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Review

Display, engineering, and applications of antigen-specific T cell receptors

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Abstract

The use of T cell receptors (TCRs) as potential therapeutic agents provides an opportunity to target a greatly expanded array of antigens, compared to those now targeted with monoclonal antibodies. With the advent of new display technologies and TCR formats for *in vitro* engineering, it should be possible to generate high-affinity TCRs against virtually any peptide antigen that is shown to bind to a major histocompatibility complex (MHC) molecule (e.g. peptides derived from viral antigens or from self proteins that are associated with the transformed phenotype). What remains, however, are challenges associated with effective targeting of very low numbers of cell surface antigens (pepMHC), fewer than the case for conventional monoclonal antibody-based therapies. This hurdle might be overcome with the attachment of more effective payloads for soluble TCR approaches, or by using TCR gene transfer into T cells that can then be adoptively transferred into patients. There is considerable work to be done on the physiological aspects of either approach, including pharmacokinetic studies in the case of soluble TCRs, and T cell trafficking, persistence, and autoreactivity studies in the case of adoptively transferred T cells. As with the field of monoclonal antibodies, it will take time to explore these issues, but the potential benefits of TCR-based therapies make these challenges worth the effort.

Keywords: Antigens; T cell immunity; High-affinity T cell receptors; Tumor targeting; Peptide-major histocompatibility complex; Monoclonal antibodies

Contents

1. Introduction

Jawed vertebrates evolved a system of adaptive immunity that relied on two different types of lymphocytes, T and B cells

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(Pancer and Cooper, 2006). The antigen-specific molecules from B cells, antibodies, are well known. The analogous antigen-specific molecules on T cells, T cell receptors (TCRs), have been characterized only in the past 20 years (Davis and Bjorkman, 1988). While the genetic mechanisms that yield extensive diversity in antibodies and TCRs are similar, there are several fundamental differences between these two classes of molecules that are of relevance to the present review. First, unlike antibodies, TCRs bind to foreign antigens only when they are presented as short peptides bound to a product encoded by the major histocompatibility complex (MHC) (Zinkernagel, 1997). This property assures that a T cell will be stimulated only by another cell type that expresses on its surface an MHC product (i.e. it restricts T cells to ''cell to cell'' interactions). A second fundamental difference is that TCRs do not undergo somatic hypermutation, and consequent affinity maturation, that is a hallmark of an antibody response (Eisen, 2001) (Foote and Eisen, 2000). Thus, virtually all normal TCRs are of relatively low affinity (Krogsgaard and Davis, 2005). Finally, unlike antibodies, TCRs function exclusively as cell surface molecules. To function optimally as a cell surface receptor, T cells exploit a signaling system that amplifies TCR:antigen interactions such that binding of only a few antigen molecules (pepMHC) can trigger T cell activation (Irvine et al., 2002; Purbhoo et al., 2004).

The importance of T cells in immune defense is now widely appreciated. Recognition and destruction of cancer cells by T cells is particularly challenging, as potential ''foreign'' antigenic peptides are almost always derived from self-proteins (Boon and Old, 1997; Rosenberg, 2001). Because T cells are deleted if they react with self (to achieve ''tolerance''), cancer cells can escape T cell immunity due to an absence of T cells with TCRs that react strongly with a cancer antigen (Ho et al., 2003). Recently, Rosenberg and colleagues have attempted to overcome this challenge by adoptive transfer of T cells that have been transduced with a tumor-specific TCR (Morgan et al., 2006). Despite encouraging results, cancer regression was observed in a limited number of the patients (2/17). As they and others have suggested, further engineering of the TCR might improve such treatments.

Notwithstanding the possible problems associated with T cell tolerance in cancer patients, surveillance of intracellular pathogens or mutated self proteins has evolved such that T cells are capable of detecting as few as 3–10 pepMHC molecules on a target cell (Krogsgaard and Davis, 2005). This recognition is accomplished despite the fact that TCRs have affinities (K_D values) in the 1–100 μM range. In contrast, monoclonal antibodies now used in therapy of some cancers typically target cell surface antigens that are expressed at much higher levels per cell (e.g. over 10,000 CD20 molecules on lymphomas) (Tsimberidou et al., 2006; Wang et al., 2006), and antibodies have been engineered to have affinities that are in the nanomolar or sub-nanomolar range (Hoogenboom, 2005). Recently, there have been efforts to apply similar strategies to engineer higher affinity TCRs in order to target this entirely distinct class of antigens, those expressed intracellularly and presented by MHC products. The display and engineering of

Table 1
Affinity-matured T cell receptors or T cell receptor fragments

TCR/high affinity mutant	Ligand	Display system	Library size	WT K_D[a]	Mutant K_D	WT k_{on} (M^{-1} s^{-1})	Mutant k_{on} (M^{-1} s^{-1})	WT k_{off} (s^{-1})	Mutant k_{off} (s^{-1})	References
2C/2C-m6 (mouse)	QL9/L^d	Yeast	1×10^5	3 μM	10 nM	6×10^3	4.2×10^4	2×10^{-2}	4.2×10^{-4}	Holler et al. (2000, 2001)
2C/2C-m33 (mouse)	SIYR/K^b	Yeast	1×10^5	32 μM	28 nM	2.3×10^3	2.3×10^5	7.5×10^{-2}	6.6×10^{-3}	Holler et al. (2003)
3.L2/3.L2-m15 (mouse)	Hb/I-E^k	Yeast	1.5×10^6	16 μM	51 nM	5.2×10^3	2.8×10^5	1×10^{-1}	6.8×10^{-3}	Weber et al. (2005)
A6/A6c134 (human)	A2-tax	Phage	3×10^6	1.8 μM	2.5 nM	1.1×10^5	Not reported	9.3×10^{-2}	2.2×10^{-4}[b]	Li et al. (2005) and Ding et al. (1999)
1G4/1G4c113 (human)	A2-NY-ESO	Phage	1×10^7	32 μM	26 pM	4×10^4	6.6×10^5	1.3×10^{-1}	1.7×10^{-5}	Li et al. (2005) and Dunn et al. (2006)
Vβ8.2/mL2.1/A52V (mouse)	SEC3	Yeast	3×10^5	9.2 μM	7.3 nM	Not reported	Not reported	Not reported	Not reported	Kieke et al. (2001) and Malchiodi et al. (1995)
Vβ2.1/D10 (human)	TSST-1	Yeast	3×10^7	0.6 μM	180 pM	Not reported	2.6×10^5	Not reported	4.6×10^{-5}	Buonpane et al. (2005)

[a] For many TCRs, multiple binding and rate constants have been reported. In these cases, we have chosen to present a single value that is within approximately 2–3-fold of the other reported values.
[b] Calculated from reported $t_{1/2}$ ($\ln 2/t_{1/2} = k_{off}$).