T Cells and Regulated Cell Death: Kill or Be Killed

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Abstract

Cell death plays two major complementary roles in T cell biology: mediating the removal of cells that are targeted by T cells and the removal of T cells themselves. T cells serve as major actors in the adaptive immune response and function by selectively killing cells which are infected or dysfunctional. This feature is highly involved during homeostatic maintenance, and is relied upon and modulated in the context of cancer immunotherapy. The vital recognition and elimination of both autoreactive T cells and cells which are unable to recognize threats is a highly selective and regulated process.

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Moreover, detection of potential threats will result in the activation and expansion of T cells, which on resolution of the immune response will need to be eliminated. The culling of these T cells can be executed via a multitude of cell death pathways which are used in context-specific manners. Failure of these processes may result in an accumulation of misdirected or dysfunctional T cells, leading to complications such as autoimmunity or cancer. This review will focus on the role of cell death regulation in the maintenance of T cell homeostasis, as well as T cell-mediated elimination of infected or dysfunctional cells, and will summarize and discuss the current knowledge of the cellular mechanisms which are implicated in these processes.

1. INTRODUCTION

Cell death was long considered a passive, uncontrolled process leading to the demise of damaged cells. However, research performed during the last several decades has revealed a plethora of cell death modes, both passive and active, which are tightly regulated to maintain organismal health (Galluzzi et al., 2018). Importantly, these processes of regulated cell death are crucial for proper development and homeostasis and are also implicated in the development, progression, and treatment of many different diseases, including those related to the immune system (Anaya et al., 2013; Ardoin and Pisetsky, 2008; Fuchs and Steller, 2011). The broad array of cell death modes has evolved out of a necessity to precisely control cell number and homeostasis with a variety of mechanisms that can achieve certain results while preventing others. For example, pyroptosis is primarily utilized for cell execution when activation of an immune response is needed, whereas apoptosis is largely immunogenically silent (Galluzzi et al., 2017; Martin et al., 2012).

T cells are an integral part of the adaptive immune system and constitute the largest proportion (45%–70%) of the peripheral blood mononuclear cells (PBMCs) (Verhoeckx et al., 2015). They have a central role in cell-mediated immunity, and the cytotoxic capacity of T cells is instrumental in eliminating pathogens. However, for T cell-mediated immunity to function properly, it needs to be controlled by complex and highly precise mechanisms, both positively and negatively (Janeway et al., 2001). For humans to mount an immune response, it is necessary to maintain a large circulating population of T cells that are able to properly recognize and rapidly respond to threats (Bluestone et al., 2010). These threats can be exogenous pathogens such as viruses and bacteria or endogenous threats such as cancerous cells (Janeway et al., 2001). However, if autoreactive

T cells are not properly culled, autoimmune disorders can develop, in which T cells attack self-tissues (Grossman and Paul, 2015). This balance is achieved by elimination of autoreactive T cells, mainly in the thymus, although a small population of autoreactive T cells may circulate in the periphery (Arakaki et al., 2014; Green et al., 2003; Hogquist et al., 2005).

On the other hand, on detection of foreign antigen, expansion of oligoclonal antigen-specific T cells is crucial for the establishment of adaptive immune responses against pathogenic challenges (Grossman and Paul, 2015; Wange and Samelson, 1996). However, following resolution of the immune response and elimination of the response-driving antigen, the expanded T cells are no longer needed. Most of these cells are eliminated via apoptosis, whereas a small number is conserved to become memory T cells (Li et al., 2017b). This culling of the expanded T cell population serves to prevent unnecessary energy expenditure but also further helps balance self-reactivity and autoimmunity (Kurtulus et al., 2010).

This review aims to summarize the present state of knowledge concerning both of these aspects of cell death regulation in the context of T cells. Namely, (1) which mechanisms of regulated cell death are implicated in the death of unwanted or faulty T cells to maintain homeostasis and (2) by what means do cytotoxic T cells kill other cells which are, e.g., infected or cancerous.

2. CELL DEATH PATHWAYS IN T CELLS

The removal of undesired or faulty cells by regulated cell death is a fundamental physiological process which is vital for development, immunity, and tissue homeostasis. Furthermore, disruption of the programmed cell death pathways can lead to abnormally high or low rates of cell death and is associated with many of the diseases that constitute the top causes of death worldwide, including cardiovascular, neurodegenerative, pulmonary, renal, and hepatic diseases, as well as cancer (Goilav, 2011; Johnstone et al., 2002; Lozano et al., 2012; Lu et al., 2014; Okouchi et al., 2007; Spetz et al., 2018; Su et al., 1997; Wang, 2014; Whelan et al., 2010). Several different modes of programmed cell death have been described in the literature in numerous biological contexts, and the study of these pathways has been instrumental in explaining the diverse biological processes involved in cell loss (Galluzzi et al., 2018). This section describes the pathways of regulated cell death which have been shown to play a role in the death of autoreactive T cells as well as elimination of activated T cells after resolution of an immune response.

2.1 Apoptosis

Apoptosis is the most studied programmed cell death mechanism and also the primary method of cell death involved in development and homeostasis (Fuchs and Steller, 2011; Galluzzi et al., 2018). Most of the culling of T cells, both concerning autoreactive T cells and activated T cells, which have played out their role, is performed via apoptotic cell death (Clayton et al., 1997; Murphy et al., 1990; Strasser et al., 1991). Apoptosis is tightly involved in the development and selection (both positive and negative) of T cells in the thymus (c.f. Fig. 1), as well as in the periphery. Defects in apoptotic regulation in T cells are known to either lead to or play a major role in diseases such as lymphoma (Johnstone et al., 2002; Straus et al., 2001) and autoimmune diseases such as systemic lupus erythematosus (Mak and Kow, 2014; Prokunina et al., 2002), rheumatoid arthritis (Hashiramoto et al., 2018; Salmon et al., 1997), and Crohn's disease (Yamazaki et al., 2005). The apoptotic process is mediated via two distinct pathways: the intrinsic (mitochondria-mediated) pathway and the extrinsic (death receptor (DR)-mediated) pathway, both of which are discussed in detail below. These can function independently, but there are also several molecules involved in both pathways through which cross talk can occur. A common characteristic for both pathways, however, is that they eventually result in activation of cysteine—aspartic proteases (caspases) which initiate and execute degradation of cellular components, to induce the morphological changes for apoptosis and prepare the cell for clearance with minimal stress to surrounding tissues (Los et al., 1995; Miura et al., 1993; Ramage et al., 1995; Sabbatini et al., 1997).

2.1.1 The Intrinsic Apoptotic Pathway

The intrinsic apoptotic pathway is regulated by the BCL-2 family of proteins, which contains both pro-survival and pro-apoptotic members that share conserved sequences called BCL-2 homology (BH) domains and maintain the balance between cell survival and death (Danial and Korsmeyer, 2004). The discovery of BCL-2 and its function in B-cell lymphoma led to the identification of a wide range of proteins within the same family, which can be classified as pro-survival, pro-apoptotic "activator" BH3-only or pro-apoptotic pore-forming effector proteins (Tsujimoto et al., 1985; Vaux et al., 1988). These proteins form an intricate signaling network of functional interactions, regulating the integrity of the mitochondrial outer membrane and its potential. Apoptosis is triggered when a pro-apoptotic pore-forming effector protein (BAX or BAK) is

activated by an activator BH3-only protein (Tait and Green, 2013). Intrinsic apoptotic pathway can be triggered by a diverse array of stimuli, such as upstream stress signals (from, e.g., chemotherapy, radiotherapy, or environmental stressors), growth factor or nutrient deprivation, or developmental cues to initiate apoptosis and conserve homeostasis or remove damaged cells. To date, eight different BH3-only proteins have been discovered and widely validated as pro-apoptotic in mammals (BIM, BID, BAD, BIK, BMF, HRK, NOXA, and PUMA) of which BIM and BID are most potent (Czabotar et al., 2013; Kim et al., 2006; Leshchiner et al., 2013; Letai et al., 2002; Wei et al., 2000). These eight proteins are characterized by a single, 9–13 amino acid BH domain called BH3, which is required for binding to pro-survival and/or pro-apoptotic pore-forming effector proteins (Glab et al., 2017). This binding is highly selective, and different BH3-only proteins have different binding affinity for different pro-survival and/or pro-apoptotic pore-forming effector BCL-2 family proteins (Czabotar et al., 2014). For instance, BIM preferentially activates BAX while BID preferentially activates BAK (Sarosiek et al., 2013; Lopez et al., 2016). The activation of the pro-apoptotic pore-forming effector proteins BAX and/or BAK results in their oligomerization, which causes formation of macropores in the mitochondrial outer membrane, leading to release of apoptogenic molecules including cytochrome *c* and SMAC (second mitochondria–derived activator of caspases) into the cytosol (Doerflinger et al., 2015; Lakhani et al., 2006). SMAC functions to inhibit XIAP (X-linked inhibitor of apoptosis protein), which is an inhibitor of the effector caspases (caspases 3 and 7) (Liu et al., 2000; Wu et al., 2000). Cytochrome *c*, together with dATP, binds to APAF1, forming an oligomeric apoptosome which binds and cleaves procaspase 9 into its mature form. This activates downstream caspases (e.g., caspase 3 and caspase 7) that dismantle the cell and promote phagocytosis (Galluzzi et al., 2009; Taylor et al., 2008). However, the pro-survival proteins in this family (e.g., BCL-2, BCL-XL, MCL-1), which contain all BH domains (BH1-4), can block apoptosis by binding and sequestering monomeric BAX/BAK or BH3-only proteins (Czabotar et al., 2014). For apoptosis to occur, pro-survival proteins within the cell must be overwhelmed and BAX and/or BAK activated.

Proteins of the BCL-2 family are expressed to various different extents in mammals and also differ in activation state, depending on tissue type, cell lineage, developmental stage, and age (Sarosiek et al., 2017; Wong and Puthalakath, 2008; Annis et al., 2016; Nakamura et al., 2016;

Soane et al., 2008; Soane and Fiskum, 2005; Robertson et al., 2009; Toman and Fiskum, 2011). Depending on the basal state of the molecules in the intrinsic apoptotic pathway, a cell can respond differently to exogenous pro-death signals (Sarosiek and Letai, 2016). Recently, a functional assay called BH3 profiling was developed, which measures apoptotic priming (proximity of cellular mitochondria to the apoptotic threshold) by delivering titrated doses of distinct pro-apoptotic signals (BH3 peptides) to mitochondria while monitoring mitochondrial outer membrane permeabilization (MOMP) and subsequent cytochrome *c* release (Ni Chonghaile et al., 2011; Ryan and Letai, 2013). Considering immune cell apoptosis, PBMCs remain primed throughout life, and BIM in particular is a key regulator in T cells in many different subsets and contexts (Bouillet et al., 1999; Enders et al., 2003; Li et al., 2017a; Sarosiek et al., 2017). Studies in $Bim^{-/-}$ mice have shown an accumulation of autoreactive lymphocytes, lack of T cell culling (negative selection) both in the thymus and periphery, and signs of autoimmune disease later in life (Bouillet et al., 2002; Hildeman et al., 2002; Hughes et al., 2006). However, for this autoimmunity to fully manifest, there is evidence to suggest that defects in the extrinsic apoptotic pathway are also necessary (Hughes et al., 2008). Mice deficient in both BIM and PUMA have been shown to spontaneously develop autoimmunity in several different organs and an accumulation of mature, single-positive ($CD4^+$ or $CD8^+$) T cells, which also suggests defects in thymic T cell culling (Gray et al., 2012). Peripherally, BIM is also involved in controlling the homeostasis of $CD4^+$ and $CD8^+$ T cells and is the major mediator of T cell elimination after the peak of immune responses (Bouillet et al., 2002; Hildeman et al., 2002; Kurtulus et al., 2015, 2011; Pellegrini et al., 2003; Weant et al., 2008; Wojciechowski et al., 2007, 2006). In contrast to $CD4^+$ T cells, $CD8^+$ T cells have higher rates of apoptosis (Foulds et al., 2002), which may be dependent on the activity of cytochrome *c* oxidase and response to reactive oxygen species (ROS) during differentiation and/or activation (Schüll et al., 2015; Tarasenko et al., 2017). Though not as nonredundant as BIM, many of the other BCL-2 family proteins play an important role in T cell development and homeostasis, including BCL-2 in naïve and memory T cell survival (Nakayama et al., 1993; Veis et al., 1993; Wojciechowski et al., 2007), and in combating BIM to promote $CD8^+$ T cell memory development (Kurtulus et al., 2011); BCL-XL in thymic development (Ma et al., 1995; Zhang and He, 2005); MCL-1 in thymic development as well as peripheral management of $CD4^+$, $CD8^+$, and

regulatory T cells (Dzhagalov et al., 2008; Opferman et al., 2003); and PUMA and NOXA in the control of T cell expansion and contraction during an immune response (Fischer et al., 2008; Kurtulus et al., 2015; Wensveen et al., 2010). Furthermore, BCL-XL expression has also been shown to be induced by phosphatidylinositol 3-kinase signaling as well as T cell antigen receptor (TCR) signaling and further enhanced by CD28, 4-1BB, and OX40 costimulation, in an NF-κB-dependent fashion (Fang et al., 1994; Lee et al., 2002; Marinari et al., 2004; Parry et al., 2005, 2003; Rogers et al., 2001).

Several ties have also been found between the intrinsic apoptotic pathway and autophagy, via Beclin-1 (a BCL-2 family-interacting protein that promotes autophagy) (Erlich et al., 2007). For example, it has been shown that mouse embryonic $Bax^{-/-}Bak^{-/-}$ fibroblasts do not undergo apoptosis but exhibit increased numbers of autophagosomes and autolysosomes, which can be blocked by knockdown of *Atg5* or *Atg6/Beclin-1* (Shimizu et al., 2004). Furthermore, the autophagy-inducing peptide Tat-Beclin-1 induces autophagic cell death in mammalian cells, which can be inhibited by inhibiting autophagy but not by inhibition of apoptosis or necroptosis (Liu et al., 2013). It has also been shown that Beclin-1-deficient T cells present increased susceptibility to apoptosis, at least in part, caused by the accumulation of the pro-apoptotic proteins BIM and caspases 3 and 8 (Kovacs et al., 2012). There is also further evidence of a cross talk between autophagy and the intrinsic apoptotic pathway, via the interaction between ATG6/Beclin-1 and BCL-2 family members. During normal metabolic conditions, ATG6/Beclin-1 is sequestered by pro-survival BCL-2 family members (e.g., BCL-2, BCL-XL, or MCL-1) through its BH3-like domain (Elgendy et al., 2011; Maiuri et al., 2007; Pattingre et al., 2005). This sequestration can be displaced by the BH3-only proteins, due to higher binding affinity to the pro-survival proteins, which frees Atg6/Beclin-1 to initiate autophagy and caspase-independent autophagic cell death (Elgendy et al., 2011). Additionally, ATG5 and ATG6/Beclin-1 can also be cleaved by caspases and calpains, respectively, converting them into pro-apoptotic proteins that mediate mitochondrial cytochrome *c* release (Wirawan et al., 2010; Yousefi et al., 2006). Taken together, these reports highlight the importance of the intrinsic apoptotic pathway as a major actor in the regulation of T cell death.

2.1.2 The Extrinsic Apoptotic Pathway

Extrinsic apoptosis is triggered by transmembrane DRs, which are members of the tumor necrosis receptor superfamily (TNFRSF). These include

FAS/CD95, TNFR-1, DR3, DR4/TRAILR1, and DR5/TRAILR2, and all harbor a specific signaling motif in their cytoplasmic domain, called a "death domain" (Galluzzi et al., 2018; Locksley et al., 2001). On binding of their respective ligands (death ligands), the receptors undergo trimerization, initiating receptor clustering and recruitment of adapter proteins (e.g., FAS-associated protein with death domain, FADD) to the death domain, forming a death-inducing signaling complex (DISC) (Ashkenazi and Dixit, 1999; Kischkel et al., 1995; Laster et al., 1988). Initiator caspases (e.g., caspase 8 and caspase 10) are then recruited to the DISC via their death effector domains or caspase recruitment domains, and subsequently undergo cleavage into their mature, active form (Boldin et al., 1996; Chun et al., 2002; Kischkel et al., 1995; Li et al., 1997; Muzio et al., 1996; Wang et al., 1999; Yang et al., 1998). These initiator caspases can then cleave downstream effector caspases (i.e., caspase 3, caspase 6, and caspase 7) that dismantle the cell (Li et al., 1997). However, in the presence of caspase inhibitors, the mechanism of cell death shifts from apoptosis to necroptosis (Vandenabeele et al., 2010).

Although the intrinsic pathway plays a more substantial role in controlling normal T cell maturation, the extrinsic pathway also contributes. Death by neglect and negative selection seem to mainly be regulated via intrinsic apoptosis (with BIM as an integral activator), and mice expressing a dominant-negative construct of FADD show normal deletion of autoreactive thymocytes (Kotzin et al., 1988; Newton et al., 1998; Palmer, 2003). However, there have been reports of the extrinsic apoptotic pathway improving the efficacy of negative selection, in cases of high antigen concentration (Kishimoto et al., 1998; Sprent and Kishimoto, 2002), and one report has showed defective negative selection and accelerated autoimmune disease in *Trail*$^{-/-}$ mice, possibly owing to a loss of JNK activation (Green, 2003; Lamhamedi-Cherradi et al., 2003). In the periphery, FAS has been shown to be upregulated during activation, but also in malignancies, and has an important role in T cell homeostasis (Itoh et al., 1991; Trauth et al., 1989; Yonehara et al., 1989; Zheng et al., 1998). FAS has also recently been identified as a regulator of the balance between different subsets of CD4^{+} T cells (Meyer zu Horste et al., 2018; Yosef et al., 2013), preventing autoimmune tissue inflammation in normal physiological settings (Korn et al., 2009). Furthermore, the essential components of FAS-mediated DISC formation are constitutively expressed in both resting and activated T cells (Zheng et al., 1998). TCR-stimulation in T cell hybridomas or activated nontransformed T cells has been shown to induce FAS ligand

and TNF expression, leading to FAS ligand binding by FAS and/or TNF binding by TNFR-1 and inducing apoptosis in an autocrine manner (Brunner et al., 1995; Dhein et al., 1995; Ju et al., 1995; Yang et al., 1995; Zheng et al., 1995). Furthermore, the identification of mutations in FAS and FAS ligand genes in patients with autoimmune lymphoproliferative syndrome (ALPS) also demonstrate the importance of FAS-mediated cell death in T cell homeostasis (Price et al., 2014). ALPS, a genetic disease signified by accumulation of high numbers of lymphocytes in the lymph nodes, liver, and spleen, shows a similar altered immune homeostasis phenotype to mice with FAS and FAS ligand deficiencies (Zheng et al., 2017).

2.1.3 Cross Talk Between the Intrinsic and Extrinsic Pathways

In some T cells, signaling via the extrinsic apoptotic pathway is sufficient to induce apoptosis. These are known as type-I cells and comprise, e.g., long-term activated and proliferating T cells (Scaffidi et al., 1999). A second type (called type-II cells) does not generate sufficient caspase activation from DR signaling alone but require amplification of the apoptotic signal (Scaffidi et al., 1998). This can be achieved via a mitochondrial amplification loop, which is initiated on top of DISC-mediated caspase activation via cleavage and activation of BH3-only protein BID, which triggers MOMP and activation of the intrinsic apoptotic pathway (Green et al., 1998; Wang, 2001). This ensures that the cellular commitment to apoptotic cell death is irreversible. T cells, shortly after activation and prior to proliferation, appear to be type-II cells, owing to inefficient DISC formation after FAS stimulation due to lower constitutive expression of the essential DISC components (Scaffidi et al., 1999; Zheng et al., 1998). Amplification of apoptotic signal has also been reported to function via caspase 3/7-mediated induction of MOMP after activation of the extrinsic apoptotic pathway, although this process seems to be nonessential in thymocyte development (Lakhani et al., 2006).

2.1.4 Thymocyte Maturation and Selection

T cells originate from hematopoietic stem cells which are formed in the bone marrow or fetal liver (Gale, 1987; Takaba and Takayanagi, 2017). Hematopoietic progenitor cells then migrate to the cortex of the thymus and are expanded into immature thymocytes (lacking CD4, CD8), which (in the majority of cases) are developed into double-positive ($CD4^+$, $CD8^+$) thymocytes (Fig. 1). TCRs are generated by DNA rearrangement

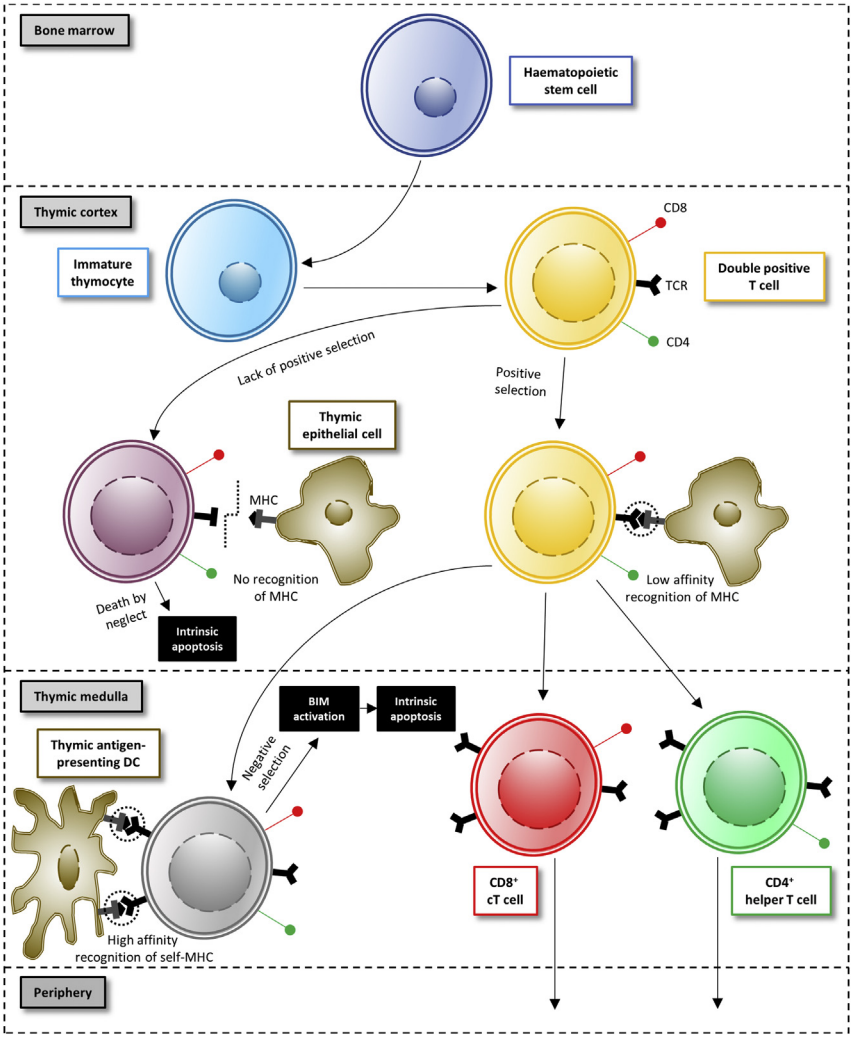

Figure 1 ***Maturation and selection of T cells.*** T cells originate from hematopoietic stem cells, formed in the bone marrow. Hematopoietic progenitor cells are expanded into immature thymocytes (lacking CD4, CD8, and TCR) in the cortex of the thymus. These are developed into double-positive ($CD4^+$, $CD8^+$) thymocytes which express TCR with different affinity for different MHC. Double-positive thymocytes go through positive selection by exposure to self-MHC—endogenous peptide complexes (expressed mainly on thymic epithelial cells). Thymocytes which recognize and interact with MHC receive survival signals from the thymic epithelial cells, whereas thymocytes with no recognition of MHC fail to receive the survival signals and are eliminated via apoptosis ("death by neglect"). The positively selected T cells migrate through the thymic medulla and undergo negative selection, where self-reactive T cells are culled. T cells (with CD4 or CD8 expression) which bind with high affinity to self-MHC complexes on thymic antigen-presenting cells are eliminated, whereas remaining $CD4^+$ and $CD8^+$ T cells are released into the periphery.

and positively selected in the thymic cortex for their capacity to recognize and bind host major histocompatibility complex (MHC) molecules expressed on cortical thymic epithelial cells (Takaba and Takayanagi, 2017). Double-positive thymocytes that are able to recognize MHC receive critical survival signals (e.g., DLL4 and IL7) from the cortical thymic epithelial cells, as well as signals to differentiate into $CD4^+$ (e.g., cathepsin L and TSSP) or $CD8^+$ (e.g., PSB11), single-positive T cells (Anderson and Takahama, 2012; Murata et al., 2007; Takada and Takahama, 2015; Takahama et al., 2012). Thymocytes showing no affinity for MHC do not receive the survival signals and so are eliminated via apoptosis, a process called "death by neglect." In this context, the intrinsic apoptotic pathway has been found to be of major importance. Glucocorticoid hormones have been known for a long time to induce apoptosis in immature thymocytes (Wyllie, 1980), and studies have shown that disrupting BCL-2 in mice enhances dexamethasone-induced thymocyte apoptosis (Veis et al., 1993), a process that is prevented by lack of BAX and BAK (Rathmell et al., 2002). Additionally, the interaction between D4 (the mouse homologue of CD99) and its ligand PILR (paired immunoglobulin−like type 2 receptor), which is located in the surface of thymic epithelial cells, has been proposed as a mechanism to regulate death by neglecting in a caspase 8-dependent manner (Park et al., 2010; Salmena et al., 2003).

Positively selected $CD4^+$ or $CD8^+$ T cells express the chemokine receptor CCR7 and migrate into the medulla, where CCL19 and CCL21 (CCR7 ligands) are highly expressed (Förster et al., 2008). Here, the T cells interact with self-antigen-presenting cells, such as bone marrow−derived thymic dendritic cells (DCs) or medullary thymic epithelial cells, resulting in the deletion of autoreactive cells (Klein et al., 2014; Perry and Hsieh, 2016). On binding to self-MHC in the medulla with an unacceptably high affinity, apoptosis again results, a process called negative selection. The negative selection functions via the TCR signaling, involving MAPK pathways (including p38 and JNK) and seems to be dependent on the length of time for which MHC is bound, which affects the timing of activation for the different MAPKs (Mariathasan et al., 2001; Rincón et al., 1998; Sabapathy et al., 2001; Sugawara et al., 1998; Werlen et al., 2003, 2000). Although most autoreactive $CD4^+$ T cells are negatively eliminated in the medulla, a portion of them differentiate into regulatory T cells, characterized by expression of FOXP3, and specialize in the control of peripheral immune tolerance (Sakaguchi, 2000). Even though BIM-mediated apoptosis is crucial for deletion of self-reactive T cells (Hughes et al., 2006), additional

research into the backup mechanisms involved in T cell death during negative selection (e.g. via BID) is needed, as loss of BIM and/or overexpression of BCL-2 rarely results in full-scale autoimmunity in mice on the C57BL/6J background (Hu et al., 2009; Kovalovsky et al., 2010; Linette et al., 1995; Sentman et al., 1991; Suen and Baldwin, 2012). Studies also suggest that caspases 3 and 7 are not necessary for positive and negative selection of thymocytes (Lakhani et al., 2006). However, BIM deficiency, abrogation of CD28/B7 costimulation, or BCL-2 transgenic overexpression has been reported to increase the proportion of nonconventional fates, such as regulatory T cells, anergic phenotype $CD4^+$ T cells, and postselection double-negative thymocytes (Burger et al., 2014; Pobezinsky et al., 2012; Stritesky et al., 2013).

2.2 Necroptosis

Necroptosis, also known as programmed necrosis, is a cell death mechanism that is morphologically similar to necrosis (which is generally considered unregulated and occurs from tissue trauma) (Majno and Joris, 1995) but is regulated via a cellular signaling cascade (Galluzzi et al., 2018; Holler et al., 2000). These types of cell death are characterized by swelling of organelles and an increase in cell volume. This is followed by lysis and disintegration of the plasma membrane (Berghe et al., 2014; Linkermann and Green, 2014; Schweichel and Merker, 1973). Contrary to apoptosis, which is generally considered an immunogenically silent mode of cell elimination, necroptosis is a proinflammatory process which leads to release of danger-associated molecular patterns (DAMPs) (Kaczmarek et al., 2013; Proskuryakov et al., 2003). Necroptosis can be induced on stimulation of Toll-like receptors 3 and 4 in the presence of caspase inhibitors, as well as the DNA-dependent activator of interferon-regulatory factors (DAI), but can also be mediated by DR ligation in certain contexts (Holler et al., 2000; Ma et al., 2005; Upton et al., 2012). In most contexts (i.e., Toll-like receptors 3 and 4, DAI and TNFR-1), receptor stimulation does not always lead to cell death but instead induces inflammation even though the cell survives (Li et al., 2017b). Necroptotic activation in these cases is dependent on Receptor Interacting Serine/Threonine Kinase (RIPK) 1 and 3 (Cho et al., 2009; He et al., 2009; Holler et al., 2000; Zhang et al., 2009). For example, TNF binding to TNFR-1 can result in the formation of a protein complex (complex 1) consisting of, e.g., TNFR-1-associated DD protein (TRADD), RIPK1 and cellular inhibitor of apoptosis protein (cIAP) 1 or 2. This complex induces a signaling cascade that activates

NF-κB and AP-1, which results in proinflammatory signals (Hsu et al., 1996; Micheau and Tschopp, 2003). This is dependent on the integrity of complex 1; however, and if destabilized, TRADD instead binds FADD and caspase 8 and forms complex 2a (Micheau and Tschopp, 2003). Complex 2a promotes apoptosis through caspase 8 and represses necroptosis by cleavage of RIPK1 and 3 (Feng et al., 2007; Lin et al., 1999; Oberst et al., 2011). When cIAP1 or 2 are inhibited, complex 2b is instead formed, consisting of RIPK1, RIPK3, FADD, cFLIP, and caspase 8, which subsequently form a large amyloid-like structure called a necrosome (Cho et al., 2009; He et al., 2009; Li et al., 2012). The necrosome is instrumental in the phosphorylation of mixed lineage kinase domain-like protein (MLKL) which then oligomerizes, translocates to the cell membrane, and mediates membrane permeabilization (Sun et al., 2012; Zhao et al., 2012). This results in death of the cell and release of DAMPs into the extracellular space (Cai et al., 2014; Chen et al., 2014; Dondelinger et al., 2014; Murphy et al., 2013; Su et al., 2014; Wang et al., 2014). These DAMPs can then activate Toll-like and other receptors on surrounding cells, leading to a further increased inflammatory response (Li et al., 2017b). In T cells, necroptosis appears to function as an alternative, backup mechanism to apoptosis, to be activated in case of inhibition of caspase 8 by viral infection (Mocarski et al., 2012; Weinlich et al., 2011). Data have shown that deletion of caspase 8 in T cells in $Bim^{-/-}$ mice is able to suppress autoimmunity via necroptotic cell death of autoreactive T cells (Bohgaki et al., 2011). The role of necroptosis in T cells under normal physiological conditions is, however, still not clear. Although loss of caspase 8 function is not commonly observed in normally functioning human cells, an inhibitor of caspase 8 encoded by human cytomegalovirus has been suggested to influence the DC-mediated activation of T cells, by stimulating a more profound release of DAMPs from dying cells (Martin et al., 2008; Skaletskaya et al., 2001). Human cytomegalovirus also blocks necroptosis downstream of MLKL via an unknown mechanism (Mocarski et al., 2012).

2.3 Pyroptosis

Pyroptosis is a highly inflammatory form of programmed necrosis, mediated by one or more of the inflammatory caspases (caspase 1, 4, and 5 in humans; caspase 1 and 11 in mice) (Brennan and Cookson, 2000; Case et al., 2013; Fink and Cookson, 2006). It is initiated following inflammasome activation and shares morphological characteristics with necroptosis, such as cell

swelling, rupture of the cell membrane, and release of DAMPs and proinflammatory cytokines (e.g., IL-1β and IL-18) (Cookson and Brennan, 2001; Fink and Cookson, 2006; Watson et al., 2000). The inflammasome is a multiprotein oligomer which promotes the cleavage and activation of procaspase 1, which then processes IL-1β and IL-18 into their mature forms (Martinon et al., 2002). Inflammasome activation can be induced by a variety of cellular stress factors, including recognition of molecular patterns expressed by invading pathogens. These patterns are monitored by pattern recognition receptors, which can detect threats both extracellularly (via e.g., Toll-like receptors or C-type Lectin Receptors) or intracellularly (via e.g., Nod-like receptors and RIG-I-like receptors) (Martinon et al., 2002; Srinivasula et al., 2002; Tschopp et al., 2003). Once activated, the inflammasome can trigger cleavage of gasdermin D, the downstream effector of pyroptosis, which then translocates to the cell membrane and forms pores by binding to phosphotidylinositol and oligomerizing (Aglietti et al., 2016; Ding et al., 2016; Liu et al., 2016; Sborgi et al., 2016; Shi et al., 2015). This typically causes membrane disruption and cell lysis; however, recent reports have shown that gasdermin D pore formation is needed for IL1β secretion from inflammasome-activated macrophages without, at least initially, compromising the viability of the macrophage (Evavold et al., 2017). Pyroptosis is an important factor in antimicrobial response because the consequential amplification of the host immune defense leads to rapid clearance of infected cells, thereby depriving the pathogen of its replicative niche (Aachoui et al., 2013; Galluzzi et al., 2018). However, this defense mechanism may be disadvantageous for T cells in some cases. For example, in HIV-infected hosts, $CD4^+$ T cells are eliminated due to abortive HIV infection. In this process, viral DNA transcripts accumulate in the cytosol, which can result in inflammasome assembly and pyroptosis (Monroe et al., 2014). This in turn leads to DAMP and cytokine release which creates further inflammation, feeding further inflammation and pyroptosis in surrounding cells and even more loss of $CD4^+$ T cells (Doitsh et al., 2014, 2010). Further research is needed to elucidate the role of pyroptosis in other T cell subsets.

2.4 Ferroptosis

Ferroptosis is a recently recognized form of regulated cell death, characterized by morphological changes such as unusually small mitochondria, condensed mitochondrial membrane densities, reduction of mitochondrial inner membrane folds (cristae), and rupture of the outer

mitochondrial membrane (Dixon et al., 2012). Ferroptosis is driven by loss of activity of the lipid repair enzyme glutathione peroxidase 4 (GPX4), leading to accumulation of lipid-based ROS (Yang and Stockwell, 2016). Activation of mitochondrial voltage-dependent anion channels and mitogen-activated protein kinases, upregulation of endoplasmic reticulum stress, and inhibition of cystine/glutamate antiporter is involved in the induction of ferroptosis. Although relatively few studies have been performed to date, a role for this cell death process in several biological processes is beginning to be revealed (Yang and Stockwell, 2016). For example, conditional deletion of *Gpx4* in T cells in mice has been shown to result in T cell ferroptosis, leading to lack of an immune response to infection and suggesting a role for GPX4 in T cell-mediated immunity (Matsushita et al., 2015).

3. T CELL-MEDIATED CELL DEATH

The main function of activated T cells is to selectively eliminate cells which are considered as potential threats to the organism. For the adaptive immune system to be activated, DCs first need to detect threat-associated antigens, as well as DAMPs which serve as adjuvant signals as a consequence of cellular stress and death (Farkas et al., 2007; Kaczmarek et al., 2013). On immune system detection of DAMPs, signaling the presence of potential threats, such as pathogens or cancerous cells, immature $CD8^+$ T cells are converted into cytotoxic $CD8^+$ T cells (cT cells) (Hivroz et al., 2012). Additionally, unconventional cT cells (e.g. $CD4^+$ CT cells) have also been observed in certain contexts (Takeuchi and Saito, 2017). cT cells express antigen-specific TCRs, which on stimulation activate effector mechanisms (illustrated in Fig. 2) to eliminate the cells from which the threat signal emanated. To maintain self-tolerance, the activity of the cT cells can be prevented by pathways known as immune checkpoints, which is imperative for maintaining homeostasis but can be detrimental to the effects of cancer immunotherapy (Pardoll, 2012). To circumvent these problems, checkpoint inhibitors (e.g., anti-CTLA4, anti-PD-1, and anti-PD-L1) have been developed and have shown durable clinical responses in a multitude of cancers (Sharma and Allison, 2015).

The cT cell effector functions are accomplished via the granule exocytosis pathway (Bossi and Griffiths, 2005; De Saint Basile et al., 2010) and/or

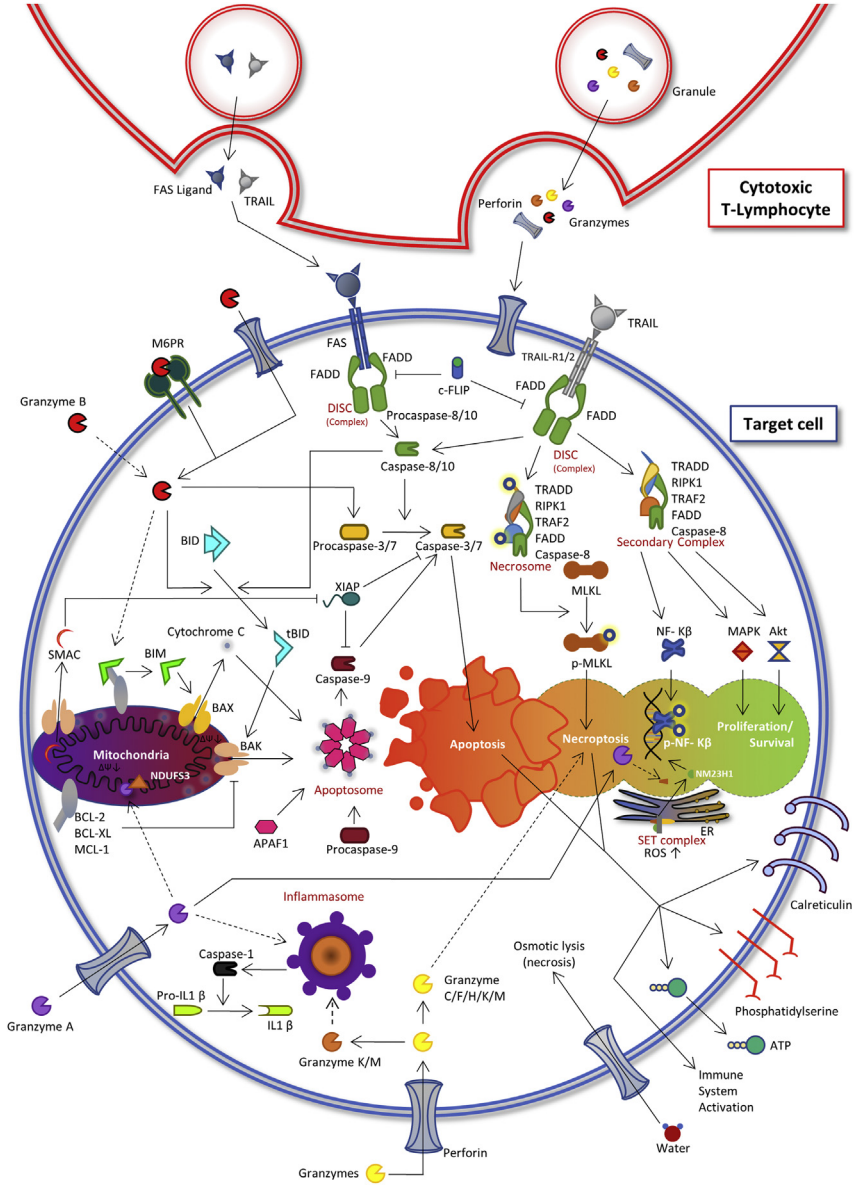

Figure 2 ***Mechanisms of T cell-mediated cell death.*** cT cells can eliminate other cells via granule exocytosis and/or the expression and release of death ligands. Granule exocytosis entails release of, e.g., granzymes and perforin (PRF1) toward the contact site of the target infected/dysfunctional cell. The granzymes then enter the cell and are capable of inducing cell death via multiple different pathways, with granzyme B-induced apoptosis being the most commonly observed. Death ligand secretion (of e.g., FAS ligand or TRAIL) is also a possible mode of elimination. In this case, cell death is most often induced via the extrinsic apoptotic pathway, although it may in some contexts lead to necroptosis.

the expression and release of death ligands (Anel et al., 1994; Takeda et al., 2001). The following section details the mechanisms involved in these effector processes as well as the scenarios in which they are utilized.

3.1 Granule Exocytosis

The granule exocytosis pathway is rapidly executed after cT cells are exposed to infected/dysfunctional somatic cells. This is characterized by mobilization of preformed, specialized cytoplasmic granules, containing the cytotoxins perforin (PRF1), granzymes, and granulysin (Chowdhury and Lieberman, 2008; Krensky and Clayberger, 2009; Milstein et al., 2011; Pardo et al., 2009; Voskoboinik et al., 2006). These granulocytes are released toward the contact site (immunological synapse) of the target infected/dysfunctional cell (Bossi and Griffiths, 2005; De Saint Basile et al., 2010). The delivery of the cytotoxins from the granules into the target cell is a matter of intense debate and has only recently begun to be clarified. According to current knowledge, the pore-forming protein PRF1 forms pores in the plasma membrane on degranulation and acts as a vehicle to allow the granzymes to enter the cytosol (Lopez et al., 2013; Metkar et al., 2011; Voskoboinik et al., 2006). Although this mechanism has been observed in physiological conditions, it is still unclear whether the alternative hypothesized mechanisms may also operate in certain contexts. These proposed mechanisms include receptor- or clathrin-mediated granzyme and PRF1 coendocytosis followed by PRF1-mediated pore formation in the endosome and subsequent granzyme release (Pipkin and Lieberman, 2007). Additionally, in cases where there is a deficit of granzyme expression, it has been proposed that PRF1 can kill target cells by itself by means of cell lysis, a mechanism that has been demonstrated in rat basophil leukemia cells transfected with PRF1 cDNA lyse Jurkat cells (Voskoboinik et al., 2004). It has also been shown that antigen-specific cT cells in granzyme knockout mice are able to induce cell death in tumor target cells, at a reduced level compared with WT mice (Hoves et al., 2011; Pardo et al., 2004; Simon et al., 1997; Torán et al., 2001). In these knockout mice, the cT cell-induced cell death does not involve caspase activation, eliminated cells are not efficiently phagocytosed by DCs and do not induce antigen cross-presentation (Hoves et al., 2011; Pardo et al., 2004; Waterhouse et al., 2006).

Granzymes are a family of serine proteases that are expressed in cT cells and NK cells (Ewen et al., 2012). In total, 6 different granzymes have been described in humans (granzyme A, B, C, H, K, and M) and 10 in mice

(Bovenschen and Kummer, 2010; Pardo et al., 2009; Voskoboinik et al., 2015). Of these, Granzyme A and B have garnered the most attention. Several of these have been shown to induce cell death in vitro, and among them, only granzyme B does so via apoptosis (Bovenschen and Kummer, 2010; Chowdhury and Lieberman, 2008; Ewen et al., 2012). For example, granzyme A-induced cell death is characterized by phosphatidylserine exposure, chromatin condensation, single-stranded DNA nicking, and ROS production and occurs without cleavage of caspases or involvement of the BCL-2 family proteins (Martinvalet et al., 2005). Current models suggest that granzyme A instead induces cell death via disruption of the ER-associated oxidative stress response SET complex via generation of ROS (Martinvalet et al., 2008). Additionally, granzyme A has also been shown to regulate proinflammatory cytokine production (e.g., IL1b) in a caspase-dependent manner, which may involve the inflammasome (Metkar et al., 2008). Granzyme B, however, can induce apoptosis via the intrinsic pathway (Heibein et al., 1999; Pinkoski et al., 2001). This is orchestrated by proteolytic activation of BID at Asp75, resulting in its translocation to the mitochondrial membrane and activation of BAX and/or BAK (Barry et al., 2000; Hameed et al., 1988; Heibein et al., 2000; Sutton et al., 2000). Rather than result in cytochrome *c* release, however, this instead leads to release of inhibitor of apoptosis proteins (IAPs) and later of SMAC, which relieves IAP inhibition of autocatalytic caspase 3 maturation, allowing it to be cleaved (Goping et al., 2003; Sutton et al., 2003). Additionally, granzyme B is also able to cleave aspartic acid residues and directly activate caspases (e.g., caspases 3, 7, 8, and 10), inducing apoptosis without the need for MOMP (Ewen et al., 2012; Odake et al., 1991). However, granzyme B species-specific differences in the affinity for direct BID and caspase cleavage have been reported (Catalán et al., 2015; Kaiserman et al., 2006; Cullen et al., 2007). Finally, granzyme B has also been reported to activate the mitochondrial pathway by disrupting MCL-1/BIM or BCL-XL complexes, allowing BIM to activate BAX and/or BAK (Catalán et al., 2015; Han et al., 2005, 2004). Concerning the remaining granzymes, they have been described to be able to induce cell death as well as regulate the production of proinflammatory cytokines, but the mechanisms are still unknown and the relevance of these granzymes during physiological conditions has been questioned (Anthony et al., 2010; Bovenschen and Kummer, 2010; Chowdhury and Lieberman, 2008; Ewen et al., 2012; Hoves et al., 2010; Joeckel and Bird, 2014; Pardo et al., 2009; Voskoboinik et al., 2015). At present, it is unknown whether other mechanisms of cell death and/or

survival such ferroptosis or autophagy-dependent cell death may regulate cell death executed by granzymes.

3.2 Death Ligand Secretion

A variety of different death ligands are expressed by cT cells, including TNFα, FAS ligand, and TRAIL. During cT-mediated cell death of target cells, these ligands are expressed at the cT cell membrane or secreted as exosome membrane-bound death ligands and activate the extrinsic (and in some cases the intrinsic) apoptotic pathway in the target cell (Martínez-Lostao et al., 2015). The use of cT cell death ligand secretion is mainly involved in a process which is classically known as activation-induced cell death, now being redubbed as TCR restimulation-induced cell death (RICD) (Martínez-Lostao et al., 2015; Zheng et al., 2017). RICD is one of the mechanisms responsible for regulating peripheral immune tolerance and functions via FAS-mediated extrinsic apoptosis (Krammer et al., 2007; Kuklina, 2013). Restimulation of TCR in cycling T cells leads to activation of RICD, dependent on the presence of T cell growth cytokines (e.g., IL2), creating a feedback mechanism called propriocidal regulation in which IL2-stimulated proliferation serves an indicator of excess T cell expansion (Lenardo et al., 1999; Lenardo, 1991; Zheng et al., 1998). The reactivation also leads to FAS ligand and TRAIL de novo synthesis in the cT cell, which in turn leads to increasing formation of death ligand exosomes and death ligand surface expression (Martínez-Lostao et al., 2015).

While FAS has been shown to be ubiquitously expressed in different tissues, the FAS ligand is restricted to T cells, particularly cT cells (Krammer, 2000; Suda et al., 1993), and cT cell FAS ligand secretion has also been reported to be involved in the removal of viruses that express FAS.

3.3 Immunosurveillance

Peripheral T cells constantly monitor our bodies for signs of pathogens or cancerous cells. This process involves not only detection but also rapid elimination of potential threats. In terms of cancer immunosurveillance, most evidence indicate that PRF1 (and consequently granule exocytosis) is a key factor for cT cell-mediated control of tumors, both during carcinogenesis and metastasis, especially for tumors of hematological origin (Bolitho et al., 2007; Kägi et al., 1994a; Pardo et al., 2002; Smyth et al., 2000a,b; Smyth et al., 1999; Torán et al., 2001; Trapani et al., 2013; van den Broek et al., 1996). Additionally, deficiency in PRF1 has been shown to enhance the oncogenic potential of several different proteins such as ABL1, BCL-2,

and MLH1 (Bolitho et al., 2009), as well as accelerate the onset and neoplastic grade of HER2/neu-driven ductal carcinoma (Macagno et al., 2014; Street et al., 2007).

The role of granzymes in immunosurveillance is much less clear, with different reports from granzyme A- and B-deficient mice showing either higher tumor formation potential or no difference, compared with WT mice for several different cancer models (Fehniger et al., 2007; Pardo et al., 2002; Revell et al., 2005; Smyth et al., 2003; Torán et al., 2001). Deficiency in other granzymes does not seem to have an effect on tumor formation, which may be due to their relatively weaker cytotoxic potential (Joeckel et al., 2011; Pao et al., 2005). It is possible that in some cases of granzyme deficiency, the alternative target cell elimination mechanism via PRF1 cell lysis may compensate and thus maintain tumor control (Voskoboinik et al., 2006).

It has also been shown that death ligand secretion may contribute to tumor immunosurveillance. For example, PRF1-deficient cT cells have been shown to induce cell death in tumor cells in vivo via FAS activation (Afshar-Sterle et al., 2014; Kägi et al., 1994b; Lowin et al., 1994), and TRAIL-mediated extrinsic apoptosis is generally considered to also play a role in cancer immunosurveillance (Cretney et al., 2002; Grosse-Wilde et al., 2008; Smyth et al., 2001; Takeda et al., 2002, 2001). Mutations in FAS and/or FAS ligand has also been correlated with higher incidence of B and T lymphoma, both in animal models and in humans (Afshar-Sterle et al., 2014; Davidson et al., 1998; Peng et al., 1996; Price et al., 2014; Straus et al., 2001). No such results have been reported regarding TRAIL/DR mutations. However, mutations in caspase 8 have been associated with an increased cytolytic immune infiltrate signature, based on data from The Cancer Genome Atlas (Rooney et al., 2015). In light of results showing that tumor cells which are resistant to extrinsic apoptosis may instead die via necroptosis following DR or FAS activation, the added immunogenicity of this cell death mode may have an impact on immunosurveillance. This may offer an explanation for reports showing that tumor cells can use TRAIL or FAS ligand to promote invasiveness and development of metastases (Azijli et al., 2013; Barnhart et al., 2004; Trauzold et al., 2006; von Karstedt et al., 2015).

3.4 Cancer Immunotherapy

Cancer immunotherapy has gained a lot of momentum in recent years, largely due to the development of checkpoint inhibitors such as anti-CTLA4 and

anti-PD-1. In these scenarios, cytotoxic lymphocytes (mainly cT cells and natural killer cells) perform the killing of cancer cells. The involvement of granule exocytosis in this killing has not been thoroughly explored, and results from the studies that have been performed are not easily interpreted (Allard et al., 2013; Seki et al., 2002; Sin et al., 2012). Studies using the immunodominant cT cell epitope, lymphocytic choriomeningitis virus (LCMV) peptide gp33, to activate virus-specific cT cell responses, have shown a dependence on PRF1, but not FAS ligand (Martínez-Lostao et al., 2015). Additionally, PRF1 was shown to contribute significantly to the antitumoral effect of the combination of BRAF inhibitors and agonistic anti-CD137 antibody in melanoma cells (Knight et al., 2013), and anti-CD137-mediated killing of lymphoma cells in mice has been shown to be dependent on both PRF1 and FAS ligand (Morales-Kastresana et al., 2013). In contrast, PRF1 deficiency did not have an effect on the in vivo efficacy of anti-CD73, anti-CTLA-4, anti-PD-1 therapy in colon, prostate, and breast carcinoma cell lines (Allard et al., 2013). Additionally, host PRF1-knockout inhibits tumor clearance during PD1-1 pathway blockade in mice with MC38 colon adenocarcinoma, while still inducing a reduction in tumor volume (Juneja et al., 2017). Similar discrepancies in PRF1-dependency have also been reported regarding IL12-mediated tumor control (Hashimoto et al., 1999; Hayakawa et al., 2001; Kodama et al., 1999; Liu et al., 2012; Schultz et al., 1999; Sin et al., 2012; Song et al., 2000), suggesting that the mechanisms may be dependent on model and/or tumor type (Smyth et al., 2000a,b).

Concerning the involvement of death ligand secretion in cancer immunotherapy, a similar complex image is portrayed. FAS ligand has been shown to be involved in IL-18-mediated elimination of B16 melanoma cells (Morales-Kastresana et al., 2013), but neither FAS ligand or TRAIL was instrumental in the antitumor effect in other melanoma models using combination therapy with BRAF inhibitors and agonistic anti-CD137 antibody (Knight et al., 2013). TRAIL inhibition has, however, been shown to block IL12 and α-galactosylceramide-mediated control of liver metastases in a renal carcinoma model (Smyth et al., 2001). In all, these studies indicate that the mechanisms involved in cT cell-mediated cell death differ between the contexts of immunosurveillance and immunotherapy. This is supported by studies analyzing both contexts in the same models, which show that mice deficient in granzyme B do not exhibit a higher susceptibility than WT mice to 3-methylcholanthrene-induced sarcomas (Torán et al., 2001) but fail to control implanted sarcomas during adoptive NK cell transfer

(Pegram et al., 2010). Additionally, PRF1-deficient mice show an increased susceptibility to forming tumors when implanted with the prostate cancer cell line RM1 (Smyth et al., 1999) but do not show a difference in tumor control after treatment with BRAF inhibitors and agonistic anti-CD137 antibody (Knight et al., 2013), compared with WT mice. PRF1 deficiency also results in higher susceptibility to implanted or oncogene-driven breast carcinoma than WT mice, but does not hamper the control of implanted breast carcinoma during treatment with checkpoint inhibitors (Allard et al., 2013; Macagno et al., 2014; Smyth et al., 1999; Street et al., 2007). Finally, mice with PRF1 deficiency also have increased metastatic susceptibility in renal cancer (Abdool et al., 2006), but this has no effect on metastasis control during IL12/α-galactosylceramide or adoptive cT cell therapy (Seki et al., 2002; Smyth et al., 2001). These differences may potentially be explained by differences in the amplitude of stimuli that are recognized by cT or NK cells (Shanker et al., 2009).

4. CONCLUDING REMARKS

Both in terms of T cell death and T cell-mediated killing, apoptosis is the primary method of elimination in developmental and homeostatic regulation. This involves mainly the intrinsic pathway (via modulation of BIM) but can also be executed via the extrinsic pathway. In the culling of unwanted T cells, other cell death pathways such as pyroptosis, necroptosis, and ferroptosis seem to function mainly as backup mechanisms which come into play only under specific conditions in which the apoptotic pathways are unavailable or inappropriate. Regarding cT cell-mediated killing, the effector mechanisms seem to differ depending on whether the cell is performing immunosurveillance or is involved in a cancer immunotherapeutic setting. In the context of cancer immunotherapy, granule exocytosis and activation of the intrinsic apoptotic pathway via PRF1 and granzyme B seems to be the most potent killing mechanism in most contexts and is even able to achieve commitment to cell death in case of target cell apoptosis deficiency (such as p53 deletion/mutation, overexpression of pro-survival BCL-2 family members, or caspase inhibition). More research is needed to elucidate the mechanisms and physiological relevance of other granzymes concerning the induction of cell death, as well as the possible existence of additional cT cell effector functions. This may be of value in predicting patient responses to, e.g., cancer immunotherapy, both in terms of the efficacy of the treatment to kill the target cell and also in terms of avoiding undesirable toxicities.

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