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REVIEW

Manipulating T cell-mediated pathology: Targets and functions of monoclonal antibody immunotherapy

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Abstract Monoclonal antibody (mAb) technology has revolutionized treatment options for T cell mediated diseases. However, a safe, clinically available anti-T cell antibody (ab) remains elusive. Experience with anti-T cell agents and their propensity for causing immune-mediated toxicities have hampered the development of anti-T cell mAb's. Furthermore, misunderstanding regarding mechanism(s) of action of particular antibodies can influence development and clinical prescription habits. For example, the anti-CD3 Ab OKT3 is consistently described as a depleting Ab even though original studies showed the mechanism to be non-lytic. Future anti-T cell mAbs are likely to be non-depletional and focused on the expansion of regulatory T cells. This review discusses how the properties of Abs can be exploited for manipulating pathological T cell responses in the clinic.

Contents

Abbreviations: Ab, antibody; ADCC, Antibody dependent cellular cytotoxicity; AICD, activation induced cell death; ATG, Anti-thymocyte globulin; ATGAM, Lymphocyte immune globulin; APC, Antigen presenting cells; CDC, Complement dependent cytotoxicity; CIA, Collagen induced arthritis; EAE, Experimental Autoimmune Encephalomyelitis; HLA, Human Leukocyte Antigen; ITAM, Immunoreceptor Tyrosine-Based Activation Motif; LFA, Lymphocyte Functioning Antigen; MHC, Major Histocompatibility Complex; MS, Multiple Sclerosis; NOD, Non-obese diabetic mouse; SMAC, Supra-molecular activation cluster; T1D, Type 1 Diabetes; TCR, T cell receptor.

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1. Introduction

The immunopathologic mechanisms driving autoimmune diseases, such as multiple sclerosis (MS) and type 1 diabetes (T1D), as well as allograft rejection are similar in that immunopathology is mediated by antigen-specific T cells. In most animal models of autoimmunity (uveitis, myocarditis, experimental autoimmune encephalitis (EAE), T1D, collagen induced arthritis (CIA) [1–5], disease development is significantly delayed or prevented by depleting or altering the function of autoreactive T cells. A number of therapies capable of modulating T cells have been tested experimentally in rodents and human clinical studies. Table 1 outlines clinically applied T cell targeting therapeutics, and associated mechanisms and observed side effects. These include (a) polyclonal Abs derived from horses or rabbits against thymocyte antigens (rabbit/equine anti-thymocyte globulin – ATG) [6]; (b) Abs and fusion proteins capable of antagonizing co-stimulation, including abatacept and Belatacept [7–11]; (c) mAb against the leukocyte antigen CD52 (alemtuzumab) [12,13]; (d) as well as Ab therapies directed against proteins, such as $\alpha 4\beta 1$ integrin (VLA-4), which are important for T cell trafficking [14]. Unfortunately, most of these therapies not only impact T cells but target various subsets of leukocytes resulting in broad immune suppression and increased risk for opportunistic infections and malignancies [15]. In addition, some therapies, including co-stimulation blockade, may not provide sufficient modulation required to inhibit strong immune reactions, such as acute allograft rejection. Next generation anti-T cell Abs will need enhanced specificity, affecting only disease relevant T cells to minimize unwanted complications. Ideal candidates may induce inactivation of T cells through non-lytic mechanism(s), promoting anergy, apoptosis and/or regulatory T cell expansion without triggering cytokine release syndrome or serum sickness associated with T cell activation and cellular depletion [16].

Here we provide a summary of potential anti-T cell mAbs and their associated functions with the aim of informing clinicians and assisting in the future development of safer and more specific T cell inactivating therapeutics.

2. Primary T cell targets

Due to limited efficacy and adverse effects associated with anti-CD3 Abs, cache with TCR targeting has waned in recent years. Notwithstanding, the TCR complex remains an attractive target since virtually all T cells express a TCR, and inhibiting TCR signaling effectively blocks activation and expansion of T cells. Notably, recent reports suggest that targeting other components of the TCR (Table 1), with anti-$\alpha\beta$TCRAb for example, may overcome the limitations associated with anti-CD3Ab [16,17]. The TCR is a multimeric complex consisting of heterodimer $\alpha\beta$ or $\gamma\delta$ chains associated with CD3 complex proteins [18]. Signaling through the $\alpha\beta$TCR occurs after the formation of a supra-molecular activation cluster (SMAC) on the T cell. The $\alpha\beta$ and $\gamma\delta$ TCR chains lack intracellular signaling domains, and therefore are dependent on the CD3 complex to initiate downstream signaling events [19] In addition to these proteins, the co-receptors (CD4 or CD8) [20,21] and CD2 [22] also play important roles in SMAC stabilization and TCR signal potentiation under normal physiological conditions.

While many TCR-specific mAbs function through non-depleting mechanisms, a variety of depleting Abs are used clinically to treat T cell pathologies (Table 1). These therapies include polyclonal cocktails (e.g. ATG) as well as Abs to antigens expressed by most cellular components of the immune system, with anti-CD52 (e.g. alemtuzumab) being the primary example. In both cases these Abs function through depleting mechanisms and are associated with long-term immune suppression. Even though alemtuzumab is expected to gain approval for the treatment of MS in 2013, a move away from such non-specific broad acting therapeutics is desirable.

2.1. TCR and accessory molecules

The most specific regulatory body approved anti-T cell agent was OKT3 (muronomab) [23]. OKT3 is no longer available potentially due to its propensity to induce intracellular tyrosine activation motif (ITAM) mediated cytokine release syndrome as well as other life threatening events. Alterations to the Fc portion of anti-CD3 Abs were engineered in an attempt to increase the safety of OKT3 [24,25], however, while reduced compared with OKT3, these Abs still induced cytokine release and were associated with narrow therapeutic indices [26–29]. Arguably this is to be expected, considering the primary physiological role of CD3 in T cell activation and the fact that anti-CD3Ab or variants thereof appear to target a similar epitope expressed within the CD3ε chain [30].