the recognition in the periphery of the ligands inducing positive selection in the thymus that results in tonic TCR signaling and increased T cell antigen sensitivity (Garbi et al., 2010). Although this hypothesis is not formally proven yet, Stefanova et al. (2002) demonstrated that recognition of the same MHC class II restriction element that drives positive selection of AND TCR transgenic CD4 T cells is required to maintain their antigen responsiveness in the periphery. Whether this finding can be generalized to other TCR specificities is still an open issue, but strongly suggests that the selecting MHC class II haplotype is required and that the mere interaction between MHC-II and the CD4 co-receptor is not sufficient to maintain antigen sensitivity (Stefanova et al., 2002).

Presently, it is still unclear whether other molecular cues between DCs and T cells participate in promoting antigen sensitivity in addition to self-MHC recognition. MHC-deficient DCs are able to partially maintain T cell responsiveness, albeit to a much lower degree than their MHC-sufficient counterparts (Hochweller et al., 2010). DCs express large amounts of costimulatory molecules such as CD80 and CD86 in the steady state. Because activation of their receptor CD28 synergizes TCR engagement of cognate antigen to bolster T cell proliferation, it is tempting to speculate that CD28 ligation may also synergize with self-MHC recognition to promote tonic TCR signaling. In addition, other mechanisms may also be involved. In this context, non-MHC-dependent contact of T cells to DCs induces a transient semi-activation of the former resulting in enhanced T cell responses to subsequent cognate antigen in a process known as “adhesion-induced T cell priming” (Kевой et al., 2001). However, this phenomenon is not specific to interaction with DCs because adhesion to other cell types, immobilized ligands or even glass had a similar effect (Randiramamampita et al., 2003).

ARE DENDRITIC CELLS REQUIRED TO MAINTAIN THE ANTIGEN SENSITIVITY OF OTHER T CELL POPULATIONS: EFFECTOR, MEMORY, AND REGULATORY T CELLS?

Presently it is unknown whether effector or memory T cells in the steady state are dependent on DC-induced tonic TCR signaling to increase their sensitivity against a subsequent challenge with cognate antigen. During infection, memory CD8 T cells interact with DCs in lymphoid and non-lymphoid sites resulting in antigen-specific reactivation (Belte et al., 2007; Waki et al., 2008). However, further experiments are needed to determine whether effector/memory T cells also depend on constant self-MHC recognition on DCs in the absence of infection to increase their sensitivity against a subsequent antigen encounter.

In the different context of simultaneous recognition of self- and cognate-antigen, effector T cells seem to be less dependent on self-MHC recognition than their naive counterparts for antigen-specific responses (Yuchi et al., 2007). Based on those findings, we hypothesize that effector/memory T cells are also less dependent on recognition of self-MHC in the steady state to increase their sensitivity to further cognate antigenic challenge.

There is some correlative evidence that DCs regulate the size of the Treg compartment in a positive manner. In mice depleted for DCs or lacking DCs constitutively, a reduced frequency of Tregs by a factor of approximately 2–3 has been reported in the spleen, LNs, and/or blood (Darrasse-Jeze et al., 2009; Bar-On et al., 2011). However, in other reports, no differences or very small differences in the number of Tregs in the spleen and/or LNs were reported in mice constitutively lacking DCs (Birnberg et al., 2008; Ohnacht et al., 2009). In addition, DC depletion did not result in decreased suppressive function of splenic Treg cells (Birnberg et al., 2008). Following depletion of DCs for 2 days in CD11c.DOG, we did not observe any alteration in the number of Treg cells, suppressive capacity or phenotype in the spleen (Figure 2 and unpublished data). Our results and those by Birnberg et al. suggest that DCs are not required to maintain the suppressive capacity of Tregs. Therefore, further studies are required to investigate the apparently contradictory results on the role of DCs in the maintenance of Treg homeostasis.

DENDRITIC CELLS LICENSE T CELLS FOR IMMUNE SYNPASE FORMATION

Following TCR signaling in response to recognition of foreign antigen, T cell surface molecules and scaffolding protein are redistributed and enriched in the contact zone between T cells and APCs, resulting in the generation and maturation of the IS. The IS is characterized by a central enrichment of TCR and CD3 molecules termed central supramolecular activation cluster (cSMAC) that is surrounded by a further cluster formed by LFA-1, also called peripheral SMAC (Grakoui et al., 1999). Initial TCR triggering results in the so-called inside-out signaling leading to activation of LFA-1 (Kinashi, 2005). In turn, activated LFA-1 binds to ICAM-1 molecules on the APC promoting firm T cell-APC adhesion (Lee et al., 2011) and further TCR/CD3 signaling events (Davis and Dustin, 2004; Fooksman et al., 2010).

Naive CD4 T cells isolated from DC-depleted mice fail at developing a mature IS following recognition of their cognate antigen (Hochweller et al., 2010), indicating that the tonic TCR signaling resulting from self-MHC recognition is also required for licensing T cells for IS maturation. In other words, do hyperresponsive T cells fail to mount a mature synapse due to defective inside-out signaling resulting in impaired TCR signal transduction and proliferation?, or is the TCR signaling cascade itself defective and, consequently, there is lack of LFA-1 activation and IS formation? These questions remain to be elucidated yet.

MODEL OF LOCATION-DEPENDENT T CELL ANTIGEN SENSITIVITY

As discussed earlier, the antigen sensitivity of naive T cells is continuously fine-tuned depending on whether or not T cells...
interact with DCs. Self-MHC recognition on DCs results in a rapid increase in the sensitivity of the TCR for a subsequent antigenic challenge, whereas lack of self-MHC recognition leads to a rapid loss of sensitivity (Stefanova et al., 2002). Both of these processes take place within minutes following initiation or disruption of DC–T cell interaction, thus the loss of T cell responsiveness to cognate antigen caused by reduced interactions is quickly reverted after reintroduction of DC–T cell contacts. Naïve T cells continuously recirculate between lymphoid organs and the systemic circulation where they spend only about 30 min (Pabst, 1988). In the blood, where self-MHC recognition on DCs is very unlikely, CD4 T cells show reduced tonic TCR signaling and responsiveness to TCR stimulation (Stefanova et al., 2002). Consequently, it has been shown recently that most of the tonic TCR signaling in the steady state takes place within the secondary lymphoid organs (Mandl et al., 2012). It is therefore crucial that naïve T cells recover quickly their TCR responsiveness upon re-entering lymphoid organs and interacting with DCs to ensure optimal responses against foreign antigens. Indeed, the state of T cell hyporesponsiveness is completely reverted 30 min after reintroducing DC–T cell interaction (Hochweller et al., 2010).

Thus, T cells appear to go through several rounds of normal and hyporesponsive states toward cognate antigen depending on their location at a given time: they are fully responsive in the lymphoid organs, where they can be primed against invading antigens, whereas they remain hyporesponsive in the blood where priming is not supported mainly due to anatomical restrictions. Presently, it is difficult to understand the physiological relevance of intermittently loosing TCR antigen sensitivity each time that T cells enter the systemic circulation. It may serve as a transient “metabolic rest” facilitating T cells to increase their tonic TCR signaling and antigen sensitivity upon re-entering lymphoid organs, where they have to be fully aware of minute amounts of foreign antigen displayed by DCs at the initial stages of an infection.

In addition, self-MHC recognition during the steady state also affects other responses mediated by T cells. Recently, Hünig’s group has shown that the proliferative response of human T cells to the superagonist CD28 TGN1412 antibody is also dependent on tonic TCR signaling maintained by MHC scanning (Römer et al., 2011; Hunig, 2012). Similarly, it has been shown that naïve CD8 T cells require self-MHC recognition in order to become proliferative in response to IL-2 and IL-15 (Cho et al., 2010). Therefore, self-MHC recognition induces tonic TCR signaling that is required not only for increasing TCR sensitivity to cognate antigen, but also for optimizing responses against other TCR-independent stimuli.

INHIBITING DENDRITIC CELL APOPTOSIS LEADS TO AN INCREASE IN DENDRITIC CELL FREQUENCY AND T CELL HYPERACTIVATION

Self-MHC recognition on DCs results in enhanced T cell antigen sensitivity and optimal proliferation in response to cognate antigen. As discussed here, a decrease in DC numbers results in hyporesponsive T cells that fail to proliferate to a normal level. Just a twofold decrease in the numbers of DCs already results in partially reduced T cell proliferation (Hochweller et al., 2010). Interestingly, the opposite also seems to apply: an increase of about threefold in the frequency of DCs results in T cell hyperactivation and autoimmunity (Chen et al., 2006). Enforced expression of the baculoviral antiapoptotic p35 protein by DCs, resulted in DC accumulation and chronic T cell hyperactivation leading to multiorgan infiltration and production of autoantibodies (Chen et al., 2006). MHC-II and CD40 expression, hallmarks of DC activation, were unaltered in that study, suggesting that T cell hyperactivation was a result of increased DC frequency rather than activation due to increased half-life. Thus, DC homeostasis in the absence of foreign cognate T cell antigen is critical to ensure optimal T cell responses to subsequent challenges with cognate antigen.
whereas too few DCs result in reduced antigen sensitivity of T cells, a sustained increase in the number of DCs apparently leads to T cell hyperactivation and autoimmunity. These findings are summarized in Figure 3 and highlight the importance in maintaining the correct size of the DC pool to promote healthy T cell responses.

**CONCLUSIONS AND OPEN QUESTIONS**

There is mounting evidence that self-MHC recognition in the periphery is critical for several processes including: (i) maintenance of tonic TCR signaling and T cell antigen sensitivity, which are critical for optimal responses to subsequent challenge with cognate antigen; (ii) synergism at the time of cognate antigen recognition leading to increased T cell responses; (iii) increased TCR-independent T cell proliferative responses to various stimuli such as superagonist CD28 TGN1412, IL-2, and IL-15. The former two are mediated by self-MHC recognition on DCs, whereas the role of DCs in providing self-MHC for the TCR-independent responses is not clear yet.

Despite these advances several open questions are remaining. Amongst these, the following are central to understand the molecular mechanisms of DC-induced tonic TCR signaling:

1. Characterization of the signaling events induced by self-MHC recognition on DCs resulting in increased T cell antigen sensitivity. It is clear that self-MHC recognition induces tonic TCR signaling by partial CD3ζ phosphorylation. The finding that the maturation of the IS is compromised in DC-less T cells, opens the possibility that beyond tonic TCR signaling, integrin (such as LFA-1) activation is impaired following stimulation with cognate antigen, leading to deficient IS maturation and thus reduced T cell proliferative responses.

2. Are there other molecular events in DC–T cell interactions that contribute to maintenance of the T cell antigen sensitivity? Hypothetically, costimulatory molecules such as CD80 and CD86 may participate in the tonic T cell signaling by partially activating CD28 in the absence of cognate antigen. Costimulation plays a key role in enhancing the proliferative response to TCR stimulation. Whether this also applies to basal TCR signaling promoted by self-MHC recognition is unclear.

3. What is the nature of the self-MHC ligands required to induce tonic TCR signaling? We have previously proposed that these are the same ligands that induce positive selection in the thymus, but it needs to be demonstrated.

4. Do memory T cells require tonic TCR signaling for enhanced responses to antigenic rechallenge? Different subtypes of memory T cells reside in lymphoid and extra-lymphoid compartments. DCs have been shown to interact with memory T cells and to be required for maximal T cell

**FIGURE 3** | Model illustrating the role of dendritic cell frequency on promoting healthy T cell responses. Under normal DC homeostasis (A), naive T cells recognize self-MHC on DCs resulting in tonic TCR cell signaling and increased antigen sensitivity. As a result, subsequent foreign antigen challenge leads to optimal T cell activation and proliferation. However, upon conditions of reduced self-MHC recognition on DCs such as DC depletion (B), T cells undergo reduced tonic TCR signaling and decreased antigen sensitivity. These T cells become hyporesponsive and are not able to undergo strong proliferation in response to antigenic challenge. On the other hand, an increase in the number of DCs (C) apparently leads to increased self-recognition and T cell hyperactivation, possibly due to increased self-MHC recognition, and autoimmunity.
reconstituting following antigen rechallenge both in lymphoid organs and in extra-lymphoid organs (Zammit et al., 2005; Vaklin et al., 2005). However, it remains open whether or not memory T cells also require tonic T cell signaling for increased antigen sensitivity.

REFERENCES

Anikieeva, N., Lebedeva, T., Clapp, A. R., Goldman, E. R., Dustin, M. L., Matteucci, H., et al. (2000). Quantum dot/peptide-MHC biosensor reveals strong CD4+ T-cell-dependent cooperation between self and viral antigens that augment the T cell response. Proc. Natl. Acad. Sci. U.S.A. 97, 16444–16451.

Barrientos, M., Igen, J. G., Koo, I. Y., Langot, J. P., Bin, E., Ghosheh, H., et al. (2006). Stromal cell network regulates lymphocyte entry, migration, and territoriality in lymph nodes. Immunity 25, 798–809.

Baron, O., Bunberg, T., Kimm, K. W., Egen, J. G., Koo, L. Y., et al. (2005). CD8+ cytotoxic T lymphocyte activation by soluble major histocompatibility complex-peptide dimers. J. Biol. Chem. 280, 23920–23928.

Ceci, S., Garcia, Z., and Bouso, P. (2005). CD8 T cells integrate signals delivered during successive DC encounters in vivo. J. Exp. Med. 202, 1247–1256.

Chen, M., Wang, Y. H., Wang, Y., Huang, L., Sandelov, H., Liu, Y. L., et al. (2006). Dendritic cell apoptosis in the maintenance of immune tolerance. Science 311, 1140–1144.

Cho, J. H., Kim, H. O., Suth, C. D., and Sproul, J. (2010). Cell receptor-dependent regulation of lipid rafts controls naive CD8 T cell homeostasis. Immunity 32, 214–228.

Derrasse-Irou, G., Deroubaix, S., Mouquet, H., Vistora, G. D., Eisenmer, T., Tan, K. H., et al. (2009). Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. J. Exp. Med. 206, 1857–1862.

Davis, D. M., and Dustin, M. L. (2004). What is the importance of the immunological synapse? Trends Immunol. 25, 323–327.

Hoff, P. J., Jiang, S., Xie, J., Li, Q., and Davis, M. M. (2009). An endogenous positively selecting peptide enhances mature T cell responses and becomes an autoantigen in the absence of microRNA miR-181a. Nat. Immunol. 10, 1152–1159.

Drewal, R. D., Islam-Lancaster, J., and Alhun, P. M. (1993). Ticking the TCR-selective T-cell functions stimulated by alien peptide ligands. J. Immunol. 149, 469–469.

Drewal, R. D., Islam-Lancaster, J., Wilson, K., Idrisbiak, J. B., and Alhun, P. M. (1995). Specific T cell recognition thresholds in the endogenous peptides evidence for multiple endogenous ligands. Immunity 3, 655–665.

Fuziwara, H., Suzuki, Y., Kobayashi, E., Makabe, R. B., Cowley, B. D., and Salt, E., and Steinman, R. M., et al. (2007). MHC-class-II degradation impairs CD4 T cell mortality and responsiveness to antigen-bearing dendritic cells in vivo. Proc. Natl. Acad. Sci. U.S.A. 104, 7181–7186.

Fussman, D. R., Vanhull, S., Vaishnav-Shauns, G., Leese, J., Blatt, D. A., Wu, D. et al. (2010). Functional anatomy of T cell activation and synapse formation. Annu. Rev. Immunol. 28, 79–105.

Garbi, N., Hammerling, G. J., Probst, H. C., and Van Der Broek, M. (2010). Tonic T cell signaling and T cell tolerance as opposite effects of self-recognition on dendritic cells. Curr. Opin. Immunol. 22, 601–608.

Gascoigne, N. R. (2000). Do T cells need endogenous peptides for activation? Nat. Rev. Immunol. 8, 485–499.

Germann, B. N., Raynoff, M., Castellino, F., Choppa, M., Egen, J. G., Huang, A. Y., et al. (2008). Making friends in out-of-the-way places: how cells of the immune system get together and how they conduct their business as revealed by intravital imaging. J. Immunol. 182, 165–181.

Graafius, A., Brenner, S. K., Sumen, C., Davis, M. M., Shaw, A. S., Allen, P. M., et al. (1999). The immunological synapse: a molecular machine controlling T cell activation. Science 285, 223–227.

Harvey, J. T., and Budivic, V. P. (2008). Shaping and reshaping CD8 T-cell memory. Nat. Rev. Immunol. 8, 107–119.

Hawk, W. R., and Carbone, F. R. (2005). Dendritic cell subsets in primary and secondary T cell responses at body surfaces. Nat. Immunol. 6, 1237–1244.

Helmick, C. F., Hempel, T. R., Marx, I. B., Liu, S., Artyomov, M. N., Zheng, H., et al. (2008). T cell sensing antigen dose governs interactive behavior with dendritic cells and sets a threshold for T cell activation. Nat. Immunol. 9, 282–289.

Hodgkinson, K., Strijger, J., Hammerling, G. J., and Garbi, N. (2008). A novel CD11c-DTR transgenic mouse for depletion of dendritic cells reveals their requirement for homeostatic proliferation of natural killer cells. Eur. J. Immunol. 38, 2770–2783.

Hodgkinson, K., Wahrne, G. H., Summar, Y., Sulfier, J., Hammerling, G. J., and Garbi, N. (2010). Dendritic cells control T cell tonic signaling required for responsiveness to foreign antigen. Proc. Natl. Acad. Sci. U.S.A. 107, 9501–9506.

Hughes, S., Fefer, L., Brenner, L., Holz, J., Ambard, F., and Jimprona, S. (2004). Distinct T cell dynamics in lymph nodes during the induction of tolerance and immunity. Nat. Immunol. 5, 1255–1262.

Huang, T. (2012). The storm has cleared: DCs in maintenance of T cell antigen sensitivity. Proc. Natl. Acad. Sci. U.S.A. 109, 20105–20109.

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Developmental kinetics and lifespan of dendritic cells in mouse lymphoid organs. Blood 108, 1754–1764.

Kanumula, W., Gemen, M. Y., and German, R. N. (2010). The in situ dynamics of dendritic cell interactions. Eur. J. Immunol. 40, 2105–2108.

Kim, L., Hümmer, M., Wiersberger, C., Köpcke, B., and Saurwein, T. E. (2005). Intracellular signalling controlling integrin activation in lymphocytes. Nat. Rev. Immunol. 5, 354–364.

Kneipp, M., Jiang, L., and Davis, M. M. (2007). A role for “self” in T-cell activation. Science 319, 236–239.

Kneipp, M., Li, Q. J., Sumen, C., Huppe, J. B., Huang, L., and Davis, M. M. (2005). Agonist/agonist endogenous peptide-MHC heterodimers drive T cell activation and sensitivity. Nature 436, 238–243.

Kreutzberg, T., Kanumula, M., Khloka, I., and Brocker, T. (2001). Dendritic cells are sufficient to cross-present self-antigens to CD8+ T cells in vivo. J. Immunol. 166, 1439–1442.

Kurz, C., Knolle, H. B., Carbone, F. R., Miller, J. F., and Heath, W. R. (1997). Class I-restricted cross-presentation of endogenous self-antigens leads to
Mempel, T. R., Henrickson, S. E., and Miller, M. J., Hejazi, A. S., Wei, S., Mandl, J. N., Liou, R., Klauschen, L., Liu, K., Waskow, C., Liu, X., Yao, K., Lim, T. S., Mortellaro, A., Lim, C. T., Garbi and Kreutzberg  
Dendritic cells and tonic TCR signaling

Von Andrian, U. H. (2004). T-cell
activation enhancement by endogenuous pMHC acts for both weak and strong agonists but varies with differentation state. J. Exp. Med. 204, 2754–2757.

Wakim, L. M., Ampulski, J., Gascoigne, N. R., and Zal, T. (2005). Non-stimulatory peptides contribute to antigen-induced CD8+ T cell receptor interaction at the immunological synapse. Nat. Immunol. 6, 785–792.

Ya, P. P., Leto, C., Ampulski, J., and Gascoigne, N. R. (2007). T cell activation enhancement by endogenuous pMHC acts for both weak and strong agonists but varies with differentation state. J. Exp. Med. 204, 2754–2757.

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