HHS Public Access

Author manuscript

Curr Opin Chem Eng. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Curr Opin Chem Eng. 2018 March ; 19: 9–20. doi:10.1016/j.coche.2017.11.006.

CD8+ T Cells and NK Cells: Parallel and Complementary Soldiers of Immunotherapy

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Abstract

$CD8^+$ T cells and NK cells are both cytotoxic effector cells of the immune system, but the recognition, specificity, sensitivity, and memory mechanisms are drastically different. While many of these topics have been extensively studied in $CD8^+$ T cells, very little is known about NK cells. Current cancer immunotherapies mainly focus on $CD8^+$ T cells, but have many issues of toxicity and efficacy. Given the heterogeneous nature of cancer, personalized cancer immunotherapy that integrates the power of both $CD8^+$ T cells in adaptive immunity and NK cells in innate immunity might be the future direction, along with precision targeting and effective delivery of tumor-specific, memory $CD8^+$ T cells and NK cells.

Graphical Abstract

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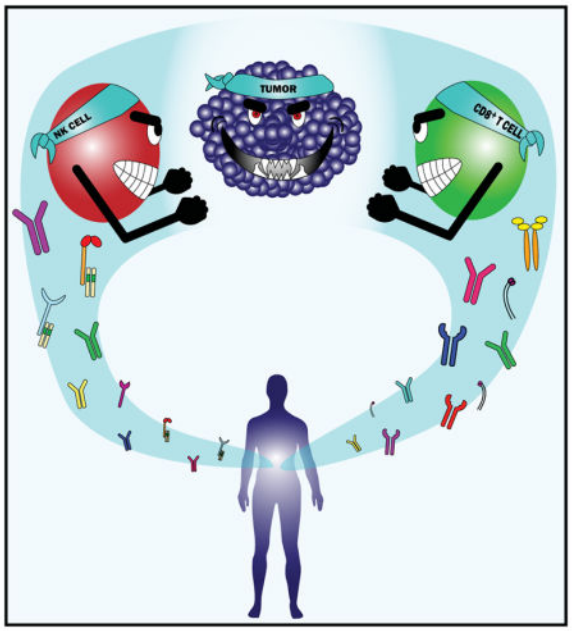
Conflicts of interest

The authors declare no conflict of interest.



Introduction

With cancer incidence rates at an all-time high[1] and immunology research booming, the prospect of cancer immunotherapies is becoming a major topic of interest in biological and chemical engineering fields. The most widely studied cell type for cellular immunotherapy is the T cell, a central component of adaptive immunity. The advent of T-cell checkpoint inhibitors, such as anti-PD-1 and anti-CTLA4 therapies [2], and chimeric antigen receptor (CAR) T-cells, such as the recently FDA-approved CD19 CAR-T cell [3], has shifted the paradigm of cancer treatment to widely applicable therapy options. However, these therapeutic strategies may precipitate autoreactive T cell responses: checkpoint inhibitors override peripheral tolerance mechanisms, and CARs cross-react with healthy tissues. Many clinical studies have unfortunately fallen short of expectations; the nature of cancer causes it to generate large heterogeneities among patients and to mutate away from its immune attackers, resulting in non-response or relapse [4–6]. This has lead researchers to investigate the use of natural killer (NK) cells, another cytotoxic immune cell, for cancer therapy. In contrast to the single dominant T cell receptor (TCR) on T cells, NK cells have a wide array of activating and inhibitory receptors that act as a balance to determine functional activity, presenting an equally large collection of potential targets. Some of these receptors, such as Ly49C and KIR2DL1, recognize a “missing-self” status: the expression of appropriate number of major histocompatibility complex class I (MHC-1) molecules represents normal self-cells and elicits an inhibitory signal to NK cells. Downregulation of MHC-1 is often evolved in tumor cells as a mechanism of immune-evasion from T cells, which require MHC-1 signaling for activation, and therefore NK cell intervention could be used as a potent relapse therapy [7]. NK cells are now considered a bridge between innate and adaptive immunity, as it was discovered that NK cells gain memory functional phenotypes after encountering target cells [8–10], similar to T cells. In this review, we will compare and

contrast two cytotoxic cells, $CD8^+$ T cells in adaptive immunity and NK cells in innate immunity, and further discuss recent advances in cancer immunotherapy involving these two cells.

$CD8^+$ T cells versus NK cells in Basic Immunology

Recognition

$CD8^+$ T cells and NK cells have different mechanisms of target recognition and signaling cascades to achieve very similar goals: to kill infected and transformed cells. The antigen recognition by T cells has been extensively studied (Fig. 1A). $CD8^+$ T cells use their T cell antigen receptors (TCRs) to recognize peptide-major histocompatibility complexes (pMHC) presented on the antigen-presenting cell surface [11]. The coreceptor CD8 assists the TCR recognition by binding to the same MHC-I molecule [12,13]. The association of TCR and CD8 with the pMHC triggers the phosphorylation of CD3 immunoreceptor tyrosine-based activation motifs (ITAMs) by Lck, a tyrosine kinase associated with the cytoplasmic region of CD8 [14]. The phosphorylated CD3 results in the recruitment and activation of ZAP-70, which in turn phosphorylates LAT. LAT kinase concatenates with TCR to facilitate signaling during activation [15]. LAT has a quite extensive signalosome, and transmits a myriad of cellular responses, including cytokine release and metabolic adjustments [14]. In addition to the TCR, a T cell has a number of accessory molecules including co-stimulatory and co-inhibitory receptors (Fig. 2A) [16]. These receptors together control the activation, differentiation and function of the T cell.

NK cell recognition is much less understood (Fig. 1B). In stark contrast to T cells, there is no single dominant receptor to mediate NK cell recognition. Rather, NK cells express an array of innate activating and inhibitory receptors (Fig. 2B) to sense their environment and respond to alterations caused by infections, stress and transformation [17]. Although it is generally believed that the balance between activating and inhibitory receptor engagements determines the activation of an NK cell, the molecular mechanism of NK cell recognition remains unclear and different models have been proposed [18–22]. The most well characterized model is the ‘missing-self’ mechanism, proposed by Klas Kärre in 1985 [7,23,24]. This mechanism describes NK cells recognition of the self-identifying MHC-I molecules by Ly49 family receptors to inhibit NK cell activation in mice. In primates, Ly49 is replaced by killer-cell immunoglobulin-like receptors (KIRs), which bind to HLA molecules to transduce inhibitory signal. The reduction or loss of MHC or HLA expression may lead to NK cell activation in a missing-self manner. In another recognition mechanism, antibody-dependent cellular cytotoxicity (ADCC), NK cell receptors FcγRIIIA and/or FcγRIIIC bind to the Fc portions of antibodies bound to a target cell, transduce an activating signals, and lead to NK cell activation [25]. Finally, the effector functions of NK cells can be enhanced by cytokines [17,26–29], and certain cytokine stimulations alone are sufficient to activate NK cells [30]. Other receptors involved in NK cell recognition include the NKG2 family, thought to regulate activity, and natural cytotoxicity receptors (NCRs), which are expressed in both humans and mice and may be regulated by cytokines. Therefore, while, many models of NK cell recognition have been proposed, these mechanisms most likely

function synchronously, and more comprehensive research is needed to elucidate the recognition mechanism of NK cells.

Specificity, Sensitivity, and Speed

Antigen-specific targeting is essential for adaptive immunity. TCRs can discriminate closely related peptides, and even one amino acid change in the peptide can lead to distinct T cell responses [31–33]. T cells are incredibly sensitive in antigen detection – even a single pMHC is sufficient to trigger T cell calcium signaling and three pMHCs can lead to $CD8^+$ T cells killing [34–36]. There are many models of T cell activation to explain the high specificity and sensitivity of T cells [37,38]. Part of this specificity and sensitivity arises from the binding structures of the pMHC-TCR interactions itself and the resulting kinetics, forces, and signals. The structure and signaling of the TCR and accessory molecules is shown in Figure 1A. It is not entirely clear why T cells have such a high specificity and sensitivity. In our opinion, the binding of a TCR to the pMHC may lead to a conformational change within the TCR. The conformational change enables the TCR to precisely decipher subtle structural differences among peptides and proportionally propagate the recognition signals to CD3 cytoplasmic domains via mechanical force, ensuring the extraordinary specificity [39–46]. Meanwhile, multiple TCRs serially engage with a single pMHC, which allows accumulation of enough stimulatory signals to reach the threshold of T-cell activation, accounting for the exquisite sensitivity [31,47–50]. However, direct experimental evidences with enough spatiotemporal resolution are needed to test such a hypothesis, and other mechanisms may be involved [37].

Like other aspects of NK cells, the specificity and sensitivity of NK cells are much less studied than those of T cells. The main theory for NK cell specificity is the sheer number of receptors on the NK cell surface, as NK cells transmit a range of responses rather than a simple dichotomy for specific recognition. This is hypothesized to be due to the integration of multiple activating and inhibitory signals received from target cells (Fig. 1B) [19,20]. In addition, NK cells are known to react to the environment; if a signal persists, NK cells will downregulate the response for that interaction. Thus far, no studies are able to determine the exact threshold of activation versus inhibition when an NK cell comes in contact with its target cell. For example, if a virus-infected cell is down-regulating its MHC I expression rather than ablating it, this is sufficient to activate an NK cell. How this changes if other inhibitory or activating ligands are also present has not yet been deciphered, nor how this response differs between NK cell subtypes. Quantitative analysis of NK cell specificity and sensitivity, though important, has not been established.

$CD8^+$ T cells and NK cells response rates are also quite different. As one of the hallmarks of innate immunity, innate immune cells are the first responders to sites of infection. Therefore, NK cells are much quicker to establish a robust response than $CD8^+$ T cells[8].

This is also exemplified by the NK cell ability to recruit T cells and other adaptive responders to sites of infection[51].

Memory

Once effector T cells and NK cells come in contact with a target cell that elicits a response, alterations must be made to this signal such that a secondary encounter with the same target cell may elicit a faster response [52]. This memory response is an evolutionary advantage, and works in different ways between T cells and NK cells.

Following exposure to target cells, $CD8^+$ T cells undergo massive clonal expansion, followed by a contraction of about 95% [53]. The 5% of remaining $CD8^+$ T cells then become memory T cells. Reinfection causes these memory cells to proliferate more rapidly than the initial naïve T cells [54]. Memory T cells are known to secrete more cytokines than effector T cells, and they also display different surface markers [52,55]. Memory T cells are further divided into central memory and effector memory based on the presence or absence of the CCR7 marker; $CCR7^-$ T cells are effector memory T cells, which have receptors to migrate to inflamed tissues and display immediate effector capabilities, whereas $CCR7^+$ T cells are central memory T cells which instead stimulate dendritic cells before differentiating into $CCR7^-$ cells [56]. These subsets are further divided based on specific surface markers [57]. There are also evidences suggesting that cytokines and chemokines are required for the reactivation of memory cells, which may be secreted by supporting innate cells [58].

NK cells had been previously classified as innate immunity due to the quick response time and lack of somatic rearrangement of receptor genes, but they have since been found to possess certain qualities of adaptive immunity [8,29,59–64]. In a seminal study by the Lanier group, it was found that NK cells undergo phases of expansion, contraction, and retention similar to that of T cells [59]. This study also found that the retained cells at the end of the contraction resulted in a robust response following a secondary exposure to infection, indicating that these cells represent NK cell memory. Mechanistically, NK cell memory has been studied mostly in the murine cytomegalovirus (MCMV) model. One of these studies found that pro-inflammatory cytokines, like IL-12, IL-18, type I IFNs, and IFN-γ, are produced upon acute infection [65]. NK cells will then undergo a proliferation phase, although it is unclear whether this phase results in a heterogeneous population [61]. The contraction phase then results in long-lasting memory NK cells that have a profound response following a secondary encounter. It is not entirely clear whether NK cell memory is antigen-specific, though Lanier group has elegantly shown that NK cells can generate antigen-specific memory using the MCMV mouse model [59]. In addition, significant data have been collected suggesting a critical role of cytokines in the generation of memory cells [62]. Studies have shown that even cytokine activated NK cells can generate memory cells that remember polarizing cytokine signals [18]. However, further studies in real diseases such as cancer, as well as in humans, are needed to fully understand NK cell memory.

$CD8^+$ T cells versus NK cells in Cancer Immunotherapies

Current Immunotherapies

$CD8^+$ T cells play a critical role in current cancer immunotherapies (Table 1). For example, as tumors evolve, some cancer cells upregulate the expression of PD-L1, interacting with PD-1 on $CD8^+$ T cells, suppressing T cell function and proliferation.

Checkpoint inhibitor anti-PD-1/PD-L1 therapy blocks this interaction, reinvigorating the killing function of $CD8^+$ T cells [66–72]. Another checkpoint inhibitor, anti-CTLA4 antibody, prevents tumor induced T cell anergy [70,73–76]. Cytokine therapy, such as treatment with IL-2 or IFN-α, is another $CD8^+$ T cell dependent treatment, which enhances local T cell activity [18,26,77,78]. Studies showed a positive correlation between the amount of $CD8^+$ tumor infiltrating lymphocytes and progression-free survival with immunotherapy [2,66,68,69,72–74,79–87]. CAR-T cells utilize the cytotoxicity of $CD8^+$ T cells to eradicate cancer [3–5,88]. CARs incorporate an extracellular programmable antigen-specific binding region with activating intracellular signaling components, such that recognition of a particular antigen expressed on a tumor cell will lead the killing by the CAR-T cell. CD19 CAR-T cell therapy has achieved gratifying success in hematological malignancies, including a recent FDA approval (FDA website: Kymriah) [3]. Other directions currently being explored are the following: include bi-specific T cell engagers [89,90], modular extracellular sensor architecture (MESA) receptors, and various applications of CRISPR-Cas9 (other $CD8^+$ T cell therapies reviewed in [75]). MESA receptors are tunable surface receptors that contain easily exchangeable ligand binding and transcription factor domains; when bound to the ligand, the receptor cleaves the transcription factor so that it may enter the nucleus and elicit a cellular response [91]. CRISPR-Cas9 is being used to alter $CD8^+$ T cell functions in various ways; for example, it is used to introduce engineered TCRs or CARs into T cells [92].

NK cell cancer immunotherapies are only recently being considered. Data have shown that NK cells have many anti-tumor capabilities [27,93]. Currently, CAR-NK cells are being engineered with the same CD3ζ chain as CAR-T cells, with similar targets (CD19, CD20, or others) via retroviral-based transduction or plasmid electroporation transfection [94]. One of the advantages of developing CAR-NK cells over CAR-T cells is that NK cells actually inhibit graft vs. host disease (GvHD), and therefore may confer greater safety than T cells [94–101]. The Rezvani group showed that NK cells could be harvested from cord blood and developed into CAR-NK cells that can be readily available “off the shelf” rather than individually tailored [98]. In addition, NK cells are present in greater numbers in peripheral blood than T cells are, making them more readily available for harvest for therapy [99]. The main limitation of current CAR-NK strategies is that they are not designed for NK cells; rather, they simply borrow the concepts of CAR-T and only use NK cells as a surrogate of T cells. The true breakthrough in developing effective CAR-NK requires a good understanding of the NK cell recognition mechanism to design genuine NK-based CAR therapies. Antibody- based therapies are being engineered such that the Fc portion can more tightly bind to FcγRIIIA to induce a more robust ADCC activation targeted to tumor cells[25,102,103]. Finally, NK cells have been shown to be involved in the T cell checkpoint inhibitor responses [102,104,105], and the first NK cell checkpoint inhibitors [106–108] and CARs [109] are now in clinical trials.

Challenges in Cancer Immunotherapy

One of the major challenges of current immunotherapies is that neither checkpoint inhibitors nor CAR T-cells are tumor-specific; checkpoint inhibitors will have a full body response and can lead to autoimmune disease, and CARs have on-target but off-tumor effects. For

example, anti-PD-1 and anti-CTLA-4 antibodies universally target all T cells expressing PD-1 and CTLA-4, causing off-target effects and may lead to the development of autoimmune diseases. The response rate of checkpoint inhibitors is also low at less than 20%, which, while this is significant compared to other cancer therapies, is far from ideal [2,110]. Many studies are looking for biomarkers to divide responders from non- responders, but there will still be a large cohort for whom these therapies do not work.

Non-tumor specific targeting is also a significant problem of CAR T cells. For example, CD19 CAR-T cells not only kill malignant B cells but also eliminate healthy B cells, which are essential in antibody generation [111,112]. In addition, CAR-T cell treatment faces the challenges of low T-cell proliferation [113,114], constant tumor mutation [115], and frequent tumor relapse [116,117]. Another major limitation of CAR-T cells is the ineffectiveness to solid tumors [4,118,119], although a few studies show promising outcomes [120–123]. Possible reasons could be the physical barrier and immunosuppressive microenvironment of solid tumors that prevent lymphocyte infiltration and survival. In addition, there are many associated toxicities, including neurological toxicity, cytokine release syndrome, anaphylaxis, and GvHD, which requires T cells to be HLA matched to the patient [4,124,125]. Many CAR-T clinical trials have been terminated due to patient death [4]. Groups are attempting to make a ‘universal’ CAR-T cell that erases the need for such transfer mechanisms, but these still are only targeting a few selected tumor antigens, which the cancer will soon evolve around [126]. Finally, the exact mechanism of action of CAR-T cells is not well understood; it is known that both $CD4^+$ and $CD8^+$ CAR-T cells are required for tumor suppression [126], but not why, and it is also known that CAR-T cells have much higher affinity for their targets and therefore become exhausted much more quickly than endogenous T cells. These mechanisms require more attention to remedy the resulting effects.

Specific challenges for NK cell therapy have yet to be identified, mostly due to the lack of research and application of NK cell based immunotherapies. One of the known challenges is the low transfection efficiency and the variable expansion process of NK cells compared to T cells [127].

Future Cancer Immunotherapy

From a science perspective, a comprehensive and systematic understanding of the complex immune system and tumor microenvironment must be acquired, as effective and precise therapies will rely on the identification of the exact mechanisms in each cancer type, as well as the unique characteristics of individual patients. While some mechanisms have been elucidated in $CD8^+$ T cells, much work remains to be done in NK cells [22,93,128–131]. In our opinion, personalized cancer immunotherapy is the future, considering each tumor and each patient is different. However, personalized medicine is currently both incredibly expensive and time consuming. Future biotechnologies and visualization techniques will hopefully allow for quick, inexpensive, and comprehensive analysis of patient tumors to better screen for potential candidates, identify the targetable mutations, and generate personalized treatments; we need to know who will benefit from these treatments, know

which treatments will be most effective for each patient, and be able to synthesize that personalized treatment accurately, efficiently, and inexpensively.

Clinically fast, effective, economic immunotherapies personalized to each cancer type should be created. Ideally, a theoretical solution could be to engineer a tunable cell to specifically combat tumor evolution. For example, NK cells could be engineered to express a specific ratio of surface receptors such that they specifically target a tumor. Alternatively, a CAR or TCR-engineered T cell could be created such that the antigen-recognition piece could be easily, quickly, and inexpensively swapped out to keep up with the evolving tumor as a personalized medicine technique. As technologies advance synchronously with our improving understanding, these feats may be monetarily feasible in the future. Another direction that should be taken is the combination of these therapies. While results are largely unimpressive for each therapy individually, it could be more effective to combine therapies in a manner reminiscent of the drug cocktails used to control HIV [132]. By incorporating aspects of both the innate and adaptive immune systems in a precisely target-specific manner, for example, combinatorial T cell and NK cell treatments could eradicate the cancer by beating the tumor evolution.

Conclusions

One central question in cancer immunology is why both $CD8^+$ T cells in adaptive immunity and NK cells in innate immunity fail to recognize and attack the forming tumors. A theory for $CD8^+$ T cells is that the $CD4^+$ regulatory T cells have heightened activity in the hypoxic environment of the tumor, leading to increased suppression of the $CD8^+$ cytolytic activity [133]. The discontinuity theory [134] states that while NK cells recognize the initial change in cell identity of tumor cells, the prolonged exposure (perseverance of the tumor) will cause desensitization and tolerance [135]. Additionally, it was recently shown that tumors might be converting NK effector cells into type 1 innate lymphoid cells [136]. Regardless, T- cell based immunotherapies such as checkpoint inhibitors have shown preliminary success in cancer treatments [68,74,78,82,90]. However, relapse from these therapies is generally the result of tumor down-regulation of MHCs, which could be combatted with a subsequent NK cell therapy. In addition, further understanding of memory development for both cell types may potentiate the ability to create a life-long single-dose treatment that could remain in cellular memory for an extended period of time. The development NK therapies could therefore have huge implications both as independent therapies and as a relapse treatment following T cell therapies. Before these therapies can be developed, however, it is imperative that we discover the precise molecular mechanisms of recognition, activation, specificity, effector function, and memory of these cells, as well as characterize the complex interactions among immune cells, in order to truly progress the field of cancer immunotherapy [51,137,138]. In conclusion, $CD8^+$ T cells and NK cells share many similarities in overall functions and cytolytic activities, but also have many differences that could be utilized advantageously in the treatment of cancer.

Acknowledgments

This work was supported by NIH grants R00AI106941 and R21AI120010, NSF Career Award 1653782, and Young Investigator Award from the Cancer Research Foundation (To J.H.). J.R. is supported by NCI T32 CA009594 at the

University of Chicago through the Committee on Cancer Biology. We would also like to acknowledge the advice and guidance from Dr. Barbara Kee (University of Chicago) for her NK cell expertise.

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• of special interest

•• of outstanding interest

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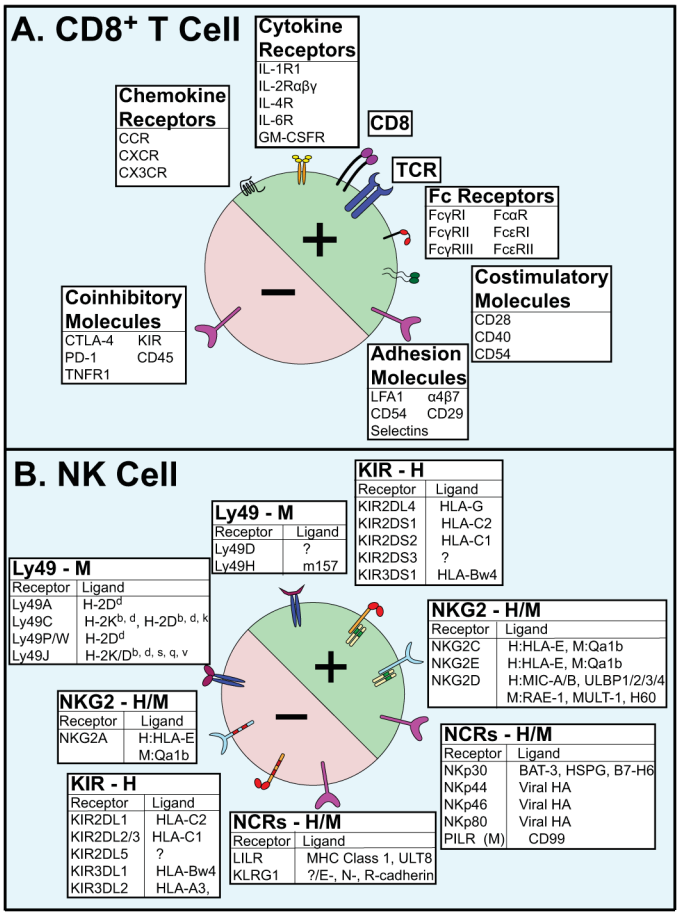

Figure 1. (A). T Cell Recognition and Signaling

The TCR and CD8 bind a pMHC presented on the antigen-presenting cell surface, causing the phosphorylation of the ITAMs of the CD3 (γ, δ, ε and ζ) chains by Lck, a tyrosine kinase associated with the coreceptor CD8. The tyrosine kinase ZAP-70 is then recruited to CD3 by binding to the phosphorylated ITAMs, leading to the phosphorylation of ZAP-70 by Lck. The activated ZAP-70 then phosphorylates LAT. Activation of LAT leads to extensive cellular adjustments, including proliferation, metabolic changes, cytolytic activity, cytokine release, and others. **(B). NK Cell Recognition and Signaling.** NK cell surface activating and inhibitory receptor-ligand interactions mediate the recognition and signaling of an NK cell. Some receptors present on each NK cell are stochastic, whereas others such as NKp46 and NKG2D are constitutive. The combinatorial threshold that must be reached to activate or inactivate the NK cell is largely unknown.

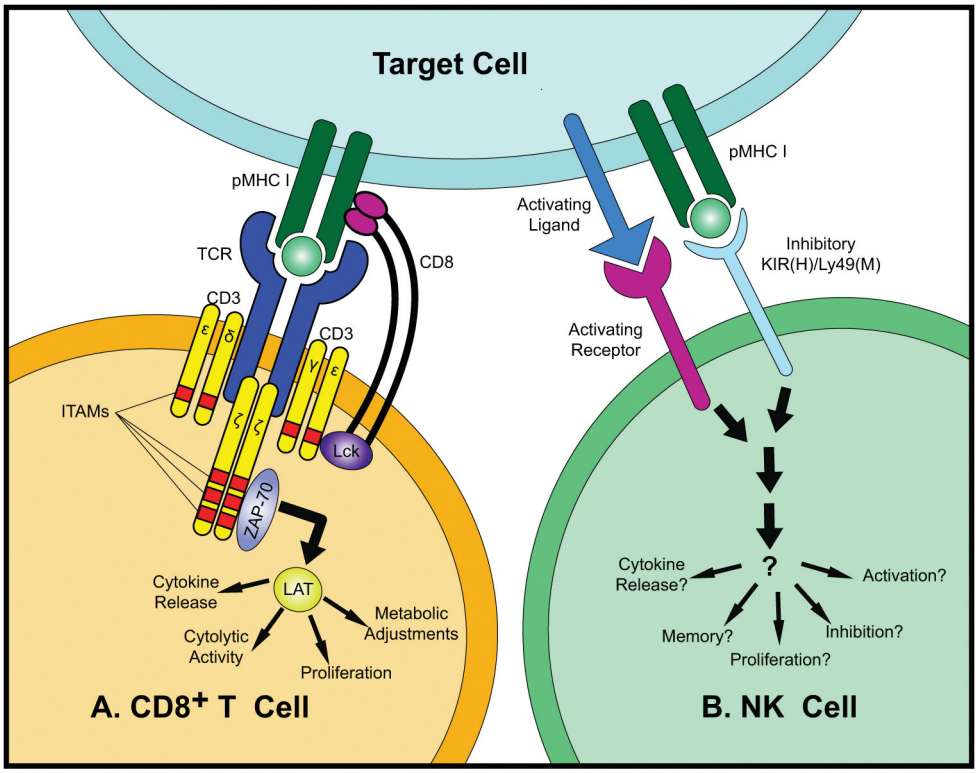

Figure 2. (A). Activating (+) and inhibitory (−) Cell Surface Molecules of CD8$^+$ T Cells

The TCR is responsible for antigen recognition. CD8 is a co-receptor to aid TCR antigen recognition. Fc Receptors (FcRs) are so named for being glycoproteins that bind the constant (Fc) region of immunoglobulins and transducing a signal. The Greek nomenclature denotes the class of immunoglobulin (α, γ, and ε,). Costimulatory and coinhibitory molecules are accessory molecules that enhance or diminish, respectively, the signal of the TCR. Adhesion molecules assist in bringing the target cell into tight contact with the CD8$^+$ T cell. Chemokine receptors are G-protein coupled receptors (GPCRs) involved in chemotactic pathways such as migration and adhesion. These receptors are so named based on how many non-conserved residues separate the binding cysteines: CCR have two adjacent cysteines, whereas CX3CR have three residues between the two cysteines. Many of the receptors indicated here denote an entire family (e.g. CCR represents CCR1-8, differentially expressed on CD8$^+$ subsets); all of these receptors have multiple possible ligands. Abbreviations: CD (Cluster of Differentiation); IL-_R (Interleukin _ Receptor); LFA (Leukocyte Function-Associated Antigen); CTLA (Cytotoxic T-Lymphocyte-Associated); KIR (Killer Immunoglobulin-like Receptor); PD (Programmed Death); TNFR (Tumor Necrosis Factor Receptor). **(B). Activating (+) and Inhibitory (−) Cell Surface Molecules of NK Cells.** NK cells express an array of activating and inhibitory receptors for recognition. Ly49 and KIR receptors are hypothesized to be a result of convergent evolution due to the presence of immunoreceptor tyrosine-based activation/inhibitor motifs (ITAMs/ITIMs, respectively). The KIR ligands are particular HLA molecules only expressed on distressed cells. Abbreviations: H (Human); M (Murine); GM-CSFR (Granulocyte Macrophage Colony Stimulating Factor Receptor); HLA (Human Leukocyte Antigen); MIC

(MHC Class I Chain- related); HA (Hemagluttinin); PILR (Paired Ig-like Receptor); LILR (Leukocyte Immunoglobulin-like Receptor); KLRG1 (Killer Cell Lectin-like Receptor G1).

Table 1

Current Cancer Immunotherapies for CD8$^+$ T Cells and NK Cells

Abbreviations: NSCLC (Non-Small Cell Lung Cancer), SCLC (Small Cell Lung Cancer), RCC (Renal Cell Carcinoma), HNSCC (Head and Neck Squamous Cell Carcinoma), MCC (Merkel Cell Carcinoma), CLL (Chronic Lymphoblastic Leukemia), ALL (Acute Lymphoblastic Leukemia), AML (Acute Myeloid Lymphoma). [5,66,73,78,91,98,106,107,109,126,139–151].

CD8+ Cell				**NK Cell**			
	Cancer Type Targeted	**Development Stage**	**Ref.**		**Cancer Type Targeted**	**Development Stage**	**Ref.**
Checkpoint Inhibitor				**Checkpoint Inhibitor**			
Anti-PD-1				Anti-KIR2D			
Nivulumab	Melanoma, NSCLC, RCC	FDA-Approved	Sgambato 2016	IPH2101 mAb	Myeloma	Pre-Clinical Research	Carlsten 2016
Permbrolizumab	NSCLC, HNSCC, cHL	FDA-Approved	Sgambato 2016	Others	Various	Phase I/II	Muntasell
Others	Various	Under Development	Kyi 2016	Anti-NKG2D		2017	
Anti-PD-L1				Monalizumab	CLL, HNSCC		
Avelumab	MCC	FDA-Approved	Kaufman 2016	Others	Various	Phase I/II	McWiliams
Atezolizumab	NSCLC	FDA-Approved	Fehrenbacher 2016	Anti-KIR		2016 Under Development	Muntasell
Others	Various	Under Development	Swaika 2015	Lirilumab	AML	2017	
Anti-CTLA-4				Others	Various		
Ipilumumab	Melanoma (NSCLC, SCLC, bladder in trials)	FDA-Approved	Larkin 2015	Anti-CD137		Phase II	Alici 2010
Others	Various	Under Development	Kyi 2016	Various	Various	Under Development	Muntasell 2017
						Phase I/II	Yonezawa 2015
Cytokine Therapy				**Cytokine Therapy**			
IL-2 Agonists	ALL, AML, Melanoma	FDA-Approved	Wu 2013	Same as CD8+ T cells; these therapies affect both cell types			Guillerey 2016
IL-15 Agonists	AML, RCC, Melanoma	Phase III	Pilipow 2015				
CAR				**CAR**			
CD-19				CD-19			
Tisangenleceucel	B-Cell Lymphoma	FDA-Approved	Mueller 2017	Cord Blood Derived	B-Cell Lymphoma	Phase I/II	Liu 2017
Others	B-Cell Lymphoma	Under Development	Frigault 2016	Others	ALL, CLL	Phase I/II	Rezvani 2017
Universal CAR	Multiple	Pre-Clinical Research	Ren 2017	CD33	AML	Phase I/II	Rezvani 2017

CD8+ Cell				NK Cell			
	Cancer Type Targeted	**Development Stage**	**Ref.**		**Cancer Type Targeted**	**Development Stage**	**Ref.**
Other CARs	Various	Pre-Clinical Research	Frigault 2016	Others	Various	Pre-Clinical	Rezvani 2017
BiTEs				**BiTEs**			
Blinatumomab	B-Cell Lymphoma	FDA-Approved	Topp 2015	?			
BCMA/CD3	Multiple Myeloma	Pre-Clinical Research	Hipp 2017				
Others	Various	Under Development	Huehls 2015				
MESA				**MESA**			
Theoretical	Various	Pre-Clinical Research	Daringer 2014	?			

*Question marks denote research yet to be done.

Curr Opin Chem Eng. Author manuscript; available in PMC 2019 March 01.