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CAR T-cell bioengineering: Single variable domain of heavy chain antibody targeted CARs

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ABSTRACT

Redirecting the recognition specificity of T lymphocytes to designated tumour cell surface antigens by transferring chimeric antigen receptor (CAR) genes is becoming an effective strategy to combat cancer. Today, CAR T-cell therapy has proven successful in the treatment of haematological malignancies and the first CD19 CAR T-cell products has already entered the market. This success is expanding CAR design for broader malignancies including solid tumours. Nevertheless, CARs such as those built on antigen-specific single chain antibody variable fragment (scFv) may induce some adverse effects. Here, we briefly review CAR T-cell bioengineering and discuss selected important initiatives for improved T-cell reprogramming, function and safety. In this respect, we further elaborate on unconventional CARs structured on single variable domain of heavy chain (VHH) antibodies (single-domain antibodies) as an alternative to scFv, because of their interesting immunological and physicochemical characteristics and unique structure, which shows a high degree of homology with human VH3 gene family.

Contents

1. Introduction

One of the most attractive strategies in adoptive cancer immunotherapy is genetic manipulation of T-cells with chimeric T-cell receptor (TcR) genes to enhance lymphocyte activation and performance against tumours [1]. Early developments of adoptive cancer immunotherapies were restricted to construction of non-functional chimeric immunoglobulin-TcR complexes [2,3]. Subsequently, Gross and colleagues [4] showed a successful attempts in chimeric antigen receptor (CAR) bioengineering by recombining the rearranged gene segments coding for an immunoglobulin variable heavy and light chains to the C region exons of the TcR α and β chains. On transfection, this engineered CAR endowed the T-cell with a non-MHC restricted cytotoxic response against the antigen-bearing target cells [4]. It is now accepted that the

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use of antibody binding regions in CARs enables T-cells to bind to tumour associated antigens (TAAs) in a non-MHC-restricted manner and respond to binding epitopes that are not usually recognized by conventional TcRs. In principle, CAR may target any cell surface molecule, thus overriding tolerance to self-antigens and the antigen recognition gaps in the physiological T-cell repertoire [5–7].

CARs are typically composed of four components: a target recognition moiety, a spacer region, a transmembrane domain, and an intracellular signalling domain. The target recognition moiety is not restricted to immunoglobulins. Non-antibody molecules such as aptamers, endothelial growth factor polypeptide, heregulin, IL-13 mutein and natural killer cell receptor NKG2D have also served as alternative targeting moieties [8–14]. The spacer region is typically composed of C_H2 and C_H3 domains (the hinge region) of the immunoglobulin heavy chain (mostly IgG1), which improves target binding and signalling. The transmembrane domain is usually composed of membrane-spanning sequences of membrane proteins such as CD4, CD8, CD28, CD3ζ, and FcεRIγ, whereas the intracellular signalling domain consists of either the ζ-chain of the TcR complex or the γ-chain from FcεRI. Historically, the first generation cytotoxic CARs were comprised of scFv-CD3ζ or scFv-Fcγ, but these cells did not show enhanced proliferation and prolonged survival. To address this problem, second generation CARs incorporated the signalling domain of a co-stimulatory molecule such as CD28, 4-1BB (CD137) and OX40 (CD134), which endowed T-cells with efficient target cell lysis, proliferation and cytokine secretion [15,16]. Subsequently, third generation CARs incorporated multiple co-stimulatory domains, as in combinations of CD28 and 4-1BB or CD28 and OX40, where engineered T-cells showed superior functional and cytotoxic activities compared with those encoding a single co-stimulatory domain [17–20].

In this perspective, we briefly examine advantages and disadvantages surrounding conventional CAR T-cell therapy, and discuss alternative initiatives in CAR T-cell engineering and function with particular emphasis on single variable domain of heavy chain (VHH) antibodies (or single-domain antibodies).

2. Advantages and limitations with CAR targeting

CAR-modified T-lymphocytes offer several advantages over T-cells expressing full-length TcRs. First, tumour-specific T-lymphocytes respond to antigens in a non-MHC-restricted manner. Therefore, the same CAR construct may be employed for treating patients of all MHC haplotypes, where the engineered T-cells may recognize and eradicate tumour cells that have down-regulated MHC expression [21,22]. Second, possible mispairing of transferred receptors with the endogenous TcR could be avoided [23]. Third, unlike conventional TcRs, the potential range of target antigens is no longer restricted to protein-derived peptides and may be extended to carbohydrate and glycolipid antigens. In addition to these, CAR transduced $CD4^+$ and $CD8^+$ T-cells could generate more durable anti-tumour helper and cytotoxic T-lymphocyte responses. Finally, CARs may improve receptor specificity through repertoire of existing monoclonal antibodies against tumour cell surface antigens.

On the other hand, there are several limitations and concerns with CAR-modified T-cells. The first important issue is antigen selection, since antigen expression level and the extent of epitope exposure on target cells can modulate CAR binding, specificity and downstream signals, and hence the overall performance in cancer cell killing [24]. Notwithstanding, empirical observations have indicated that the CAR's spacer region affect T-cell specificity and function [25], but no definitive structure-activity principles have yet emerged [26,27]. Another limitation is the non-MHC restricted nature of the CAR-modified T-cells and the possible presence of soluble antigens (antigens released by the tumour into the circulation), which can potentially decrease CAR T-cell functionality and hence its therapeutic efficacy [28,29]. In addition to this, CAR targeting should be restricted to TAA's that are minimally expressed in healthy tissues as to avoid possible autoimmune responses.

A variety of CAR engineered T-cells targeting tumour specific antigens such as CD19, CAIX, CD20, α-folate receptor (FR), carcinoembryonic tumour antigen (CEA) and CD30 have been generated and investigated in clinical trials [30–35]. However, immunogenicity could be a problem in CAR T-cell therapies, where immune responses are typically towards the extracellular antigen recognition domain (e.g., scFvs, derived from murine origin) [30–32]. Indeed, human anti-mouse antibody (HAMA) responses may competitively block CAR binding to cell surface antigens and thus affect the efficacy of immunotherapy and in vivo persistence of CAR-modified T-cells. Immunogenicity has also surfaced with CARs incorporating humanized scFvs regions [36], and perhaps such immunological risks may even apply to CARs with antigen recognition domains based on fully human antibodies [37].

Finally, tumour cells may escape T-cell surveillance due to poor antigen expression by target cells or mutation of antigenic epitopes recognized by T-cells. Thus, the extent of tumour escape will be dependent on antigenic diversity and polyclonality of the T-cell response [38,39]. A serious limitation concerning monoclonality of the effector T-cells is the emergence of tumour cell escape-variants that are no longer affected by CAR-modified T-cells [40,41].

3. Recent initiatives in improving CAR T-cell engineering and function

3.1. Variable domain heavy chain antibody (VHH) targeted CARs

The discovery of heavy-chain antibodies (HCAbs) has provided new opportunities in biological targeting and synthetic biology [42]. These unique forms of antibodies were initially found in camelids and unlike a conventional IgG1 it lack light chains and the C_H1 domain, and comprises only heavy chains, where each heavy chain contains a short single variable hinge (termed VHH or nanobody) and two constant domains (C_H2 and C_H3) [43]. VHH is the smallest intact functional antigen-binding fragment of HCAbs. The architectural features of VHHs include four framework regions (FRs) forming the core structure of the immunoglobulin domain, and three complimentarity-determining regions (CDRs), which engages in antigen binding [43,44]. CDRs display non-canonical structures in CDR1 and CDR2 loops, a relatively longer CDR3 loop compared with those in human and mouse antibodies, and a second intra-domain disulfide bond that connects CDR3 with the CDR1 [43].

Camelid VHHs are distinctly close to human germ-line sequences (i.e., sequences are very similar to family III of human variable heavy chain with more than 80% similarity) [43,44]. Accordingly, camelid VHH domains remain a valuable source of easily humanized single-domain antibody drugs [43]. VHHs are small (~15 kDa), almost half of the molecular weight of scFv [43,44]. Furthermore, they are highly soluble and highly stable at high temperatures (80–92 °C) and extremes of pH ranges and can bind to their target at high concentrations of chaotropic agents [43]. The affinities of VHH fragments fall in the nanomolar to picomolar range and their binding kinetics is comparable to those of conventional antibodies [43]. VHHs also express a low tendency for aggregation, a known cause of immunogenicity in therapeutic proteins [45]. As a result of these collective properties, VHHs are being deployed in different experimental and clinical settings, including targeting of uncommon or hidden epitopes and more recently in CAR T-cell engineering [43,46–50]. As a success story in the development of VHH drugs, Cablivi (caplacizumab) is the first regulatory approved nanobody, [The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use] indicated for acquired thrombotic thrombocytopenic purpura.

There are limited efforts in CAR bioengineering with single-domain antibodies. In this respect, our own efforts have focused on developing CAR-modified T-cells using an anti-MUC1 VHH as the targeting moiety

with the spacer regions of the human IgG3 [51,52], where the PhiC31 integrase system was used as an integration tool for VHH targeted CAR constructs to decrease the risk of insertional mutagenesis and long-term transgene expression [53]. Incorporation of a co-stimulatory domain (OX40) into the anti-MUC1 VHH CAR construct has further optimized T-cell activation and IL-2 production [54]. For creating a third generation VHH targeted chimeric antigen receptors with a safety switch, we also constructed a regulated dimerization system with caspase 8 as a suicide gene system and showed its efficacy in vitro as a proof of concept [54].

Others have developed a new VHH against CD38 (an oncogenic marker over-expressed in multiple myeloma) and constructed a CD38-CAR that was composed not only of the engineered VHH as the targeting domain, but also 4-1BB and CD3ζ as the co-stimulatory and activating domains, respectively [55]. This strategy eradicated CD38 positive tumours both in vitro and in vivo with transduced $CD3^+$ T-cells. To counter the outgrowth of antigen escape variants, another study has engineered functional CARs with a tandem of two single VHH domains targeting CD20 and HER-2 [56].

3.2. CAR redirecting by oligoclonal VHHs

Multi-targeting CAR T-cells that recognizes different antigenic epitopes on a cell-surface antigen can mount a more effective cytotoxic response compared with T-cells that largely rely on a single epitope. Thus, an engineered polyclonal CAR T-cell could potentially prevent the development of tumour cell escape variants, since the probability of losing all target epitopes in a tumour cell is rather low [57]. To this end, efforts have been directed to generate and characterise a panel of epitope-distinct engineered T-cells that express the second and third generation of CARs with TAG-72 and HER-2 specific VHHs as targeting moieties [45,58,59]. These attempts have provided the proof-of-concept and demonstrated the feasibility of employing epitope-distinct VHHs for generating the oligoclonal engineered T-cells that are able to strikingly recognize different epitopes on an antigen and specifically lyse the antigen-expressing cells [45,58,59]. These examples mirror the use of non-competitive antibody combinations to combat tumours (e.g., trastuzumab and pertuzumab that bind to different subdomains of the HER2 extra cellular domain) in a synergistic manner [60]. Another similar approach is the NanoCAR technology; a strategy that generates CAR T-cells armed with two single-domain antibodies capable of simultaneously triggering two cancer-killing pathways [56,61].

3.3. Alternative emerging approaches in CAR function improvement and safety

Recently, a switchable universal CAR platform (termed UniCAR system) was introduced to improve the safety of CAR T-cell therapy as in overcoming cytokine release syndrome and "on-target", "off-tumour" reactions [62]. UniCAR comprises two components; a UniCAR T-cell and a replaceable tumour-specific target module (TM). The UniCAR construct is also formed from an extracellular antibody-derived binding moiety, a transmembrane domain and intracellular activation motifs (CD3ζ and CD28 for signal transduction). However, unlike conventional CARs, the extracellular binding domain of UniCARs does not recognize a certain TAA on target cells. Instead, a short peptide epitope (UniCAR epitope) is employed to tag the TM. Accordingly, UniCAR-modified T-cells are inactive, but the TM, confers the UniCAR system its tumour specificity. As an example, a bivalent epidermal growth factor receptor TM (α-EGFR-EGFR) was shown to successfully redirected UniCAR T-cells to tumour cells expressing low levels of EGFR and induced effective killing [62]. However, a potential problem associated with this approach is the need to engineer the targeting antibody each time.

Other popular approaches in safety improvement have included split T-cell dosing and employing short-lived T-cells [63], incorporation of suicide genes in T-cell reprogramming [53,64,65], and combination approaches involving targeted T-cells and chemotherapy [66]. More complex approaches have included the introduction of antigen sensing circuits controlled by the SynNotch receptor [67] and multiplex genome edited T-cells [68,69]. For instance, the SynNotch receptor consists of an antigen sensing extracellular domain, which on binding to its specific antigen triggers the proteolytic activity of the intercellular domain. After proteolysis and transcription factor release, transgene expression is activated [70]. Thus, by placing the CAR-expressing sequence downstream of a promoter regulated by SynNotch transcription activator may improve CAR T-cell selectivity. Indeed, antigen detection via SynNotch could accumulate T-cells in the malignant tissue prior to CAR expression. Next, on recognizing the second antigen CAR will activate the T-cell. Through this mechanism, T-cells may discriminate between malignant cells expressing only one of the antigens and those with two combined antigens on their surface [67]. With respect to multiplex genome editing, a transcription activator-like effector nuclease (TALEN)-mediated editing approach has been used for the production of TcR and CD52 deficient T-cells, where the engineered T-cells did not mediate graft-versus-host disease [68]. In another study, T-cell receptor and deoxycytidine kinase (dCK) were processed using TALEN editing system in order to overcome both graft-versus-host and host-versus-graft diseases [69].

There are examples of alternative bioengineering initiatives, which potentially can improve CAR T-cell safety and target specificity. One such approach is the split, universal, and programmable CAR system (SUPRA) that presents a combination of many features in one package [71]. These smart CAR T-cells are modular, flexible and controllable by means of a leucine zipper as their extracellular domain (which is complementary to another zipper known as ZipFv) attached to the intended antigen-binding domain. A single universal "zip CAR" can bind to several scFvs specific for multiple antigens with various affinities. The ZipFvs may express different affinity for each other and the leucine zipper, allowing their utilization for off switch functions and combinatorial antigen sensing mechanism. Furthermore, splitting the intracellular signalling domains of CAR construct may aid antigen recognition in an orthogonal pattern. Moreover, to control response quality independently, distinct receptors have been engineered and inserted to different subtypes of T-cells (CD4 and CD8) [71]. Through this system, the immune response against cancer would be tuneable by altering the affinity and the dosage of each zip CAR and changing the T-cell subset expressing the receptor.

4. Clinical studies

4.1. Haematological malignancies

Haematological malignancies have been at the forefront of CAR T-cell therapies (Table 1). CD19 (expressed on B cells, but not on other

Table 1
Examples of CAR T-cells in clinical trials for haematological malignancies.

Target	CAR generation	Malignancy	Reference
CD20	3rd	$CD20^+$ Lymphoma	[92]
CD19	2nd	Multiple Myeloma	[93]
CD22	2nd	B-ALL, DLBCL, NHL, FL	[94]
CD19	2nd	B cell leukaemia	[95]
CD19	2nd	Relapsed and refractory CLL	[96]
CD19	2nd	Relapsed and refractory ALL	[97]
CD33	2nd	AML	[98]
CD20	2nd	DLBCL	[99]
CD19	2nd	ALL, DLBCL	[100]
CD19	2nd	CLL, DLBCL	[101]
CD19	2nd	Relapsed and refractory ALL	[73]
CD19	2nd	ALL, CLL	[102]
CD20	3rd	FL, Mantle cell lymphoma	[103]

ALL = Acute lymphoblastic leukaemia; AML = Acute myeloid leukaemia; B-ALL = B-cell ALL; CLL = Chronic lymphocytic leukaemia; DLBCL = Diffuse large B-cell lymphoma; FL = follicular lymphoma; NHL = Non-Hodgkin lymphoma.

Table 2
Examples of CAR T-cell trials for solid tumours.

Target	CAR generation	Malignancy	Reference
HER-2	2nd	Sarcoma	[85]
CEA	2nd	Adenocarcinoma liver	[104]
IL13RA2	1st	Glioblastoma	[105]
CAIX	1st	Renal cell carcinoma	[106]
HER-2	3rd	Colorectal cancer	[107]
GD2	1st	Neuroblastoma	[84]
CD171	1st	Neuroblastoma	[108]
α-folate receptor	1st	Ovarian cancer	[30]

HER-2 = Human epidermal growth factor receptor 2; CEA = Carcinoembroyonic antigen; IL13Ra2 = Interleukin 13 receptor subunit α-2; CAIX = Carbonic anhydrase IX; GD2 = Disialoganglioside GD-2; CD171 = Neural cell adhesion molecule L1.

normal or malignant tissues) is the most investigated target to date [72]. Indeed, CD19 CAR T-cell therapies have been a great success in the treatment of patients with B cell malignancies [73–76]. The first CAR T-cell therapeutic, Kymriah (CD19 CAR T-cell, tisagenlecleucel), has already received approval from the US Food and Drug Administration (FDA) and the EMA for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia that is refractory or in second, or later relapse. More recently, FDA has also given approval to Kymriah for treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma. EMA has further approved Kymriah for diffuse large B-cell lymphoma in adults whose cancer has come back or did not respond after two or more previous treatments. Currently, there are nearly 500 different CAR T-cell-based clinical trials being conducted across the world. Worth an estimated of $170 million, the market of CAR T-cell is expected to maintain a compound annual growth rate of 46.2% from 2019 to 2028. These enviable figures are partly due to Kymriah's demonstrated efficacy.

Other targets that are frequently expressed on B cells and non-Hodgkin lymphoma are CD20 and CD22 [77,78], which may be used in CAR T-cell engineering and particularly in cases where CD19 is down regulated or mutated [79,80]. Indeed, leukaemia's that re-emerge after CD19-directed therapy has a higher rate of CD19 splice variation/mutation. Accordingly, bi-specific CARs may address these problems. For instance, an anti-CD20-CD19 bi-specific CAR T-cell was able to kill patients' chronic lymphocytic leukaemia cells in vitro [81]. Furthermore, this approach also cleared paediatric acute lymphocytic leukaemia with a mixed $CD19^{+}CD20^{+}/CD20^{-}$ phenotype from the blood and bone marrow of transplanted mice, whereas anti-CD20 CAR T-cells did not improve the condition [81]. A phase I clinical study is currently evaluating the safety, efficacy and duration of response of anti-CD19 anti-CD20 bi-specific CAR redirected autologous T-cells in patients with high risk, relapsed $CD19^{+}$ and $CD20^{+}$ haematological malignancies [82]. A phase I study of CD19/CD20 bi-specific nanobody-derived CAR T-cells is also ongoing in patients with refractory/relapsed B cell lymphoma [83].

4.2. Solid tumours

There are limited studies with CAR T-cells in the treatment of solid tumours (Table 2), since selection of appropriate safe targets for T-cell engineering is challenging. Nevertheless, some clinical studies have shown promising results [84,85]. For instance, in one study 19 patients with neuroblastoma were treated with GD2 specific CAR T-cells, where 3 patients showed complete remissions [84]. In a trial involving 19 HER-2 positive sarcoma patients treatment with HER-2 CAR T-cells resulted in disease stabilization in 4 patients up to 14 months [85].

5. Conclusions

CAR T-cells, either on their own right or in combination with other therapies, are in the frontline of advanced cell therapies and hundreds of clinical trials with engineered T-cells are underway [86]. However, not all patients benefit from such therapies (including combination strategies) and the toxicity issue remains a major concern as discussed above. Holistic approaches to CAR design and engineering are therefore needed not only to further improve the clinical outcome [81], but also to mitigate adverse reactions. To this end, and at least from the perspective of improving the therapy, CD19/CD20 bi-specific nanobody-derived CAR T-cells have now entered clinical trials [83]. Whether CARs built on VHHs and non-antibody entities could bring improved opportunities for safer and more effective T-cell re-programming in patients remain to be seen. Perhaps, VHH-based CARs can be employed in combination protocols involving nanoparticles/drug carriers decorated with bi-specific or multi-specific non-overlapping single-domain antibodies targeting tumour antigens [87]. Improved technologies are also in place for single-domain antibody humanisation and identification of potential immunogenic sequences [88,89]. Nevertheless, the unexpected toxicity in a phase I study of TAS266 (an agonistic tetravalent single-domain antibody targeting the DR5 receptor) is a reminder that immunogenic responses to single-domain antibodies can still occur [90]. While we await further developments in T-cell reprogramming and decentralised manufacturing [91], the current success story of CAR T-cells is expected to generate interest and investment in combating autoimmune diseases and challenging viral infectious diseases through T-cell bioengineering and re-programming.

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