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T-memory cells against cancer: Remembering the enemy

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ABSTRACT

Background: Recently various types of immunotherapies have made immense progress in combating cancer. Adoptive cell therapy, being one of the most favorable forms of immunotherapy, is rapidly moving from bench to bed.

Main body: Different types of T-memory cells are being used as promising candidates for adoptive cell therapy: T effector memory (T_{EM}) cells which are terminally differentiated memory cells and attain effector function soon after re-stimulation; T central memory (T_{CM}) cells which differentiate into effector T-memory subsets and T-effector cells after antigenic stimulation; and tissue T resident memory (T_{RM}) cells which fight the tumor insult at the peripheral tissues. Recently, a new subtype of T-memory cells, T stem cell memory (T_{SCM}) have been identified as the most favorable candidate for adoptive cell therapy as they exhibit higher persistence, anti-tumor immunity and self-renewal capacity in the tumor-bearing host.

Conclusion: In this review, we briefly describe the concept and types of T-memory cells as well as their role as potential candidates for anti-cancer immunotherapy.

1. Background

1.1. The battlefield

Cancer is a leading cause of death worldwide, having caused 8.8 million deaths globally in 2015 [1]. One major reason for poor prognosis of patients suffering from this disease is immune evasion by cancer cells that dampen the anti-tumor immune response. Studies done in animal models have unraveled various physiological barriers within the tumor microenvironment which result in the avoidance of immune surveillance by cancer cells. Immune evasion by the tumor can be divided into two general categories: (a) induction of tolerance by the cancer cells and (b) development of regulatory/immune suppressive cells within the tumor microenvironment [2]. It has been known for some time now that the tumor microenvironment consists of only about 30% of tumor cells, majority of the rest being various cells of the immune system like T cells, B cells, dendritic cells, NK cells, macrophages, suppressive cells like T-regulatory (Treg) cells and myeloid-derived suppressor cells (MDSCs), etc. [3]. Hence, mobilizing these cells to develop anti-tumor immune responses has been a major focus area of researchers for the last two decades [4]. In the constant battle between tumor and immune cells, immunotherapy has emerged as a novel anti-cancer treatment strategy that largely bypasses the adverse side-effects of conventional therapeutic regimens and causes successful eradication of various types of cancers [5]. As T cells play a major role in the development and maintenance of adaptive immune response, particularly $CD8^+$ cytotoxic T cells which are found in large proportions in the tumor core and invasive margins, they opened up a vast horizon of research, as potent contenders for immunotherapy [6].

1.2. T-memory cells: Trained soldiers ready for combat

At present, various cell-based immunotherapy methods, like adoptive cell transfer (ACT) and chimeric antigen receptor (CAR) T cell therapy, are showing promising results in improving the overall survival of patients with advanced cancers like melanoma, lung, prostate, gastric and leukemia [7–11]. Autologous lymphocytes isolated from the patients' blood, tumor tissue or lymph nodes are expanded *ex-vivo*, activated with tumor-specific antigens or genetically modified and then reinfused into the patient, alone or with a cocktail of cytokines. Usually,

Abbreviations: ACT, Adoptive cell transfer; Akt, protein kinase B; CAR, Chimeric antigen receptor; CCR7, Chemokine receptor-7; CD, Cluster of differentiation; CTLA4, Cytotoxic T lymphocyte-associated protein-4; GZMB, Granzyme-B; IFNγ, Interferon-γ; IL, Interleukin; MDSCs, Myeloid-derived suppressor cells; NK cells, Natural killer cells; PD-1, Programmed cell death protein-1; TA, Tumor antigen; T_{CM}, Central memory T cells; T_{EM}, T effector memory cells; TGFβ, Transforming growth factor-β; TILs, Tumor-infiltrating lymphocytes; TNFα, Tumor necrosis factor-α; Treg, T-regulatory cells; T_{RM}, Tissue resident T cells; T_{SCM}, Stem cell memory T

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a combination of $CD8^+$ and $CD4^+$ T cells are harvested from the patient [12].

Initial studies conducted on metastatic melanomas consisted of the administration of tumor-infiltrating lymphocytes (TILs) to patients. However, these TILs, which majorly consisted of T-effector cells, were unable to persist for long *in vivo*, despite administration of cytokines such as IL2, a T-cell growth factor [13]. In a study by Rivoltini et al., it was observed that in spite of the presence of tumor antigen (TA)-specific T cells in melanoma patients, instances of significant tumor regression were rare due to some impeding factors [14]. Efforts at expanding effector T cells from naïve ones were made, as a goal of vaccination. However, this technique also did not hold much promise due to the small population of TA-specific naïve T cells present. Further, it was observed that even the adoptive transfer of a large number of TA-specific naïve cells was unable to reduce the tumor burden in murine models [15]. This information led to the search for a cell type which would show better anti-tumor efficacy along with enhanced longevity in the tumor-bearing host.

T-memory cells came across as the ideal choice as previous research has shown that due to prior antigen-exposure, a large frequency of memory cells have tumor antigen specificity [16]. There occurs a severe loss of T-memory cells during tumor progression has been reported by many including our group, indicating a constant rivalry between cancer and T-memory cells [17]. Hence it can be naturally inferred that by increasing the memory population, the tumor load can be reduced successfully. This hypothesis was further strengthened by the observation that effector cells generated from memory cells to be capable of prolonged survival *in vivo* [18]. The candidature of immunologic memory being used in treatment was further corroborated by the recent success in checkpoint blockade therapy, using monoclonal antibodies against cytotoxic T lymphocyte-associated protein-4 (CTLA4) and programmed cell death protein-1 (PD1) on T cells, where it was detected that therapeutic PD1 blockade in 53 patients upregulated $CD8^+$ T-memory cells [19]. Recently the presence of high densities of T-memory cells in patients with colorectal cancer has been directly correlated with better overall and disease-free survival compared to patients with low densities of the same, further making them coveted contenders for immunotherapy [20].

1.3. Immunologic memory: Training the soldiers

T-memory cells form the rapid action task force of the immune system. They are a heterogeneous population of long-lived, antigen-experienced cells that represent immunologic memory. These cells are characterized by the capacity of self-renewal, clonal expansion and faster attainment of effector functions upon antigen re-stimulation or challenge [21]. Between the two types of T cells, $CD8^+$ cells have been studied widely about neoplasia and it has been seen that they form a vital wing of the adaptive immune response to cancer. On encountering their cognate antigen, $CD8^+$ naïve T cells undergo rapid proliferation and differentiate into a huge number of effector cells. A small population of these cells which express unique features survives past the contraction phase to become self-renewing, long-lived memory cells with recall abilities [22].

1.4. Epigenetics: The blueprint of the battle

Several recent studies have interestingly pointed out that the epigenetic landscape is responsible for retaining the transcriptional blueprint of the initial immune response in these cells, thus offering the rapid response of protective immunity [22,23]. Epigenetic regulations involve chemical modifications of the DNA and histones to develop either open chromatin states that are transcriptionally permissive (e.g., H3K9 acetylation, H3K4 methylation, etc.) or closed chromatin states that are repressive in nature (e.g., H3K9 methylation, sumoylation, etc.). Differential DNA methylation at the CpG islands of promoters and enhancers and histone acetylation states of key genes regulating memory-specific functions help to establish the faster recall property typical of these cells [22,24]. A study by Crompton et al. has shown that various permissive epigenetic modifications are associated with effector gene loci (*IFNγ, PRF, GZMB*) in memory cells leading to faster and robust effector functions. It was also observed that gradual epigenetic remodeling drives the differentiation of T-memory cells from naïve ones [25].

1.5. Types of T cell memory: The different brigades

The repertoire of T-memory cells comprises the following major subtypes: T central memory (T_{CM}), T effector memory (T_{EM}) and tissue-resident memory (T_{RM}) [26,27]. Recently, another less differentiated subtype has been discovered called T stem cell memory (T_{SCM}) [28,29]. Each subtype is characterized by specific cell surface markers, unique homing properties, and special functional attributes. Apart from the glycoprotein CD45RO, which is expressed by most-memory cell types, T_{CM} express the homing receptor, CD62L/L-selectin, which is a cell adhesion molecule helping the lymphocytes to enter secondary lymphoid tissues through the high endothelial venules. They also express the C−C chemokine receptor-7 (CCR7), further facilitating their trafficking to secondary lymphoid organs. T_{EM} lack both these markers that enable them to migrate to non-lymphoid tissues [16,26,30,31]. The central memory cells produce more IL2 compared to effector memory subsets that produce higher amounts of effector cytokines upon re-stimulation [22]. As the name suggests, T_{RM} is not-circulating-memory cells that reside in the peripheral tissues of initial antigen encounter and are characterized by phenotypic markers CD69 and CD103 [27,32]. T_{SCM} show attributes of both naïve and memory cells and their phenotypic markers include CD45RA, CD62L, and CCR7. These cells show maximum longevity *in vivo* and can give rise to other memory subsets due to their stem-like nature [22] (Fig. 1).

1.6. Central memory and effector memory T cells: The armory

An elaborate study of the tumor-infiltrating lymphocytes (TIL) was conducted by Fridman et al. and a direct correlation between TIL containing high densities of $CD8^+/CD45RO^+$ memory cells and disease-free/overall survival of patients was established for various cancers including breast, colorectal, head, and neck, melanoma, etc. [21,33]. It was also reported that the bone marrow of breast cancer patients harbors dormant tumor cells as well as T-memory cells [16]. Interestingly, the number of memory cells was found to be proportionate to the size of the primary tumor [34]. Only the memory subpopulation, when stimulated and adoptively transferred into NOD/SCID mice, could infiltrate and reject the tumor xenotransplants [16,35]. Beckhove and group showed that tumor-specific T_{CM} and T_{EM} cells, which were present in larger frequencies in the bone marrow of patients, could be specifically activated to develop selective homing capacities to the tumor site and cytotoxic abilities that led to tumor regression in xenotransplant mice models [16]. The question remained as to which of the two memory subtypes were more potent in eliciting the required anti-tumor response. Studies have shown, that because of their greater proliferative potential, T_{CM} provides enhanced protection to tumor-bearing host than T_{EM}, when applied with concomitant cancer vaccines [21,33]. Berger et al. have reported that populations of $CD8^+$ T cells obtained from clonally expanded T_{CM} show longer persistence *in vivo* than T_{EM}-derived effector cells, thus reinforcing the concept of T_{CM} efficacy in targeting tumor cells [31]. However, it was also suggested that continuous antigen exposure resulted in corrupt or phenotypically and functionally altered $CD8^+$ T-memory cells that skewed the anti-tumor response towards non-responsiveness. This is a major cause of ineffectiveness of the prevailing immunotherapeutic strategies [33].

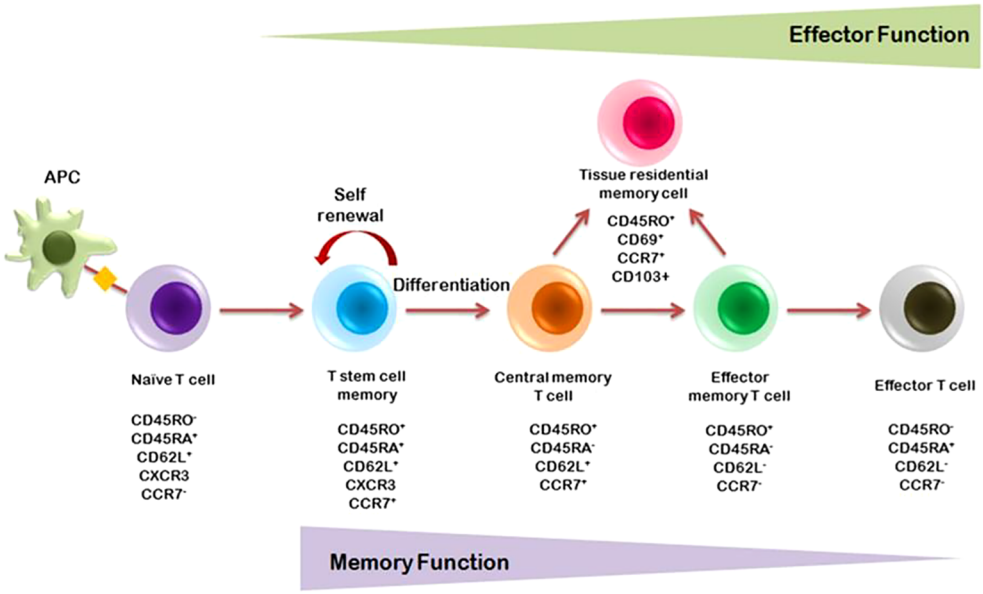

Fig. 1. Linear model of T cell differentiation from T naïve cells to effector T cells and their surface marker profiles. On encountering their cognate antigen, the naïve T cells sequential differentiate into T stem cell memory (TSCM), T central memory (TCM), T effector memory (TEM) and effector T cells. Tissue-resident T-memory cells belong to another subtype found in the peripheral tissues. All these cells are characterized by their unique cell surface markers.

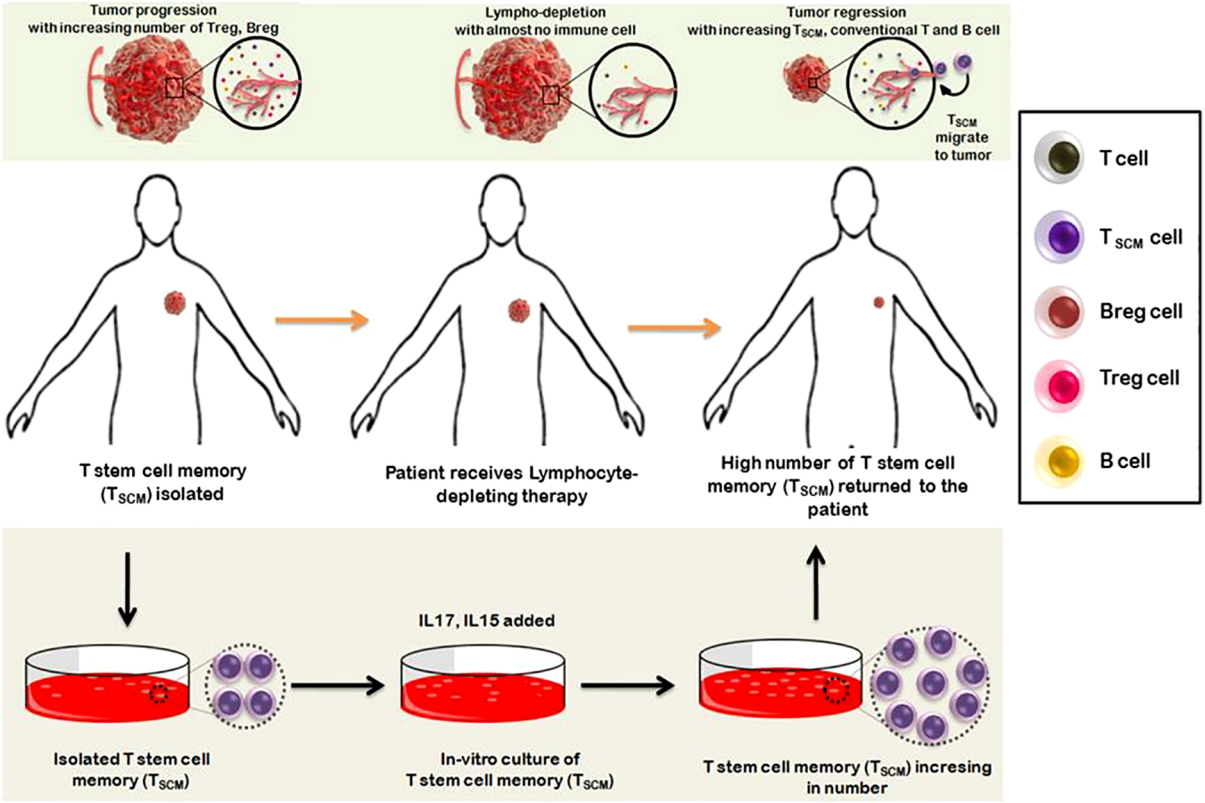

Fig. 2. Adoptive cell transfer therapy using T stem-like memory cells to treat the tumor. T stem-like memory cells isolated from the tumor tissue is cultured in vitro using cytokines like IL15, IL17 and then transferred back into the patient after lymphodepletion. During tumor progression, the main immunosuppressive cells like Treg, Breg and MDSCs increase, suppressing the conventional immune response. Because of lymphodepletion, these cells are destroyed, and then the injection of TSCM into lymphodepleted patient causes tumor regression.

1.7. Tissue-resident T-memory cells: The frontier fighters

Besides central and effector T cell T-memory here is an important subset of T-memory cells that reside in tissues which have a role in rapid protective immunity known as tissue-resident T-memory cells (T_{RM}) [36]. T_{RM} cells express the chemokine receptor CCR7, the glycoprotein CD69, and the integrin CD103. TNFα, IL15, TGFβ, and IL33 are involved in the maintenance of T_{RM} cells which are present in the respiratory tract, gastrointestinal tract, reproductive tract, skin, brain, kidney, joint and other tissues both in human as well as in rodent systems [27]. Without recruitment of T cells from blood, tissue-specific memory can respond rapidly to pathogen challenge at these particular sites through that barrier epithelium because they are specific for antigens that have been encountered previously [36]. A study of transcriptional profiling in lung cancer associated TIL revealed that patients with high-levels of T_{RM} cells had a better anti-tumor response [32].

These cells also produce IFNγ that aids in anti-tumor immunity [27]. Recent studies depict that a quantitative increase in T_{RM} cells acts as a marker for the efficiency of cancer vaccines [37]. Therefore, vaccination should aim at the increased generation of anti-tumor tissue resident T-memory cells.

1.8. T Stem cell memory cells: The chief of the army

Stem T-memory (T_{SCM}) cells represent a small, approximately 2–4% of the total T cell, the population in the periphery. It represents the earliest developmental stage of all the T-memory cells and displays various properties of stem cells, one of them being self-renewal, that helps them to survive longer, the other being differentiation into various other memory and effector subsets which can be deployed to elicit an effective immune response [38,39]. These properties of T_{SCM} have sparked interest in their prospective therapeutic role in cancer [39]. T_{SCM} have been shown to reside preferentially in the lymph nodes and reported to differentiate into T_{CM} and T_{EM} cells having a greater life span as well as superior anti-tumor response compared to the other cells [40]. These properties of T_{SCM} may be utilized to reduce the current therapeutic limitations of the ACT and mount a better long-lasting immune response. Although these cells were demonstrated to have potent anti-tumor activity in various animal tumor models, it is not viable to treat cancer patients with naturally occurring T_{SCM} cells because of its small proportion in circulating lymphocytes [41]. Therefore, various strategies that can expand and generate T_{SCM} *in vitro* need to be defined (Fig. 2). Gattinoni et al. showed that $CD8^+$ T_{SCM} could be generated through induction of Wnt/β-catenin signaling [28]. TWS119, which mimics Wnt-signalling, was shown to increase the proportion of T_{SCM} which are phenotypically characterized as $CD44^{low}CD62L^{high}$ and also express stem cell antigen-1 (Sca-1), B-cell lymphoma-2 and CD122. They were able to secrete IL2 and IFNγ upon antigen stimulation and underwent cell division after ACT [42]. Cieri et al. showed that these stem-like T cells could be generated from naïve precursors by stimulation with IL17 and IL15 [43]. T_{SCM} were also generated from naïve precursors by inhibiting AKT-signalling [38]. Thus it is particularly attractive to use them for adoptive immunotherapies. These *ex vivo* generated T_{SCM} were shown to have superior anti-tumor activity as compared to more differentiated ones in multiple melanoma-bearing mice [44]. This special class of T-memory cells is well equipped to improve several cancer therapeutic strategies, as shown by various experiments done in mice models, where they have triggered tumor destruction and improved survival in mice.

1.9. Treg memory cells: The spies

Whatever may be the choice of therapy, the efficacy of the treatment is compromised due to the presence of suppressor cells, a majority of them belonging to the $CD4^+$ T cell lineage; called T-regulatory cells (Tregs) [45,46]. There are reports suggesting that Treg infiltration to tumor site is directly linked to the poor clinical outcome of patients with various solid cancers like hepatocellular carcinoma, ovarian and breast cancers [6,47,48]. Recently the generation of Treg memory cells has also been reported in a tissue-specific antigen inducible mouse model [49]. These cells have been categorized into central ($CD4^+CD25^+FOXP3^+CCR7^+CD45RA^-$) and effector ($CD4^+CD25^+FOXP3^+CCR7^-CD45RA^-$) Treg memory cells [50]. Treg memory cells increase the long-term persistence of antigen-specific Treg cells with potent immunosuppressive properties despite the elimination of cognate antigen [49]. It has also been observed that Treg effector memory cell percentage is much higher than Treg central memory in the peripheral blood of tumor patients [50]. But, their specific roles in cancer progression and metastasis are yet to be established. However, although suppressor cells pose a threat to the successful application of T-memory cell immunotherapy, lymphoid-depletion before treatment holds the promise of better clinical outcome in patients.

2. Conclusion

T-memory cells have been studied extensively concerning infections. It is only in the last decade that research involving the role of these cells in the progression of cancer has come to limelight. From prior and ongoing research, it is evident that the progressive accumulation of permissive epigenetic modifications marks the transition of T memory cells from stem-like to effector subtypes and finally to the terminally differentiated effector cells. We can also infer that among the various T-memory cells, the less differentiated stem memory and central memory cells provide superior anti-tumor immunity than their more-differentiated effector memory counterparts. Also, the disruption or depletion of Treg cells may restore anti-tumor immunosurveillance. Thus, a better understanding of the mechanisms underlying the development and maintenance of the memory cells will enable us to manipulate this unique pool of cells to mount effective anti-tumor response alone or in combinatorial therapy against cancer.

Future perspectives

By now, the feasibility of ACT is well established, and current optimization and standardization procedures aim to improve it further. Though the cost and time for the treatment are high compared to other treatment options, various ongoing projects are trying to tackle both these issues for an effective treatment for the masses. Clinical trials have demonstrated high efficacy but at the same time treatment-related toxicity and transient tumor regression. The choice of a tumor antigen, such that the specific antigen has little or no expression in healthy tissues, is vital to reduce systemic toxicity. Advanced isolation techniques of anti-tumor T cells from patient samples may act as a double-edged sword, increasing specificity and reducing toxicity simultaneously. Various other strategies can be employed in conjugation with the ACT to get better outcomes, such as antibodies that block co-inhibitory molecules, antibodies or drugs which mediate angiostasis, local delivery of cytokines and chemotherapeutic agents to improve intratumoral T cell infiltration, etc. Also, the role of $CD4^+$ T cells in cancer is an area which requires more attention. Till date, there is very limited knowledge about the involvement of these cells in the development and progression of the disease. Another major piece of the puzzle that is yet to be solved is the role of T-memory cells in the relapse of cancer. Mechanistic knowledge about the contribution of the memory population in recurrence of cancer might hold the secret to the better overall and relapse-free survival of patients in the long-run.

Declarations

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Consent for publication: Not applicable
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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

IS undertook the background literature study and prepared the initial draft of the review; SP prepared the figures and helped in editing and extending the initial draft; AD helped in making the figures and made language and other technical corrections to the draft; UB helped in the preparation of the references; GS supervised the entire project

and made final corrections to the draft. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

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References:

[1] WHO|Cancer. http://www.who.int/mediacentre/factsheets/fs297/en/. Accessed 31Aug 2017.
[2] C.G. Drake, E. Jaffee, D.M. Pardoll, Mechanisms of immune evasion by tumors, Adv. Immunol. 90 (2006) 51–81.
[3] S. Hadrup, M. Donia, P. Straten, tho, Effector CD4 and CD8 T cells and their role in the tumor microenvironment, Cancer Microenviron. 6 (2) (2013) 123–133.
[4] J.F.A.P. Miller, M. Sadelain, the journey from discoveries in fundamental immunology to cancer immunotherapy, Cancer Cell 27 (4) (2015) 439–449.
[5] D. Chen, X. Zhang, Cellular immunity augmentation in mainstream oncologic therapy, Cancer Biol. Med. 14 (2) (2017) 121–128.
[6] W.H. Fridman, F. Pagès, C. Sautès-Fridman, J. Galon, The immune contexture in human tumours: impact on clinical outcome, Nat. Rev. Cancer 12 (4) (2012) 298–306.
[7] P.W. Kantoff, C.S. Higano, N.D. Shore, E.R. Berger, E.J. Small, D.F. Penson, et al., Sipuleucel-T immunotherapy for castration-resistant prostate cancer, N. Engl. J. Med. 363 (5) (2010) 411–422.
[8] D.L. Porter, W.-T. Hwang, N.V. Frey, S.F. Lacey, P.A. Shaw, A.W. Loren, et al., Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia, Sci. Transl. Med. 7 (303) (2015) 303–339.
[9] S.A. Quezada, K.S. Peggs, Exploiting CTLA-4, PD-1 and PD-L1 to reactivate the host immune response against cancer, Brit. J. Cancer 108 (8) (2013) 1560–1565.
[10] G.-Q. Zhang, H. Zhao, J.-Y. Wu, J.-Y. Li, X. Yan, G. Wang, et al., Prolonged overall survival in gastric cancer patients after adoptive immunotherapy, World J. Gastroenterol. WJG 21 (9) (2015) 2777–2785.
[11] M.E. Dudley, S.A. Rosenberg, Adoptive-cell-transfer therapy for the treatment of patients with cancer, Nat. Rev. Cancer 3 (9) (2003) 666–675.
[12] S. Farkona, E.P. Diamandis, I.M. Blasutig, Cancer immunotherapy: the beginning of the end of cancer? BMC Med. (2016) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4858828/. Accessed on 31 Aug 2017.
[13] S. Lee, K. Margolin, Tumor-infiltrating lymphocytes in melanoma, Curr. Oncol. Rep. 14 (5) (2012) 468–474.
[14] L. Rivoltini, M. Carrabba, V. Huber, C. Castelli, L. Novellino, P. Dalerba, et al., Immunity to cancer: attack and escape in T lymphocyte-tumor cell interaction, Immunol. Rev. 188 (2002) 97–113.
[15] W.W. Overwijk, M.R. Theoret, S.E. Finkelstein, D.R. Surman, L.A. de Jong, F.A. Vyth-Dreese, et al., Tumor regression and autoimmunity after reversal of a functionally tolerant state of self-reactive CD8+ T cells, J. Exp. Med. 198 (4) (2003) 569–580.
[16] P. Beckhove, M. Feuerer, M. Dolenc, F. Schuetz, C. Choi, N. Sommerfeldt, et al., Specifically activated memory T cell subsets from cancer patients recognize and reject xenotransplanted autologous tumors, J. Clin. Invest. 114 (1) (2004) 67–76.
[17] S. Bhattacharyya, D.M.S. Hossain, S. Mohanty, G.S. Sen, S. Chattopadhyay, S. Banerjee, et al., Curcumin reverses T cell-mediated adaptive immune dysfunctions in tumor-bearing hosts, Cell Mol. Immunol. 7 (4) (2010) 306–315.
[18] L. Gattinoni, D.E. Speiser, M. Lichterfeld, C. Bonini, T memory stem cells in health and disease, Nat. Med. 23 (1) (2017) 18–27.
[19] A. Ribas, D.S. Shin, J. Zaretsky, J. Frederiksen, A. Cornish, E. Avramis, et al., PD-1 blockade expands intratumoral memory T cells, Cancer Immunol. Res. 4 (3) (2016) 194–203.
[20] F. Pagès, A. Berger, M. Camus, F. Sanchez-Cabo, A. Costes, R. Molidor, et al., Effector memory T cells, early metastasis, and survival in colorectal cancer, N. Engl. J. Med. 353 (25) (2005) 2654–2666.
[21] C.A. Klebanoff, L. Gattinoni, P. Torabi-Parizi, K. Kerstann, A.R. Cardones, S.E. Finkelstein, et al., Central memory self/tumor-reactive CD8+ T cells confer superior antitumor immunity compared with effector memory T cells, Proc. Natl. Acad. Sci. U.S.A. 102 (27) (2005) 9571–9576.
[22] P. Dogra, H.E. Ghoneim, H.A. Abdelsamed, B. Youngblood, Generating long-lived CD8 T cell memory: insights from epigenetic programs, Eur. J. Immunol. 46 (7) (2016) 1548–1562.
[23] A.M. Woodworth, A.F. Holloway, The role of epigenetic regulation in transcriptional memory in the immune system, Adv. Protein Chem. Struct. Biol. 106 (2017) 43–69.
[24] N. Weng, Y. Araki, K. Subedi, The molecular basis of the memory T cell response: differential gene expression and its epigenetic regulation, Nat. Rev. Immunol. 12 (4) (2012) 306–315.
[25] J.G. Crompton, M. Narayanan, S. Cuddapah, R. Roychoudhuri, Y. Ji, W. Yang, et al., Lineage relationship of CD8(+) T cell subsets is revealed by progressive changes in the epigenetic landscape, Cell Mol. Immunol. 13 (4) (2016) 502–513.
[26] E.J. Wherry, V. Teichgräber, T.C. Becker, D. Masopust, S.M. Kaech, R. Antia, et al., Lineage relationship and protective immunity of memory CD8 T cell subsets, Nat. Immunol. 4 (3) (2003) 225–234.
[27] C.O. Park, T.S. Kupper, The emerging role of resident memory T cells in protective immunity and inflammatory disease, Nat. Med. 21 (7) (2015) 688–697.
[28] L. Gattinoni, X.-S. Zhong, D.C. Palmer, Y. Ji, C.S. Hinrichs, Z. Yu, et al., Wnt signaling arrests effector T cell differentiation and generates CD8+ memory stem cells, Nat. Med. 15 (7) (2009) 808–813.
[29] L. Gattinoni, C.A. Klebanoff, N.P. Restifo, Paths to stemness: building the ultimate antitumour T cell, Nat. Rev. Cancer 12 (10) (2012) 671–684.
[30] E.C. Butcher, L.J. Picker, Lymphocyte homing and homeostasis, Science 272 (5258) (1996) 60–66.
[31] C. Berger, M.C. Jensen, P.M. Lansdorp, M. Gough, C. Elliott, S.R. Riddell, Adoptive transfer of effector CD8+ T cells derived from central memory cells establishes persistent T cell memory in primates, J. Clin. Invest. 118 (1) (2008) 294–305.
[32] A.-P. Ganesan, J. Clarke, O. Wood, E.M. Garrido-Martin, S.J. Chee, T. Mellows, et al., Tissue-resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer, Nat. Immunol. 18 (8) (2017) 940–950.
[33] C.A. Klebanoff, L. Gattinoni, N.P. Restifo, CD8+ T-cell memory in tumor immunology and immunotherapy, Immunol. Rev. 211 (2006) 214–224.
[34] M. Feuerer, M. Rocha, L. Bai, V. Umansky, E.-F. Solomayer, G. Bastert, et al., Enrichment of memory T cells and other profound immunological changes in the bone marrow from untreated breast cancer patients, Int. J. Cancer 92 (1) (2001) 96–105.
[35] M. Feuerer, P. Beckhove, L. Bai, E.F. Solomayer, G. Bastert, I.J. Diel, et al., Therapy of human tumors in NOD/SCID mice with patient-derived reactivated memory T cells from bone marrow, Nat. Med. 7 (4) (2001) 452–458.
[36] M. Nizard, H. Roussel, M.O. Diniz, S. Karaki, T. Tran, T. Voron, et al., Induction of resident memory T cells enhances the efficacy of cancer vaccine, Nat. Commun. 8 (2017) 15221.
[37] M. Nizard, H. Roussel, E. Tartour, Resident memory T cells as surrogate markers of the efficacy of cancer vaccines, Clin. Cancer Res. 22 (3) (2016) 530–532.
[38] A.B. van der Waart, N.M.P. van de Weem, F. Maas, C.S.M. Kramer, M.G.D. Kester, J.H.F. Falkenburg, et al., Inhibition of Akt signaling promotes the generation of superior tumor-reactive T cells for adoptive immunotherapy, Blood 124 (23) (2014) 3490–3500.
[39] J.K. Flynn, P.R. Gorry, Stem memory T cells (TSCM)—their role in cancer and HIV immunotherapies, Clin. Transl. Immunol. 3 (7) (2014) e20.
[40] L. Xu, Y. Zhang, G. Luo, Y. Li, The roles of stem cell memory T cells in hematological malignancies, J. Hematol. Oncol. J. Hematol. Oncol. 8 (2015) 113.
[41] E. Lugli, M.H. Dominguez, L. Gattinoni, P.K. Chattopadhyay, D.L. Bolton, K. Song, et al., Superior T memory stem cell persistence supports long-lived T cell memory, J. Clin. Invest. 123 (2) (2013) 594–599.
[42] Y. Zhang, G. Joe, E. Hexner, J. Zhu, S.G. Emerson, Host-reactive CD8+ memory stem cells in graft-versus-host disease, Nat. Med. 11 (12) (2005) 1299–1305.
[43] N. Cieri, B. Camisa, F. Cocchiarella, M. Forcato, G. Oliveira, E. Provasi, et al., IL-7 and IL-15 instruct the generation of human memory stem T cells from naive precursors, Blood 121 (4) (2013) 573–584.
[44] A. Redeker, R. Arens, Improving adoptive T cell therapy: the particular role of T cell costimulation, cytokines, and post-transfer vaccination, Front. Immunol. 7 (2016) 345.
[45] D.M. Hossain, A.K. Panda, A. Manna, S. Mohanty, P. Bhattacharjee, S. Bhattacharyya, et al., FoxP3 acts as a co-transcription factor with STAT3 in tumor-induced regulatory T cells, Immunity 39 (2013) 1057–1069.
[46] S. Chakraborty, A.K. Panda, S. Bose, D. Roy, K. Kajal, D. Guha, G. Sa, Transcriptional regulation of FOXP3 requires integrated activation of both promoter and CNS regions in tumor-induced CD8$^+$Treg cells, Sci. Rep. 7 (2017) 1628.
[47] D.E. Speiser, P.-C. Ho, G. Verdeil, Regulatory circuits of T cell function in cancer, Nat. Rev. Immunol. 16 (10) (2016) 599–611.
[48] T.J. Curiel, G. Coukos, L. Zou, X. Alvarez, P. Cheng, P. Mottram, et al., Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival, Nat. Med. 10 (9) (2004) 942–949.
[49] M.D. Rosenblum, S.S. Way, A.K. Abbas, Regulatory T cell memory, Nat. Rev. Immunol. 16 (2) (2016) 90–101.
[50] M. Beyer, J.L. Schultze, CD4+CD25highFOXP3+ regulatory T cells in peripheral blood are primarily of effector memory phenotype, J. Clin. Oncol. 25 (18) (2007) 2628–2630.