Chapter 5
Cell-Based Immunotherapy for HCC: Our Experiences and Future Directions

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Abstract One of the most exciting advances in recent cancer treatments is the success of immunotherapy including dendritic cell-based vaccine and antibody treatment against the molecules regarding immune checkpoints like PD-1 and CTLA-4. Because the effect and application of current conventional treatments for intermediate or advanced hepatocellular carcinoma (HCC) including chemotherapy and trans-catheter arterial chemoembolization (TACE) are limited, novel immunotherapy is really desired to develop. We summarized status of completed or ongoing clinical trials of cell-based immunotherapy for HCC. Of those trials cytokine-induced killer cells (CIK) or dendritic cells (DC)-based immunotherapies revealed promising results. Future directions of immunotherapy for HCC are also discussed.

Keywords Dendritic cell • Vaccine • Adoptive transfer • T cell • Clinical trial

5.1 Limitation of Conventional Treatments and Advantage of Immunotherapy for Intermediate to Advanced HCC

Currently, conventional treatments for intermediate or advanced HCC are TACE or chemotherapy, respectively [1–3]. TACE is a procedure to inject an embolic agent with cytotoxic drug, resulting in ischemic necrosis of the tumor. The benefit of TACE in unresectable HCC was demonstrated in two randomized control trials [4, 5]. However, anti-tumor effect of TACE is limited in intrahepatic HCC lesions, and

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extra-hepatic lesions are not applicable for the TACE. Advanced HCCs with extra-hepatic lesions or vascular invasion in the liver are treated by oral molecular targeting drug, sorafenib. Discontinuation of the sorafenib treatment is often necessary due to the reasons other than progression of HCC, like liver dysfunction, skin disease and fluid retention [6]. Arterial infusion of cytotoxic drug, 5FU and cisplatin, is another option as a treatment for intermediate or advanced HCC [7]. Although the conventional treatments prolong overall survival, those are limited in patients with good hepatic reserve. Immunotherapy should be more suitable for HCC patients with liver dysfunction, because the antigen-specific immunotherapy specifically targets cancer cell, not background hepatocytes. The first DC-based peptide vaccine for castration-resistant prostate cancer patients, sipuleucel-T, approved by Food and Drug Administration (FDA) in United States caused no severe adverse effects [8]. Sipuleucel-T is comprised of DC loaded with prostatic acid phosphatase (PAP) peptide and specifically targets prostate cancers. Sipuleucel-T significantly prolonged overall survival (median survival time; MST 25.8 months) compared with control (MST 21.7 months). The success of sipuleucel-T shed a light in efficiency of immunotherapy and possibility of the therapy to prolong survival in other cancers. Because HCC patients often have impaired hepatic reserve, HCC-specific treatments with little adverse effects are really desired. Thus, HCC-specific immunotherapy is one of the promising treatments.

5.2 The Current Cell-Based Immunotherapy Trials

Four randomized control trials (RCT) of cell-based immunotherapy for HCC were reported (Table 5.1). All trials were based on infusion of the lymphocytes stimulated with IL-2 in addition to anti-CD3 or other cytokines. Kawata et al. first reported safety of lymphokine-activated killer cells (LAK) which derived from peripheral blood mononuclear cells (PBMC) and then were stimulated with IL-2, but the infusion of LAK didn't improve both disease-free survival (DFS) and overall survival (OS) [9]. Methods to activate PBMC was then improved by adding various cytokines and anti-CD3, and the activated cells were called cytokine-induced killer cells (CIK) which include activated non-specific αβT cells and $CD3^{+}CD56^{+}$ NKT cells. CIK treatment first showed clinical benefit in the HCC patients after radical haptic resection in 2000. Takayama et al. reported that lymphocytes generated from PBMC by the stimulation with IL-2 and anti-CD3 significantly prolonged disease-free survival compared with control arm [10]. Hui and colleagues also reported infusion of CIK generated by stimulation with IL-2, anti-CD3, IFN-γ and IL-1α increased DFS rate [11]. Weng et al. also demonstrated clinical benefit of CIK after radical hepatic resection of HCC as the prolonged DFS [12]. However, all 4 RCT failed to prolong OS by infusion of cytokine-stimulated lymphocytes including LAK and CIK. Two meta-analyses of adoptive immunotherapy in postoperative HCC also revealed no benefit in OS although did benefit in DFS [13, 14]. Prolongation of DFS by CIK was only achieved after radical resection of HCC. Kawata's study targeted advanced HCC by LAK with adriamycin, resulting

Table 5.1 Randomized control trials of cell-based immunotherapy for HCC

Study	Treatment arm	Control arm	Number of patients	Outcomes	Treatment arm vs control arm (%)	*p*-value
Takayama et al. [9]	CIK	Radical resection	150	5-year DFS	38 vs 22	$p<0.05$
	Radical resection			5-year OS	68 vs 62	$p>0.05$
Weng et al. [11]	CIK	TACE + RFA	85	1-year recurrence	9 vs 30	$p<0.05$
	TACE + RFA			1.5-year OS	100 vs 100	$p>0.05$
Hui et al. [10]	CIK + IL-2	Radical resection	127	5-year DFS	23 vs 11	$p<0.05$
	Radical resection			5-year OS	38 vs 37	$p>0.05$
Kawata et al. [8]	LAK + IL-2	adriamycin	24	3-year DFS	50 vs 25	$p>0.05$
	Adriamycin			3-year OS	71 vs 74	$p>0.05$

CIK cytokine-induced killer cells, *DFS* disease-free survival, *HCC* hepatocellular carcinoma, *IL-2* interleukin-2, *LAK* lymphokine-activated killer cells, *OS* overall survival, *RFA* radio-frequency ablation, *TACE* trans-catheter arterial chemoembolization

in no effect in DFS. Benefit of CIK therapy may be limited in prolongation of DFS of patients who undergo radical resection. Novel cell-based immunotherapy which prolongs OS even in advanced HCC, hopefully chemotherapy-resistant HCC, is really desired to develop.

Clinical trials of immunotherapy using other cells than CIK or LAK are ongoing or were completed according to the databases of clinical trials. According to ClinicalTrial.gov, eight cell-based immunotherapies were conducted as clinical trials so far (Table 5.2). Innate lymphoid cells including NK cells, NKT cells and γδT cells were used as effector cells in 3 trials. No evidence was demonstrated by phase III clinical trials with those innate lymphoid cells so far in any types of cancer, but in theory NK cells, NKT cells or γδT cells can target lack of MHC class I on cancer cells or phosphate antigen induced by abnormal metabolism in the tumor microenvironment. Tumor-infiltrating lymphocytes in 2 trials or dendritic cells in 2 trials were used to target cancers by tumor-specific immune responses.

In Japan, seven cell-based immunotherapies were conducted as clinical trials so far according to UMIN (Table 5.3). Two trials were γδT cell-based immunotherapy. Four trials were DC-based immunotherapy which intended to induce HCC-specific immune responses. As tumor antigen, tumor lysate was pulsed in DC in 1 trial (UMIN000005820). To load more specific tumor antigen in DC, tumor antigen mRNA-encoding DC was used in 1 trial (UMIN000005836). DC stimulated with OK-432, inactivated streptococcus pyogenes, were used in 1 trial to activate DC (UMIN000001701). Thus, various cell types and techniques were examined in the current clinical trials to enhance anti-tumor immune responses against HCC.

Table 5.2 Clinical trials of immunotherapy for HCC registered in ClinicalTrial.gov

Cell type	Cancer	Phase	Facility	ID
γδT	HCC	I	Rennes University Hospital	NCT00562666
NK, IL-2-activated	HCC	I	University of Miami	NCT01147380
NK & NKT	Various cancers including HCC	I	Envita Medical Center, Inc.	NCT00909558
TIL	HCC, nasopharyngeal, breast	I	Sun Yat-sen University	NCT01462903
DC loaded with AFP peptides	HCC	I/II	Nantes University Hospital	NCT01128803
DC	HCC, melanoma, renal cell	II	Clinica Universidad de Navarra	NCT00610389
$CD8^+$ TIL	Metastatic cancers including HCC	II	National Cancer Institute, NIH	NCT01174121
CIK	HCC	III	Sun Yat-sen University	NCT01749865

AFP alpha feto protein, *CIK* cytokine-induced killer cells, *DC* dendritic cells, *HCC* hepatocellular carcinoma, *IL-2* interleukin-2, *NK* natural killer cells, *NKT* natural killer T cells, *TIL* tumor-infiltrating lymphocytes

Table 5.3 Clinical trials of immunotherapy for HCC registered on UMIN in Japan

Cell type	Cancer	Phase	Facility	UMIN ID
Naïve T cells	HCC	II	Kyoto Prefectural University of Medicine	UMIN000003861
γδT	HCC	pilot	Tokyo Medical University	UMIN000004583
γδT	HCC	pilot	The University of Tokyo	UMIN000001418
DC	HCC	pilot	Tokyo Medical University/The University of Tokyo	UMIN000000971
DC, encoding cancer antigen mRNA	HCC, pancreatic	pilot	Yamaguchi University	UMIN000005836
DC, OK432-stimulated	HCC	I/II	Kanazawa University	UMIN000001701
DC, tumor lysate-pulsed	Various cancers including HCC	I/II	Tokyo Women's Medical University	UMIN000005820

DC dendritic cells, *HCC* hepatocellular carcinoma

5.3 DC-Based Immunotherapy for HCC

Among various types of cell-based immunotherapy, sipuleucel-T is the only therapy which was verified to prolong overall survival of prostate cancer in phase III trial [7]. Sipuleucel-T comprises DC pulsed with tumor-specific antigen, PAP. If tumor-antigen

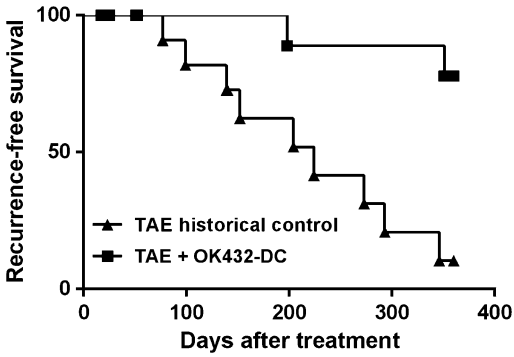

Fig. 5.1 Recurrence-free survival of patients with hepatocellular carcinoma treated with trans-catheter arterial embolization (TAE) with or without infusion of OK-432-stimulated DC. $N = 13$ in TAE + OK-432-DC group and $N = 11$ in TAE historical control group

is known, DC-based immunotherapy is a promising therapy to treat HCC according to the success in sipuleucel-T. Palmer reported that phase II trial of tumor lysate-pulsed DC infusion for patients with unresectable advanced HCC achieved disease control rate 28 % (combined partial response and stable disease) [15]. In the trial, hepatocellular carcinoma cell line HepG2 was used for source of tumor lysate. What is the best to load in DC, autologous tumor lysate, cell line-derived lysate, or HCC-specific peptides, is still controversial and to be determined in future.

We activated autologous DC from cancer patients with OK-432 before the infusion [16]. OK432-activated DC expressed high level of co-stimulatory molecules like CD80, CD83, and CD86. OK-432-stimulated DC also highly produced IL-12p40 and IFN-γ and revealed high tumoricidal activity against HCC cell lines like Hep3B and PLC/PRF/5 in *in vitro* assay. After TAE OK-432-stimulated DC were injected in hepatic artery via catheter. OK432-stimulated DC significantly prolonged recurrence-free survival compared to historical TAE control ($P = 0.0017$; Fig. 5.1). Although IFN-γ responses with PBMC specific to hTERT which is highly expressed by HCC as tumor antigen didn't significantly increase after the OK-432-stimulated DC treatment, serum level of TNF, IL-9 and IL-15 was significantly higher in OK-DC group than TAE control patients. In mouse model of OK-DC treatment for HCC, OK-DC clearly induced tumor-specific immune responses against colon cancer cells [17]. It is still controversial that under which mechanism OK-432-stimulated DC exerts anti-tumor effect, tumor-specific immunity or non-specific direct killing. Although the mechanisms underlying the prolonged DFS caused by OK-432-stimulated DC treatment should still be elucidated, DC-based immunotherapy is a promising treatment for HCC.

5.4 Strategies to Enhance the Effects of DC-Based Cancer Vaccine

In addition to the success in sipuleucel-T for prostate cancer, DC-based vaccines are showing promising results in the clinical trials for other types of cancer. Phase III trial of DCVax-L (Northwest Biotherapeutics), NCT01582672 or NCT01875653

are underway for glioblastoma, renal cell carcinoma or melanoma, respectively [18, 19]. Based on the promising results in DC-based vaccine in various cancers, further strategies to enhance the effect of DC-based therapy are now developing. Combined immunotherapy with DC and CIK for various cancers is also ongoing. Meta-analysis of non-randomized trial demonstrated that chemotherapy + DC + CIK therapy increased the 3-year overall survival rates (RR 11.67, 95 % CI 2.28 to 56.69, $P = 0.003$) and progression-free survival (RR 0.64, 95 % CI 0.34 to 0.94, $P < 0.0001$) in patients with non-small cell lung cancer compared with those treated with chemotherapy alone [20]. Infusing more than 2 immune cells might synergistically enhance anti-tumor immune responses. RCT is required to verify the clinical benefit of DC and CIK combination therapy.

One of the most exciting advances in recent cancer immunotherapy is the success of breaking immune checkpoints to prolong survival of cancer-bearing patients. Development of antibodies against negative regulators of T cell, CTLA-4 and PD-1, induced high clinical responses in various cancers [21–23]. Breaking tolerogenic aspects of tumor-infiltrating T cells might enhance effect of DC-based vaccine to induce tumor-specific cytotoxic T cell populations. Combining DC immunotherapy with anti-CTLA-4 antibody was feasible and well tolerated in advanced melanoma patients and induced high clinical responses compared to either treatment alone [24]. Blockade of PD-1 as well as inhibitory cytokine IL-10 or TGF-β may augment anti-tumor effect of DC-vaccine therapy [25].

Because massive cell death of the cancer releases damage-associated molecular pattern (DAMP) and subsequent acute inflammation accompanied with the production of cytokines and chemokines, it activates tumor-infiltrating DC [26]. This provides a rationale for combining DC-based therapy with radio-frequency ablation (RFA) or TACE which destroy large part of cancer tissues. As support of the idea, we reported that activation of endogenous DC population and subsequent anti-tumor T cell responses are induced by injection of ECI301, an active variant of CCL3, only if the injection was combined with RFA treatment of liver cancer [27]. Moreover, infusion of OK-432-stimulated DC prolonged DFS in combination with TAE in the clinical trial [16] and OS in combination with RFA in murine model [17]. Conventional chemotherapy also augments anti-tumor immune effects by innate cells activated by gut commensal bacteria and probably pathogen-associated molecular pattern (PAMP) [28]. Radiation increases release of lipopolysaccharide from gut to blood, resulting in activation of DC and the enhanced cytotoxicity of adoptively transferred T cells [29]. Thus, combination of DC-based vaccine and conventional cancer therapy including RFA, TACE, chemotherapy and radiation will be tested to see clinical benefit.

5.5 Future Perspective

Although DC-based immunotherapy is the only cell-based immunotherapy which has been approved by FDA so far, whether the infused DC induce effective anti-tumor immunity depends on immunosuppressive background of the host and

strategies to break the tolerant environment [30]. Adoptive transfer of tumor-specific T cells will target cancer independently of immunosuppressive milieu in cancer-bearing hosts if enough number of the T cells is infused [31]. Genetic engineering enabled to induce large number of tumor-specific TCR-transgenic T-cell ex vivo [32–34]. The transfer of tumor antigen-specific TCR-transgenic T cells eradicated some metastatic solid tumors like melanoma in clinical trials. Complete responses or partial responses were observed with gp100-targeting T-cell transfer in 6.3 or 12.5 % of metastatic melanoma patients, respectively [34]. Partial responses were achieved by NY-ESO-1-targeting T-cell transfer in 67 % of synovial cell sarcoma patients, and 27.2 % melanoma patients accompanied with 18 % complete responses [33]. TCR targeting HCC-specific antigen is required for establishment of efficient T-cell transfer therapy for HCC. The emerging development of induced pluripotent stem (iPS) cell technology might further enable to produce large number of tumor-specific TCR-bearing T cells by generating iPS from tumor-infiltrating lymphocytes [35].

Even if "good" tumor-specific antigens are used, DC or tumor-specific T-cell-based immunotherapy cannot overcome heterogeneity in cancer tissues. Because a cancer tissue includes heterogeneous cancer cell populations, some populations should be resistant to tumor-specific immunotherapy. One possible method to overcome the heterogeneity is targeting cancer stem cells (CSC) in the tissue [36]. If antigens specific to CSC are known, DC or TCR-transgenic T-cell therapy might regress whole cancer tissues including heterogeneous populations. In leukemia model, Wilms Tumor 1 (WT1) and cancer testis antigen termed PRAME are potential antigens related to cancer stem cells, and the vaccine using those antigens killed leukemic stem cells [36]. Because CSC-specific antigens are still unknown in HCC, further examination of the antigens is required.

References

1. Reataza M, Imagawa DK. Advances in managing hepatocellular carcinoma. Front Med. 2014;8(2):175–89. doi:10.1007/s11684-014-0332-4.
2. Raza A, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol. 2014;20(15):4115–27. doi:10.3748/wjg.v20.i15.4115.
3. Osaki Y, Nishikawa H. Treatment for hepatocellular carcinoma in Japan over the last three decades: Our experience and published work review. Hepatol Res. 2014. doi:10.1111/hepr.12378.
4. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734–9. doi:S0140-6736(02)08649-X [pii] 10.1016/S0140-6736(02)08649-X.
5. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164–71. doi:10.1053/jhep.2002.33156. S0270913902877138 [pii]
6. Nojiri S, Kusakabe A, Fujiwara K, Shinkai N, Matsuura K, Iio E et al. Clinical factors related to long-term administration of sorafenib in patients with hepatocellular carcinoma. Cancer Manag Res. 2012;4:423–9. doi:10.2147/CMAR.S38684cmar-4-423 [pii].

7. Yamashita T, Arai K, Sunagozaka H, Ueda T, Terashima T, Mizukoshi E et al. Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. Oncology. 2011;81(5–6):281–90. doi:10.1159/000334439000334439 [pii].
8. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–22. doi:10.1056/NEJMoa1001294.
9. Kawata A, Une Y, Hosokawa M, Wakizaka Y, Namieno T, Uchino J, et al. Adjuvant chemoimmunotherapy for hepatocellular carcinoma patients. Adriamycin, interleukin-2, and lymphokine-activated killer cells versus adriamycin alone. Am J Clin Oncol. 1995;18(3):257–62.
10. Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet. 2000;356(9232):802–7. doi:10.1016/S0140-6736(00)02654-4. S0140-6736(00)02654-4 [pii].
11. Hui D, Qiang L, Jian W, Ti Z, Da-Lu K. A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma. Dig Liver Dis. 2009;41(1):36–41. doi:10.1016/j.dld.2008.04.007S1590-8658(08)00199-0 [pii].
12. Weng DS, Zhou J, Zhou QM, Zhao M, Wang QJ, Huang LX et al. Minimally invasive treatment combined with cytokine-induced killer cells therapy lower the short-term recurrence rates of hepatocellular carcinomas. J Immunother. 2008;31(1):63–71. doi:10.1097/CJI.0b013e31815a121b00002371-200801000-00008 [pii].
13. Xie F, Zhang X, Li H, Zheng T, Xu F, Shen R et al. Adoptive immunotherapy in postoperative hepatocellular carcinoma: a systemic review. PloS One. 2012;7(8):e42879. doi:10.1371/journal.pone.0042879PONE-D-12-08994 [pii].
14. Zhong JH, Ma L, Wu LC, Zhao W, Yuan WP, Wu FX, et al. Adoptive immunotherapy for postoperative hepatocellular carcinoma: a systematic review. Int J Clin Pract. 2012;66(1):21–7. doi:10.1111/j.1742-1241.2011.02814.x.
15. Palmer DH, Midgley RS, Mirza N, Torr EE, Ahmed F, Steele JC, et al. A phase II study of adoptive immunotherapy using dendritic cells pulsed with tumor lysate in patients with hepatocellular carcinoma. Hepatology. 2009;49(1):124–32. doi:10.1002/hep.22626.
16. Nakamoto Y, Mizukoshi E, Kitahara M, Arihara F, Sakai Y, Kakinoki K, et al. Prolonged recurrence-free survival following OK432-stimulated dendritic cell transfer into hepatocellular carcinoma during transarterial embolization. Clin Exp Immunol. 2011;163(2):165–77. doi:10.1111/j.1365-2249.2010.04246.x.
17. Nakagawa H, Mizukoshi E, Iida N, Terashima T, Kitahara M, Marukawa Y, et al. In vivo immunological antitumor effect of OK-432-stimulated dendritic cell transfer after radiofrequency ablation. Cancer Immunol Immunother. 2014;63(4):347–56. doi:10.1007/s00262-013-1514-7.
18. Radford KJ, Tullett KM, Lahoud MH. Dendritic cells and cancer immunotherapy. Curr Opin Immunol. 2014;27:26–32. doi:10.1016/j.coi.2014.01.005S0952-7915(14)00006-5 [pii].
19. Polyzoidis S, Keyoumars A. DCVax(R)-L-developed by Northwest Biotherapeutics. Hum Vaccin Immunother. 2014;10(11):3139–45. doi:10.4161/hv.29276.
20. Chen R, Deng X, Wu H, Peng P, Wen B, Li F. Combined immunotherapy with dendritic cells and cytokine-induced killer cells for malignant tumors: a systematic review and meta-analysis. Int Immunopharmacol. 2014;22(2):451–64. doi:10.1016/j.intimp.2014.07.019S1567-5769(14)00283-5 [pii].
21. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. New Engl J Med. 2010;363(8):711–23. doi:10.1056/NEJMoa1003466NEJMoa1003466 [pii].
22. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54. doi:10.1056/NEJMoa1200690.

23. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65. doi:10.1056/NEJMoa1200694.
24. Ribas A, Comin-Anduix B, Chmielowski B, Jalil J, de la Rocha P, McCannel TA et al. Dendritic cell vaccination combined with CTLA4 blockade in patients with metastatic melanoma. Clin Cancer Res 2009;15(19):6267–76. doi:10.1158/1078-0432.CCR-09-12541078–0432.CCR-09-1254 [pii].
25. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer. 2012;12(4):237–51. doi:10.1038/nrc3237nrc3237 [pii].
26. Iida N, Nakamoto Y, Baba T, Kakinoki K, Li YY, Wu Y, et al. Tumor cell apoptosis induces tumor-specific immunity in a CC chemokine receptor 1- and 5-dependent manner in mice. J Leukoc Biol. 2008;84(4):1001–10. doi:10.1189/jlb.1107791.
27. Iida N, Nakamoto Y, Baba T, Nakagawa H, Mizukoshi E, Naito M, et al. Antitumor effect after radiofrequency ablation of murine hepatoma is augmented by an active variant of CC Chemokine ligand 3/macrophage inflammatory protein-1alpha. Cancer Res. 2010;70(16):6556–65. doi:10.1158/0008-5472.CAN-10-0096.
28. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science. 2013;342(6161):967–70. doi:10.1126/science.1240527342/6161/967 [pii].
29. Paulos CM, Wrzesinski C, Kaiser A, Hinrichs CS, Chieppa M, Cassard L, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. J Clin Invest. 2007;117(8):2197–204. doi:10.1172/JCI32205.
30. Swartz MA, Iida N, Roberts EW, Sangaletti S, Wong MH, Yull FE, et al. Tumor microenvironment complexity: emerging roles in cancer therapy. Cancer Res. 2012;72(10):2473–80. doi:10.1158/0008-5472.CAN-12-0122.
31. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol. 2012;12(4):269–81. doi:10.1038/nri3191nri3191 [pii].
32. Kershaw MH, Westwood JA, Darcy PK. Gene-engineered T cells for cancer therapy. Nat Rev Cancer. 2013;13(8):525–41. doi:10.1038/nrc3565nrc3565 [pii].
33. Robbins PF, Morgan RA, Feldman SA, Yang JC, Sherry RM, Dudley ME et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol. 2011;29(7):917–24. doi:10.1200/JCO.2010.32.2537JCO.2010.32.2537 [pii].
34. Johnson LA, Morgan RA, Dudley ME, Cassard L, Yang JC, Hughes MS et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood. 2009;114(3):535–46. doi:10.1182/blood-2009-03-211714blood-2009-03-211714 [pii].
35. Sachamitr P, Hackett S, Fairchild PJ. Induced pluripotent stem cells: challenges and opportunities for cancer immunotherapy. Front Immunol. 2014;5:176. doi:10.3389/fimmu.2014.00176.
36. Dhodapkar MV, Dhodapkar KM. Vaccines targeting cancer stem cells: are they within reach? Cancer J. 2011;17(5):397–402. doi:10.1097/PPO.0b013e318233e73000130404-201109000-00018 [pii].