



# Can we use Adoptive T Cells to Treat Viral Hepatitis-Associated Liver Cancer?



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## Opinion

We are witnessing the rapid advancement of immunotherapy, in particular of adoptive cellular therapy, against cancers over the past decade. Currently, adoptive cellular therapy comprises of three classes, i.e., by using tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR)-, or T-cell receptor (TCR)-engineered T cells [1]. While TILs are obtained through the isolation from tumor mass, the latter two methods obtain T cells through the genetic engineering. The CAR- and TCR-engineered T cells are gaining popularity due to, partly, their ability to evade the immune suppression, frequently observed on tumor-specific T cells. These gene-modified T cells would permit the immune system to confer an adequate immuneresponse, which is naturally may not present at all [1].

Several published articles on the distinction between the TCR- and CAR-engineered T-cell systems are available (please read review [2] in particular). The TCR is an  $\alpha\beta$  heterodimer receptor, naturally expressed on T-cell surface, which binds to a particular peptide-MHC complex. The TCR associates with a six-subunit complex of CD3 to provide intracellular signaling domains, which is a prerequisite for a T cell to confer an immune response. In addition, the presence of co-receptor CD4 or CD8 supports the responsiveness of a T cell to be activated by TCR binding to as few as one peptide-MHC complex. This sensitive, yet specific, system allows T cells to physiologically target intracellular antigens, in a form of peptide-MHC complexes [2]. The CAR refers to a synthetic construct typically comprising a single-chain antibody fragment, an extracellular domain/hinge, a trans membrane domain as well as one or more intracellular signaling domains (e.g., CD28 or 4-1BB). Since the CAR system uses an antibody fragment, this system is useful to target cell surface antigens, independent of MHC. In addition, pathologic cells, e.g., cancerous cells, usually express a particular cell surface antigen at high density, hence these kinds of target cells can be recognized and eliminated by the CAR-engineered T cells [2]. Due to the pronounced differences between the CAR and TCR

systems, it is indeed difficult to directly compare between these two systems. Nonetheless, it is fair to state that the CAR system has a more potential to be utilized in a wide population, since it does not face any MHC restriction. On the other hand, the TCR is a more sensitive system than the CAR due to its capability to recognize and respond to as few as one peptide-MHC complex [2].

As mentioned above, the CAR and TCR systems are currently tested against cancers. While the CAR-engineered T cells are not yet effective against solid tumors partly due to the local immunosuppressive tumor environment, it has been demonstrated that the CAR treatment against CD19 antigen, expressed by B cells, resulted in complete remission in several patients of B-cell malignancies. Despite its efficacy, the CAR therapy however is associated with several side effects. In general, it could cause the cytokine release syndrome due to high levels of released TNF- $\alpha$  and IL-6 [3]. In particular of the CD19-specific CAR therapy, it could result in B-cell aplasia that prompts for exogenous administration of immunoglobulin [2]. Trials using the TCR-engineered T cells demonstrated some success in treating both solid and hematological tumors [2]. However, the current TCR-engineered T cells target tumor-associated antigens (e.g., MAGE-A3 or NY-ESO-1), which are actually self antigen per se [4]. This implies that the TCR-generated T cells could respond to similar peptide-MHC complexes in healthy tissue, although are presented at low levels, resulting insignificant morbidity and mortality [5,6]. Thus, despite these two systems are potentially efficacious to be used to treat cancers, their safety profiles need to be addressed and properly rectified before they can be routinely used in the clinical setting.

It has been known that functional T-cell responses are required to control HBV and HCV replication and even to eliminate viral infection [7,8]. Therefore, the CAR and TCR systems have been studied as well in the context of HBV and HCV infection. Pertaining to HCV infection, both systems were mainly

studied in vitro, i.e., by targeting HLA-A2-restricted epitopes in HCV NS3 and NS5A proteins as well as HCV E2 glycoprotein for the TCR and CAR system, respectively [9-11]. Both systems demonstrated their efficacy in controlling HCV replication in vitro with a reasonable level of cytotoxicity. Nonetheless, subsequent in vivo and clinical studies would be required to confirm whether these in vitro successes could be replicated without a profound risk of morbidity or mortality. Another hindrance for using adoptive T-cell therapy to treat chronic HCV infection is the current availability of potent antiviral drugs to cure HCV-infected patients [12], hence questioning the necessity to adopt this mode of treatment in a clinical setting.

With regard to HBV infection, the not-so-fortunate situation pertaining to a lack of potent anti-HBV drug accelerates studies on the adoptive T-cell therapy. A research group led by Ulrike Protzer uses the CAR system (targeting HBV envelope protein) and has tested this system in HBV-transgenic mice thus far. This group demonstrated that the CAR-engineered T cells were able to control HBV replication with a transient liver damage in vivo. It also appears that the presence of HBV antigens in murine sera did not interfere with the functionality of HBV-specific CAR-engineered T cells [13]. The HBV-specific TCR-engineered T-cell research is primarily led by Antonio Bertoletti's group, targeting certain MHC-restricted epitopes within viral antigens, e.g., within HBV surface or core antigens. This group indeed has demonstrated that the TCR-engineered T cells were able to control HBV replication in cell lines and xenograft mice [14,15]. Taken together, both the CAR- and TCR-engineered T cells have merits to be further developed as a treatment tool against chronic HBV infection. Saying this, however, both methods carry a potential danger to cause significant liver inflammation, thus liver damage. Therefore, more safety studies are required to provide sufficient evidence in order to support these treatment modes for patients with chronic HBV infection.

Nonetheless, it has been acknowledged that chronic viral hepatitis contributes to the majority incidence of primary hepato cellular carcinoma/HCC [16]. In line with the primary usage of adoptive T-cell therapy against cancers, this mode of treatment has a potential to be used to treat HBV- or HCV-associated HCC. It is important to point out that a high frequency of HBV DNA integration is observed in the genome of HBV-related HCC cells, resulting in the expression of HBV antigens by tumor cells [17]. This allows the usage of TCR-engineered T cells to treat HBV-associated HCC. HBV antigens are not expressed by healthy tissue (unlike self antigens), hence theoretically can serve as better target antigens in certain HCC cases. However, since non-cancerous, but HBV-infected, hepatocytes also express HBV antigens, these hepatocytes can be attacked by HBV-specific TCR-engineered T cells. This potentially can cause severe liver damage. Therefore, Bertoletti's group decided to treat a liver transplanted patient who developed extra hepatic HCC metastasis, as the first use of HBV-specific TCR-engineered T cells in a clinical setting [18]. This group indeed demonstrated

the clinical potential and safety of using HBV-specific TCR-engineered T cells by smartly chose a suitable patient [18]. This milestone study indeed suggests that the adoptive T-cell therapy can be used against a selected group of HBV-associated HCC cases, such as to prevent or treat HCC recurrence in liver-transplanted patients with HBV-positive HCC [19]. In contrast, HCV as an RNA virus does not integrate with the host genome. Therefore, despite a study demonstrated the utilization of HCV-specific TCR-engineered T cells against HCV-associated HCC in cell lines and xeno graft mice [20], it will be difficult to select a suitable group of HCV-associated HCC patients in order to be treated with this therapy mode. In conclusion, we are entering a new exciting era where adoptive T-cell therapy is extensively studied against viral hepatitis-associated liver cancer. The author is optimistic that eventually the adoptive T-cell therapy will serve as a novel alternative, yet effective, treatment to HBV-associated HCC patients.

### References

1. June, CH, Riddell SR, Schumacher TN (2015) Adoptive cellular therapy: a race to the finish line. *Sci Transl Med* 7(280): 280ps7.
2. Harris, DT, David M, Kranz (2016) Adoptive T Cell Therapies: A Comparison of T Cell Receptors and Chimeric Antigen Receptors. *Trends Pharmacol Sci* 37(3): 220-230.
3. Ramos, CA, Heslop HE, Brenner MK (2016) CAR-T Cell Therapy for Lymphoma. *Annu Rev Med* 67: 165-183.
4. Vigneron N (2015) Human Tumor Antigens and Cancer Immunotherapy. *Biomed Res Int* 2015: 948501.
5. Linette GP, Stadtmauer EA, Maus MV, Rapoport AP, Levine BL, et al. (2013) Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood* 122(6): 863-871.
6. Morgan RA, Chinnsamy N, Abate-Daga D, Gros A, Robbins PF et al. (2013) Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. *J Immunother* 36(2): 133-151.
7. Bertoletti, A and C, Ferrari (2016) Adaptive immunity in HBV infection. *J Hepatol* 64(1 Suppl): S71-83.
8. Jo J, Lohmann V, Bartenschlager R, Thimme R (2012) Experimental models to study the immunobiology of hepatitis C virus. *J Gen Virol* 92(Pt 3): 477-493.
9. Pasetto A, Frelin L, Aleman S, Holmström F, Brass A, et al. (2012) TCR-redirection of human T cells inhibit hepatitis C virus replication: hepatotoxic potential is linked to antigen specificity and functional avidity. *J Immunol* 189(9): 4510-4519.
10. Sautto GA, Wisskirchen K, Clementi N, Castelli M, Diotti RA, et al. (2016) Chimeric antigen receptor (CAR)-engineered T cells redirected against hepatitis C virus (HCV) E2 glycoprotein. *Gut* 65(3): 512-523.
11. Zhang Y, Liu Y, Moxley KM, Golden-Mason L, Hughes MG, et al. (2010) Transduction of human T cells with a novel T-cell receptor confers anti-HCV reactivity. *PLoS Pathog* 6(7): e1001018.
12. European Association for the Study of the Liver (2017) EASL Recommendations on Treatment of Hepatitis C *J Hepatol* 66(1): 153-194.
13. Krebs, Böttinger N, Huang LR, Chmielewski M, Arzberger S, et al. (2013) T cells expressing a chimeric antigen receptor that binds hepatitis B virus envelope proteins control virus replication in mice. *Gastroenterology* 145(2): 456-465.

14. Gehring AJ, Xue SA, Ho ZZ, Teoh D, Ruedl C, et al. (2011) Engineering virus-specific T cells target HBV infected hepatocytes and hepatocellular carcinoma cell lines. *J Hepatol* 55(1): 103-110.
15. Koh S, Shimasaki N, Suwanarusk R, Ho ZZ, Chia A, et al. (2013) A practical approach to immunotherapy of hepatocellular carcinoma using T cells redirected against hepatitis B virus. *Mol Ther Nucleic Acids* 2: e114.
16. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 45(4): 529-538.
17. Brechot C, Pourcel C, Louise A, Rain B, Tiollais P (1980) Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* 286(5772): 533-535.
18. Qasim W, Brunetto M, Gehring AJ, Xue SA, Schurich A, Khakpoor A (2015) Immunotherapy of HCC metastases with autologous T cell receptor redirected T cells, targeting HBsAg in a liver transplant patient. *J Hepatol* 62(2): 486-491.
19. Koh S, Anthony Tanato Tan, Lietao Li, Antonio Bertoletti (2015) Targeted therapy of Hepatitis B virus-related hepatocellular carcinoma: present and future. *Diseases* 4(1): 10.
20. Spear TT, Callender GG, Roszkowski JJ, Moxley KM, Simms PE, et al. (2016) TCR gene-modified T cells can efficiently treat established hepatitis C-associated hepatocellular carcinoma tumors. *Cancer Immunol Immunother* 65(3): 293-304.



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