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Dysregulation of CD8$^+$ lymphocyte apoptosis, chronic disease, and immune regulation

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1. ABSTRACT

Expansion of CD8$^+$ lymphocyte subsets are found in many states with chronic antigenic exposure including HIV, multiple myeloma, rheumatoid arthritis, CMV infection, transplantation and even normal aging. These expansions are characterized by the expression of CD57 antigen and the loss of CD28$^-$. These lymphocytes are thought to represent clonally expanded cytotoxic T lymphocytes (CTL) that have become senescent and lack proliferative ability. These cells also demonstrate suppressive properties and have been linked with immunodeficiency raising the question of the function of these cells in relationship to immunoregulation. Alterations in the CD95/Fas apoptotic pathway and changes in pro-survival factors such as Hsp27 likely contribute to this lymphocyte subset expansion. Further understanding of the normal CD8$^+$ lymphocyte response to antigen and the factors that lead to abnormal continued expansion in certain disease states will be crucial to understanding the pathogenesis of chronic antigenic stimulation.

2. INTRODUCTION

Lymphocytes are a crucial part of the immune system and are the major cells involved in the adaptive immune response. CD8$^+$ cytotoxic T lymphocytes play an important role in the body's response to viral pathogens as well as tumor and foreign antigens. Usually, CD8$^+$ cells expand rapidly in response to antigen, and then die by apoptosis. However, in conditions with chronic antigenic exposure there are often clonal expansions of CD8$^+$ lymphocytes that express the CD57 antigen and these conditions are often associated with immunosuppression. In this article we will review conditions where CD8$^+$CD57$^+$ lymphocytes are expanded and look at dysregulation of apoptosis as a possible mechanism for this expansion.

3. NORMAL LYMPHOCYTE LIFESPAN

Naïve CD8$^+$ lymphocytes circulate in the body including the blood and secondary lymphoid organs until they encounter an antigen presenting cell which is

Table 1. Conditions associated with an increased percentage of $CD8^+CD57^+$ lymphocytes

Condition	Reference
Human Immunodeficiency Virus	12, 13, 14
Cytomegalovirus	12, 13, 14
Multiple Myeloma / hematologic malignancy	29,30,31,32
Large Granular Leukemia	34,35
Bone Marrow Transplantation recipients	25,26
Solid Organ Transplantation recipients	23
Rheumatoid Arthritis	21,22
Normal Aging	10,11

expressing peptide in the context of MHC I. In the presence of cytokines such as IL-2 and IL-12 and other co-factors, the antigen specific $CD8^+$ lymphocytes proliferate rapidly. Their expansion is rapid and massive with up to a 50,000 fold increase in antigen specific lymphocytes (1, 2). After the stimulus is removed, or the infection cleared, the antigen specific lymphocyte numbers fall dramatically. The lymphocytes die by apoptosis, allowing the restoration of the balance of CD4 and CD8 lymphocytes without an inflammatory reaction that would be generated by necrosis.

While the majority of lymphocytes die, a population of memory $CD8^+$ lymphocytes remains. The markers of memory $CD8^+$ lymphocytes are debated, but include the lack of CCR7 and CD27 and the expression of $CD45RA^+$ (3). Using HIV as a model, it is believed the $CD8^+$ differentiation in response to antigen begins with lymphocytes expressing $CD8^+CD28^+CD27^+$ and ends with $CD8^+CD27^-CD28^-CCR7^-CD62L^-$ lymphocytes (4). In HIV infection, it has been hypothesized that the expression of CD57 may better define an effector memory $CD8^+$ T cell than the lack of CD27 antigen. Furthermore, $CD57^+$ expression by $CD8^+$ cells was shown to be a marker of proliferative inability and replicative senescence (5, 6).

Having a diverse $CD8^+$ T cell population as well as a population of memory lymphocytes able to respond to antigen re-challenge is important for immunologic health. If memory cells become dysfunctional or senescent cells become expanded, it may increase susceptibility to infection or autoimmunity.

4. EXPANSION OF $CD8^+CD57^+$ LYMPHOCYTES

In certain disease states, and even in normal aging, a clonal expansion of a $CD8^+$ lymphocyte subset with unknown function has been reported (Table 1). Studies examining T cell receptor (TCR) rearrangements have shown that in normal adults, there are clonal expansions of the $CD8^+$ lymphocyte population in 30% of subjects and it is estimated to occur in more than half of adults (7). Large oligoclonal expansions in the $CD8^+$ subset are described in the $CD8^+CD57^+$ population (8). The normal percentage of $CD8^+$ lymphocytes expressing the $CD57^+$ antigen ranges from 5-20% with a mean of 15-16% (8, 9). $CD8^+CD57^+$ lymphocytes have been found to expand with aging in normal hosts (10, 11). It is unclear what the stimulus is for this expansion, however viral, alloimmune, or tumor antigens may be responsible.

It is well recognized that expansion of $CD8^+$ lymphocytes can occur in response to chronic viral infections. CMV and HIV infection (12-14) have both been associated with expansions of the $CD8^+CD57^+$ lymphocyte subset. Moreover, we found an increase in $CD8^+CD57^+$ lymphocytes in the lungs of patients with later stage HIV (CD4 less than 500) (15). This is in agreement with earlier studies that show an increase in the percentage of $CD57^+$ expressing $CD8^+$ lymphocytes in bronchoalveolar lavage fluid of HIV infected subjects (16). $CD8^+CD57^+$ lymphocytes in both HIV and CMV infection have been shown to contain viral specific effector cells (5, 17, 18). Another viral infection that is known to have $CD8^+$ clonal expansions is chronic hepatitis C infection and these expansions have been associated with cirrhosis and fibrosis in this disease. Treatment with IFN-alpha increased the differentiation towards $CD8^+CD57^+CD28^-$ lymphocytes, and these cells decreased if virus was eliminated (19). Either persistent virus or viral antigens appear to be necessary to maintain viral specific $CD8^+$ lymphocytes (20).

In addition to viral infections, clonal expansions of senescent $CD8^+CD57^+$ lymphocytes have been reported in some rheumatologic or autoimmune conditions such as rheumatoid arthritis and in response to alloimmunity (21, 22). In transplantation recipients, 71% of cardiac transplant patients and 44% of renal transplant patients were found to have clonal expansion of the $CD8^+CD57^+$ subset (23). Similarly, expansion of this subset was found after renal and liver transplantation, and was correlated with a poorer prognosis (24). After bone marrow transplantation (BMT), clonal expansion of $CD8^+CD57^+$ lymphocytes has also been reported (25, 26). Some studies have shown a correlation between graft versus host disease (GVHD) and expansion of $CD8^+CD57^+$ cells (27). However, another study showed no relationship to GHVD, but that $CD8^+CD57^+$ expansion was correlated with CMV infection and a low risk of relapse (28). It is unclear if alloantigen leads to expansion of the $CD8^+CD57^+$ subset after transplantation or what the responsibe antigen may be in the case of autoimmunity. Another possibility is that chronic infections may be responsible for the expansion in these conditions.

In multiple myeloma and patients with hematologic malignancy (29-32), there is an increase in large granular lymphocytes ($CD8^+CD57^+$) that are clonally expanded raising the question of whether they are tumor specific CTL. It has been shown that in multiple myeloma, high levels of marrow $CD8^+CD57^+$ cells correlated with improved survival (33). However, on the other end of the spectrum, T cell large granular leukemia (LGL) is defined by clonal expansion of $CD3^+CD8^+CD57^+$ large granular lymphocytes (34, 35). This form of LGL, as opposed to the NK cell version, has a variable progression, with up to 85% of cases having an indolent clinical course (36). It is found mostly in the elderly and associated with autoimmunity or neutropenia (37).

Chronic viral infections, alloimmune and autoimmune conditions as well as certain hematologic malignancies all have expansion of $CD8^+CD57^+$ lymphocytes. Chronic antigen exposures resulting in

clonally expanded lymphocyte populations implicate replicative senescence as the reason for these expansions. It remains to be determined if $CD57^+$ cells play a role in the immunosuppression seen in these conditions, but it is plausible to draw a correlation between chronic disease, immunosuppression, and clonal expansions of $CD8^+$ lymphocytes.

5. FUNCTION OF $CD57^+$

$CD57^+$ cells are defined by reactivity to the antibody HNK-1. The HNK-1 name is derived from the ability of the antibody to mark Human Natural Killer cells (9). It has also been called leu-7 and then CD57. HNK-1 is a carbohydrate epitope that is found in many glycoproteins and glycolipids in various tissues in the body (38). In the immune system, NK cells and a subset of $CD3^+$ lymphocytes express CD57 (9). The HNK-1 carbohydrate is expressed in neural tissue and in the eye (39). It is also found as a component of a large number of glycoproteins, many of which have a role in cell adhesion (38). HNK-1 was recently shown to be a part of GP130, a subunit of the IL-6 receptor. HNK-1 allows IL-6 to bind to GP130 through the cytokine's carbohydrate recognition domain (40).

Although HNK-1 has been extensively studied in the nervous system, and the $CD8^+CD57^+$ expressing leukocytes have been investigated, the exact function of HNK-1/CD57 on an immune cell is unknown. While molecular mechanisms have failed to show the signaling pathway or function of the CD57 receptor, much has been learned about the function of these cells based on cell separation experiments. Lymphocytes that express the antigen are clonally expanded, senescent CTL. They have defects in proliferation (5), but are able to secrete high levels of INF-gamma upon TCR stimulation (41), and interestingly, they express high levels of Fas and FasL (15).

6. LINKS TO AUTOIMMUNITY, IMMUNE DEFICIENCY AND IMMUNE SUPPRESSION

The same conditions that show expansion of $CD8^+CD57^+$ lymphocytes also display immune deficiency such as the autoimmune disease rheumatoid arthritis (RA), large granular leukemia (LGL), multiple myeloma (MM), late stages of HIV infection, and after solid organ or bone marrow transplantation, suggesting a correlative relationship. Some have proposed a relationship between CD8+ replicative senescence and immune deficiency seen in aging and also in HIV infection (39, 42, 43). Senescent CTL expansion may contribute to immune dysregulation by several mechanisms, including: 1) senescent cells may develop intrinsic regulatory properties, 2) they may allow the formation of autoimmunity by contributing to an ineffective CTL pool, and 3) they may increase susceptibility to infection.

6.1. Regulatory properties

Interestingly, regulatory or suppressive properties have been attributed to the $CD8^+CD57^+CD28^-$ cell population. These $CD8^+CD57^+$ lymphocytes have been shown to inhibit pokeweed mitogen induced Ig production (14), inhibit lymphocyte proliferation (29) and secrete a soluble inhibitor of cytolytic function which is yet to be identified (16). In BMT patients the $CD8^+CD57^+$ cell population inhibits alloreactive cytotoxic T lymphocyte killing (44). In addition, others have shown the $CD8^+CD57^+$ population suppressed the generation of CMV specific CTL (45).

It was found that $CD8^+CD28^-$ lymphocytes also have regulatory functions in controlling susceptibility to an autoimmune disease. In an experimental autoimmune encephalomyelitis model $CD8^+CD28^-$ cells suppressed disease activity (46). While the difference between $CD8^+CD28^-$ and $CD8^+CD57^+$ lymphocytes have not yet been defined, it is known that both populations have undergone multiple rounds of replication, and are felt to be terminally differentiated, senescent cells.

After BMT, $CD8^+CD57^+$ expansion in the blood correlated with graft vs. host disease. Limited data also suggests they are expanded in the lungs of patients after BMT undergoing evaluation for chronic lung disease post transplant (47, 48). The regulatory lymphocytes isolated from BMT patients are capable of inhibiting an alloimmune response through secretion of a soluble factor (44). Recent work has identified a subset of $CD8^+CD28^-$ lymphocytes that possess suppressive function. These $CD8^+CD28^-$ lymphocytes can be generated *in vitro* by multiple rounds of alloimmune stimulation (49). These lymphocytes are anergic and are capable of suppressing alloimmunity. The importance of these cells is demonstrated by examining them in cardiac transplantation in humans (50). $CD8^+CD28^-$ lymphocytes were expanded after cardiac transplantion, and suppressed an alloimmune response by rendering dendritic cells tolerogenic through interaction with $CD4^+$ T cells (51). Interestingly, alterations in $CD8^+CD28^-$ lymphocytes have been described in autoimmune diseases (46, 52).

Another interesting possible mechanism for immune suppression may be due to the fact that $CD8^+$ lymphocytes that have undergone multiple rounds of cell division express inhibitory NK cell receptors (iNKR) (53). Increased expression of iNKR has been shown on the $CD8^+CD57^+$ lymphocyte (54, 55). Increased concentrations of iNKR have been found on lymphocytes in HIV and may contribute to ineffective CTL activity (56). The exact function of these receptors on lymphocytes is unknown, but they may inhibit the CTL response and down regulate Activation-Induced-Cell-Death (AICD) in memory $CD8^+$ lymphocytes (57, 58).

6.2.Formation of autoimmunity from an ineffective CTL pool

After BMT, there appears to be a "switch" that occurs in acute to chronic GVHD, which is likely similar to the shift between acute and chronic rejection after solid organ transplantation. Several lines of research point to a switch in the immune phenotype – from a TH1 to TH2 predominant disease, from a $CD8^+$ to $CD4^+$ infiltrate, and from a condition that clinically resembles alloimmunity to a

condition that resembles autoimmunity. Classic murine models of GVHD use unirradiated parental into F1 semi-allogeneic transplants. Transplanting one parental strain gives a condition that resembles acute GVHD (C57BL/6 (H-2^b)→ B6D2F1 (H-$2^{b,d}$)) while transplanting the other parental strain gives a disease resembling chronic GVHD (DBA/2J (H-2^d)→ B6D2F1 (H-$2^{b,d}$)) (59, 60). The distinction between acute and chronic GVHD is mediated by classic donor anti-host CD8+ CTL activity (61). Acute GVHD models show an expansion of donor $CD8^+$ CTL whereas chronic GVHD models show a reduction of donor anti-host CTL activity. The importance of $CD8^+$ CTL in the prevention of chronic GVHD has been further studied in models using cytokines (IL-12 and IL-18) known to potentiate the activity of $CD8^+$ CTL and induce immune responses toward TH1. These models which utilized IL-12 to treat mice with chronic GVHD, resulted in several manifestations of acute GVHD caused by induction of host specific $CD8^+$ CTL (62). However, IL-12 was unable to reverse established chronic GVHD. Another study used IL-18 treatment of mice with chronic GVHD to prevent and treat the formation of chronic GVHD through the induction of donor anti-host $CD8^+$ CTL (63). These studies highlight the importance of $CD8^+$ cytotoxic T lymphocytes in the development of acute GVHD, and suggest that donor anti-host $CD8^+$ CTL prevent the formation of chronic GVHD. It is intriguing to think that after transplantation, the formation of exhausted or senescent CTL may actually control acute GVHD or rejection by eliminating the allogeneic CTL. In certain circumstances it may also allow the formation of chronic autoimmune disease by the inability of dysfunctional CTL to remove autoreactive cells, or a change in the overall immune phenotype.

6.3. Increased susceptibility to infection

Some have hypothesized that the clinical manifestations of LGL are due to alterations in apoptosis or other functions of $CD8^+CD57^+$ lymphocytes (37). A subset of patients with Felty's syndrome (RA, splenomegaly, and neutropenia) had suppression of neutrophil precursors in the presence of $CD8^+CD57^+$ cells (64). Serum from patients with LGL had high levels of FasL and triggered apoptosis in normal neutrophils (65) leading to the thought that increased $CD8^+CD57^+$ cells expressing high levels of FasL may lead to the neutropenia and immunosuppression seen in LGL (37). Others have suggested persistent antigenic challenge to the expanded T cell clone may also contribute to the pathogenesis of disease in LGL (66). These authors have hypothesized that challenge of this CTL population lead to an aggressive immune response and manifestations of LGL may be a magnified version of the transient neutropenia and immunosuppression seen after a normal viral infection.

7. ALTERATIONS IN APOPTOSIS AND PROLIFERATION

Senescent, suppressive, antigen specific cells accumulate in certain conditions. A main property of a senescent cell is the lack of proliferative ability. If proliferation can not explain their expansion, perhaps alterations in apoptosis may account for their increased numbers. Senescent cells have been shown to display resistance to apoptosis (67, 68).

Normal lymphocyte apoptosis can occur by 2 general pathways (69). AICD is caused by restimulation of the TCR in expanded activated T cells without appropriate co-stimulation. A primary mediator of this pathway is the CD95/Fas receptor (70), although other members of the TNF receptor family can also trigger this apoptosis including TNFR1 and TRAIL receptors (69). These cell surface receptors activate the caspase cascade leading to cell death. The other pathway is by "starvation" or absence of the appropriate survival signals, and is termed "Activated Cell-Autonomous Death" (ACAD). This pathway works through variations in the balance of pro-apoptotic (BIM) and anti-apoptotic (Bcl-2 and Bcl-X_L) mitochondrial proteins (69). Many studies have shown that BIM is critical for down regulation of $CD8^+$ lymphocytes after chronic viral infection (71, 72). This pathway also results in activation of the caspase cascade. In addition to these two pathways being responsible for clearing activated T cells after an immune response, there are likely other pathways that are caspase independent (73).

We found that $CD8^+CD57^+$ lymphocytes expressed more Fas and Fas ligand on their cell surface and were more sensitive to spontaneous apoptosis *in vitro*, through the caspase-3 pathway, than their $CD8^+CD57^-$ counterparts in both HIV and in normal subjects (15). However, with advanced HIV infection, at a time when the total number of $CD8^+CD57^+$ cells are increasing, the percentage of $CD57^+$ cells undergoing apoptosis declines. This suggests that a dysregulation of apoptosis occurs as disease progresses and perhaps a "relative" failure of normal $CD57^+$ apoptosis. $CD57^+$ lymphocytes from HIV subjects have been shown to be extremely sensitive to mitogen induced AICD and it has been hypothesized that $CD57^+$ cells are constantly being produced in conditions of antigenic stimulation and then rapidly die (5).

These results are in agreement with others that have shown $CD8^+CD57^+$ cells have increased tendency for apoptosis. $CD57^+$ cells have been shown to express less survivin (an anti-apoptotic molecule) (74). Several studies have shown that CD3 triggered apoptosis is increased in $CD8^+CD57^+$ cells and functions by the caspase-3 pathway (35, 74, 75). In one study TCR stimulation was not as potent an apoptotic signal as CD3 (74). Another study showed anti-CD2 antibody triggered apoptosis in $CD8^+CD57^+$ cells (76).

Alterations in apoptosis are used to explain the expansion of the $CD8^+CD57^+$ population in LGL (37). Studies using whole peripheral blood mononuclear cells (PBMC) from patients with LGL have found cells resistant to Fas stimulated apoptosis despite increased levels of Fas and FasL expression (77). The PI3K and STAT3 (Signal Transducers and Activators of Transcription) pathway have been found to be upregulated in $CD8^+$ cells and PBMC from patients with LGL and play a role in this Fas resistance (78, 79). Long term (more than 8 weeks) antigen activated cells from normal donors, *in vitro*, developed

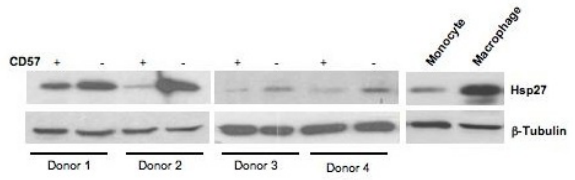

Figure 1. Differential expression of Hsp27 in purified CD8$^+$CD57$^+$, CD8$^+$CD57$^-$, monocytes, and macrophages by immunoblotting with anti-Hsp27-antibodies (4 representative donors). For lymphocytes twice the amount of lysates were loaded as compared with monocyte and macrophage lysates. The same membranes were immunoblotted with anti-β-tubulin antibodies.

features of effector memory cells (loss of CD28, CD62L and CCR7) as well as Fas and AICD resistance. In this study PI3K inhibition also restored sensitivity to Fas stimulation (80).

Interestingly, in MM, a decrease in Fas has been reported, using mean fluorescent intensity (MFI), as compared with other studies of apoptosis and CD57 (30). It has been suggested that dysregulation of apoptosis may explain T cell dysfunction in MM (29). However, contrary to this model, in patients with hematologic malignancies, CD8$^+$CD57$^+$ cells had increased tendencies to undergo apoptosis in culture (32).

There are many pro and anti apoptotic markers and pathways. One interesting regulator is the heat shock protein (Hsp) family. Expression of the small Hsp27 is protective against cellular stress. It has been shown to regulate apoptosis through protein interactions (81). It can interact with pro-caspase-3 to inhibit caspase-3 activation (82, 83). Recently, we showed that Hsp27 plays a key role in regulating monocyte/macrophage lifespan through direct interactions with the aminoterminal domain of caspase-3 (84). Others have shown that Hsp27 can inhibit the Fas apoptotic pathway (85) and this can be independent of the caspase system by blocking the interaction of Daxx with Fas (86). We have found that CD8$^+$ lymphocytes express much lower levels of Hsp27 than monocytes and that expression of Hsp27 is consistently lower in CD8$^+$CD57$^+$ than CD8$^+$CD57$^-$ lymphocytes from PBMC obtained from buffy coats (Figure 1). An age related decrease in expression of Hsp27 has been noted by one group (87). It is intriguing to hypothesize that Hsp27 may be downregulated in effector lymphocytes as they age and may participate in their increased susceptibility to AICD. It will be equally intriguing to examine if changes in levels of Hsp27 after long term antigen stimulation *in vitro* or conditions with chronic antigenic stimulation *in vivo* can mediate changes in this lymphocyte population's sensitivity to apoptotic stimuli and AICD.

Interestingly, the programmed death receptor 1 (PD-1) has been found to be upregulated on CD8$^+$ lymphocytes in conditions with chronic, poorly controlled viral stimulation. PD-1 is found in a remarkably high number of "exhausted" CD8$^+$ cells and blocking the PD-1 pathway can restore proliferative ability to antigen specific CD8$^+$ cells in a murine lymphocytic choriomeningitis virus (88), in HIV infection (89, 90), and in hepatitis C infection (91). HIV specific CTL expressing PD-1 had increased sensitivity to spontaneous apoptosis and CD95/Fas mediated apoptosis (92). PD-1 may be one explanation for the proliferative defect and increased apoptosis seen in CD8$^+$ lymphocytes during chronic antigenic stimulation. PD-1 also appears to be crucially important for the development of CD8$^+$ lymphocyte tolerance (93). Mice deficient in PD-1 develop a lupus like disease (94) and autoimmune dilated cardiomyopathy (95), and others have shown the PD-1 pathway important in autoimmune diabetes in mice (96). While CD57$^+$ and PD-1 co-expression is higher in HCV (97), in HIV it appears the CD8$^+$ cells expressing high levels of PD-1 have less or no difference in CD57$^+$ expression (89, 92).

Another interesting change in the survival pathways in CD57$^+$ expressing cells may be due to expression of inhibitory Natural Killer Cell Receptors (iNKR). There are many members of the NK receptor family. Some are activating and some are inhibitory. CD94/NKG2A is an inhibitory heterodimer which binds the HLA-E ligand in humans or Qa-1 in mice. These receptors are upregulated on CD57$^+$ cells (41), and have been shown to play a role in cell survival by blocking apoptosis (98). The expression of iNKR on CD8$^+$ cells has been associated with decreased susceptibility to apoptosis and elevated levels of the anti-apoptotic molecule Bcl-2 (B-cell CLL/lymphoma 2) (57, 99). Cell survival through iNKR may be regulated through binding to the PI3K/AKT pathway (100). CD94 expression is upregulated by IL-15 (101).

Cytokines play an important role in cell survival, proliferation and apoptosis. Interleukin 15 (IL-15) is a critical regulator for the proliferation of memory CD8$^+$ lymphocytes (102). IL-15 has been shown to be important for CD8$^+$ cell survival in the contraction phase after *Listeria monocytogenes* infection in mice, and that together with IL-7 may regulate the development of memory CD8$^+$ cells. Other studies have also shown that IL-7 and IL-15 may play a role in homeostatic proliferation of naïve CD8$^+$ cells through increased proliferation and decreased apoptosis (103). IL-15 induces the anti-apoptotic Bcl-2 expression in CD8$^+$ lymphocytes and is one mechanism by which it decreases apoptosis and prolongs cell survival (102-105). One study in HIV showed IL-15 decreased the susceptibility of lung BAL cells to spontaneous and triggered apoptosis (106). However, IL-15 causes little or no increase in proliferation in CD8$^+$CD57$^+$ lymphocytes as compared with CD8$^+$CD57$^-$ cells in HIV, indicating an insensitivity to this cytokine (5, 41). This is consistent with another study that showed while IL-7 and IL-15 are important for homeostatic proliferation of CD8$^+$ cells after acute infection; in chronic infections virus specific CD8$^+$ lymphocytes are maintained by viral peptides and not IL-15 (20). Further investigation into the role of IL-15 on CD8$^+$CD57$^+$ cells is needed to determine its role in apoptosis.

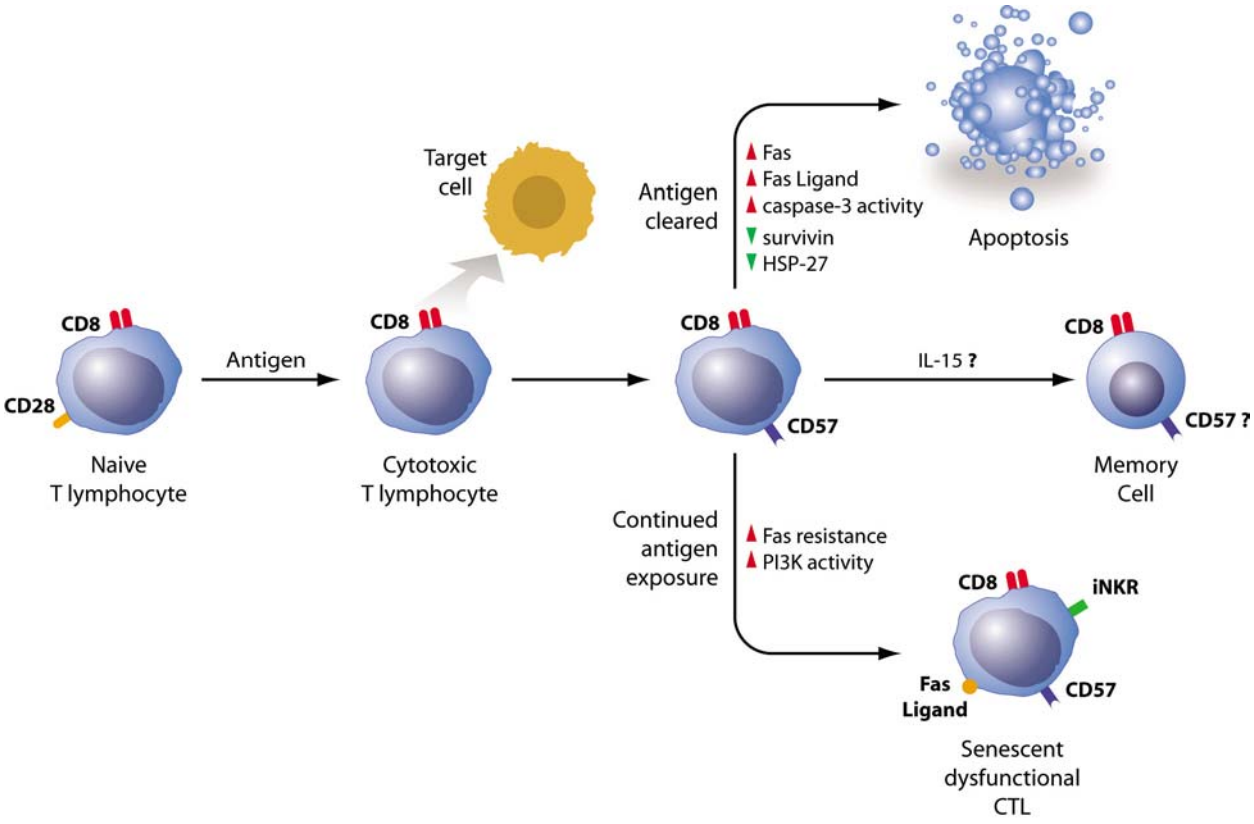

Figure 2. A proposed mechanism for cytotoxic T lymphocyte maturation and the relationship to CD57 expression. Naïve CD8 cells express CD28, as they mature and become CTL they lose CD28 expression, but they gain CD57. Many studies have shown $CD57^+$ cells are sensitive to apoptosis and this correlates well with the normal down regulation and contraction of a $CD8^+$ immune response. Lymphocytes that express $CD57^+$ in normal conditions have many features, which may predispose them to apoptosis including increased Fas, FasL, and caspase-3 expression, as well as decreased survivin and Hsp27. A small portion of lymphocytes develop into memory cells and this may be dependent on IL-15 exposure. Whether $CD8^+$ memory lymphocytes express CD57 is unknown. In conditions with continued antigenic exposures, dysregulation of normal lymphocyte apoptosis may contribute to the expansion of these senescent $CD8^+CD57^+$ expressing lymphocytes.

At first glance some of these studies appear contradictory; however, taken together, they may support the hypothesis that $CD8^+$ cells are destined to undergo AICD after antigenic expansion. A subset of these cells become resistant to CD95/Fas mediated apoptosis and develop into a memory population. However, in certain disease states with chronic antigenic stimulation, dysregulation of either apoptosis or survival pathways lead to sometimes dramatic expansions of this effector/memory phenotype (Figure 2).

8. CONCLUSION

In summary, $CD8^+$ cells expressing $CD57^+$ antigen seem to play a role in immunoregulation through various mechanisms including: dysregulation of apoptosis, the secretion of a soluble inhibitor of cytolytic activity, the expression of FasL, the upregulation of PD-1 which may lead to tolerance or contribute to their proliferative inability, and the increased expression of inhibitory NK receptors. The mechanism of immunoregulation may occur through different pathways and have vastly different outcomes depending on the condition. In chronic uncontrolled viral infection, or in multiple myeloma (if the $CD8^+CD57^+$ cell is a tumor specific CTL) the immunodeficiency may be the result of CTL becoming exhausted and ineffective. Restoring their function, increasing proliferation, and decreasing apoptosis may help to combat the immune deficiency. In transplantation or in RA, the accumulation of these exhausted CTL may contribute to tolerance and downregulation of the alloimmune response, and reversing their senescent state may have deleterious effects. There is a complex relationship between anergy, apoptosis, and autoimmunity. Alterations in apoptosis may be responsible for the clonal expansion of senescent $CD8^+$ lymphocytes and understanding $CD8^+$ lymphocyte maturation and death is important in chronic viral infections, cancer, and autoimmunity.

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Abbreviations: AICD: Activation induced cell death, TCR: T cell receptor, GVHD: graft versus host disease, HIV: human immunodeficiency virus, CMV: cytomegalovirus, PD-1: programmed death receptor 1, NK: natural killer, IFN: interferon, BMT: bone marrow transplantation, CTL: cytotoxic T lymphocyte, LGL: large granular leukemia, RA: rheumatoid arthritis, FasL: fas ligand, Hsp: heat shock protein, HCV: hepatitis C virus, iNKR: inhibitory NK cell receptors, PBMC: peripheral blood mononuclear cells, MM: multiple myeloma, ACAD: activated cell-autonomous death, TCR: T cell receptor, MFI: mean fluorescent intensity.

Key Words: CD57, HNK-1, Lymphocyte, Memory Cell, Apoptosis, Senescence, Hsp27, Caspases, Bone Marrow Transplant, Review

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