MINIREVIEW

Soluble T-Lymphocyte Antigen-Specific Immunoproteins: A Progress Report[1] (44088)

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The specificity of the immune system is determined by membrane-bound and extracellular proteins specific for the immunogen. B lymphocytes amplify their specific recognition of antigen by the production of soluble immunoglobulins with combining sites identical (or very similar) to the heavy and light chain variable regions of the B-cell membrane immunoglobulin receptor for antigen. Antigen-specific T-lymphocyte function is also induced by cell membrane–associated, immunoglobulin-like receptors for antigen. These T-cell receptors for antigen (TCR) recognize specifically fragments of antigen processed by antigen-presenting cells and presented in association with class I or II glycoproteins encoded by genes in the major histocompatibility complex (MHC) (1, 2).

Although the membrane-associated TCR is specific for MHC/peptide, some T cells produce soluble proteins that bind native (non-processed) antigen specifically, and some of these immunoproteins mediate immunoregulation and/or hypersensitivity (reviewed in Refs. 3–5). In a previous minireview (3), soluble (extracellular) antigen-specific T-cell immunoproteins were described, and it was concluded that future studies "require definition of the molecule through sequence of amino acids and/or nucleotides." This updated minireview will consider serological, structural, and molecular/genetic evidence suggesting strongly that soluble antigen-specific T-cell immunoproteins are related to or derived from the TCR. Moreover, the demonstration of *in vivo* activity of soluble antigen-specific T-cell immunoproteins suggests a critical role for these molecules in maintaining immunologic homeostasis.

Characteristics of Soluble Antigen-Specific T-Cell Immunoproteins

Table I divides soluble antigen-specific T-cell immunoproteins into functional groups: proteins that induce immunoregulatory (suppressor) T cells (T suppressor T-cell inducer factor [TsFi] and proteins that effect immunoregulation (TsFe) or "protect" cells from TsFe-induced immunoregulation (contrasuppressor factor [TcsF]). TsFi and TsFe are distinguished by monoclonal (6, 7) antibodies and functionally may be restricted by MHC class II (TsFi) or class I (TsFe) gene products. However, TsFi, TsFe, and TcsF all bind specifically to non-processed antigen (review in Refs. 4 and 5). A variety of molecular species with TsFe and TsFe activity (M_r 25,000–110,000) have been described (1–5). These species probably are aggregates of M_r 22,000 hydrophobic "protomers." A recent report describing the stabilization of TsFi in octylglucoside (6) should facilitate efforts to purify and characterize these soluble antigen-specific T-cell immunoproteins.

T-cell immunoproteins defined only by their ability to bind specifically to native antigen are given the generic term T-cell antigen-binding molecule (TABM). Our laboratory has characterized TABM by isolation using antigen affinity chromatography and antigen-capture assays as shown in Figure 1 (8–12). Soluble antigen-specific T-cell immunoproteins produced by T-cell hybridomas have also been demonstrated by the ability of these proteins in solid phase to capture soluble antigen (13). Like TsFi and TsFe, TABM have been found

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Table I. Characteristics of Soluble Antigen-Specific T-Cell Immunoproteins

	TsFi	TsFe	TcsF	TABM
Anti-TCR Cα	+	+	+	+
Anti-TCR Cβ	−	+	±	+
Anti-TsFi	+	−	n.t.	+
Anti-TsFe	−	+	n.t.	+
Anti-TABM/TsFi	+	+	n.t.	+
Anti–IL-10	+	+	n.t.	+
Prostaglandin E	n.t.	+	n.t.	n.t.
GIF	n.t.	+	n.t.	n.t.
Amino acid sequence similarity	n.t.	n.t.	n.t.	TCR Cα TCR Vα Ig Vκ FrIII Pre-TCR α
Inducer of immunoregulatory T cells	+	−		+
Effector of immunoregulation	−	+		+
Inhibitor of immunoregulation (contrasuppression)	−	−	+	n.t.

n.t. = not tested.

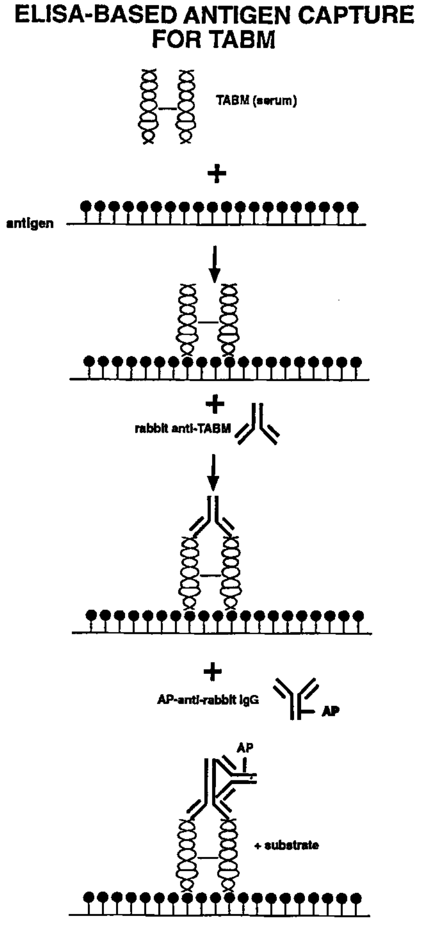

Figure 1. ELISA-based antigen capture for TABM. TABM in serum or other fluids are added to antigen-coated wells of microtiter trays. After washing, a rabbit anti-TABM is added, and bound anti-TABM detected by alkaline-phosphatase-conjugated goat anti-rabbit IgG. *P*-nitrophenyl phosphate substrate is added, and the optical density of the well determined. TABM are represented as non-covalently linked dimers of M_r 25,000 polypeptide chains. The dimers are linked by disulfide bonds. Larger, disulfide-linked polymers are likely.

to have a range of molecular sizes from M_r 22,500–110,000 (reduced) and appear to be composed of hydrophobic (>45% nonpolar amino acids) (10, 11) protomers that readily aggregate. Functionally, TABM have TsFi or TsFe activity (14–16). As shown in Table I, more recent structural, functional, and serologic information supports the contention that TABM provide antigen specificity to antigen-specific immunoregulatory T-cell factors.

Epitopes Associated with Soluble Antigen-Specific T-Cell Immunoproteins

There is a growing body of evidence that TsFi, TsFe, and TABM are recognized by monoclonal antibodies to TCR Cα- and (sometimes) Cβ-chains (Table I). Generally, this evidence has been obtained by adsorbtion of immunoregulatory activity in T-cell hybrid culture medium or serum to affinity beads conjugated with monoclonal anti-TCR Cα or Cβ antibodies (17–27). TsFi, TcsF, and TABM absorb to anti-TCR Cα affinity beads and some are adsorbed to both anti-TCR Cα and anti-TCR Cβ affinity beads. Because TsFi and some TABM are not adsorbed by anti-TCR Cβ antibodies, there are probably TCR $C\alpha^+$, $C\beta^+$ and TCR $C\alpha^+$, $C\beta^-$ molecules. Anti-TCR affinity beads may be better tools to adsorb TsFi or TsFe activity, while the antibodies may not be as effective in enzyme-linked immunosorbent assay (ELISA) or immunoblotting. This could be due to a lower affinity of these antibodies for TsFi or TsFe or these antibodies are not as effective in immunoassay with very small amounts of antigen. On the other hand, anti-TCR Cα, but not anti-TCR Cβ, detect TABM binding to 1–2 μg of antigen in an antigen capture ELISA such as shown in Figure 1 (19, 20). In addition, a TABM purified by antigen affinity was identified by monoclonal anti-TsFi and anti-TCR Cα, but not anti-TCR Cβ (28). Thus, present information on TsFi, TsFe, and TABM produced *in vitro* or *in vivo* suggests that these immunoproteins are TCR $C\alpha^+$, $C\beta^-$ or TCR $C\alpha^+$, $C\beta^+$.

In addition to I-J determinants (6, 15), antigen-specific immunoregulatory T-cell "factors" associated with interleukin-10 (IL-10) (6) or glycosylation inhibition factor (GIF) (29, 30) have also been reported. Moreover, a TCR $C\alpha^+$ molecule associated with a non-specific suppressor factor (NSF) has been described in human ascitic fluid (31). NSF has been cloned (32) and is likely ubiquitin and/or transforming growth factor–β (TGFβ). These associated cytokines may be adsorbed to the antigen-specific T-cell protein or incorporated by post-synthetic modification (29, 30). The close association between T-cell antigen-specific immunoproteins and immunoregulatory cytokines led to the suggestion (5) that TsFi and TsFe function by "delivering" immunoregulatory cytokines to an appropriate target.

Table II. Molecular Genetics of Soluble Antigen-Specific T-Cell Immunoproteins

	TsFi	TsFe
Expression of TCR Vα	+	+
Expression of TCR Vβ	−	+
Expression of TCR Cα	+	+
Expression of TCR Cβ	−	+

Structural Properties

A detailed picture of soluble antigen-specific T-cell immunoproteins will require the elucidation of their primary structure and the purification of amounts sufficient for physicochemical analysis. Because TABM are >45% nonpolar amino acids (10, 11), the hydrophobic nature of these immunoproteins causes considerable difficulty in their characterization. A sequence of amino acids of the amino terminus or peptides prepared by treatment of TABM with cyanogen bromide demonstrated that monoclonal TsFi/TABM specific for azobenzenearsonate (ABA) or nitrophenyl acetate (NP) are similar (but not identical) to each other (11) and showed a FrIII immunoglobulin light chain variable framework and a TCR α-chain variable region framework. In addition, an amino acid sequence of a tryptic peptide of an NP-specific TABM derived from a T-cell hybridoma showed striking similarly to a TCR Cα peptide and to a pre-TCR α-chain (28). Monoclonal anti-TCR Cα antibodies and polyclonal antibodies prepared against a murine recombinant TCR pre-α-chain (provided by J. J. Marchalonis) bind to a synthetic peptide based on the amino acid sequence of the TABM (Cone RE, unpublished observation). In summary, the emerging protein structural picture suggests that TABM are similar, but not identical, to TCR α-chains.

Molecular Genetics

Genes encoding TABM/soluble antigen-specific T-cell factors have not yet been cloned, but elegant functional studies point to T-cell receptor genes as being directly or indirectly responsible for these immunoproteins (Table II). T-cell hybridomas lacking a TCR Cβ or Vβ gene do not produce TsFe and expression of TCR β gene in a (previously) TCR β^- mutant restores expression of TsFe (27). Moreover, transfection of antisense for TCR α-chains prevents constitutive expression of a soluble TsFi. Transfection of an α-chain from a T-cell hybrid specific for a synthetic peptide (poly-18) confers the ability to produce a poly-18–specific immunoregulatory peptide (33). In vitro translation of a TCR α-chain produce an M_r 30,000 polypeptide chain that binds non-processed antigen and has immunoregulatory activity, while a translated TCR β-chain is not suppressive (33). Thus, soluble antigen-specific immunoregulatory proteins produced by T-cell hybrids express TCR α (and sometimes Cβ) epitopes and require the expression of TCR Cα and/or Cα and Cβ genes. Whether these proteins are identical or analogous to the TCR remains to be determined. The ability to express or inhibit expression of TsFi and TsFe by transfection of TCR genes implicates the TCR in expression of immunoregulatory proteins, and *in vitro* translation suggests that soluble TCR chains may indeed comprise the antigen-binding element of an antigen-specific immunoregulatory protein. Perhaps these immunoproteins detectably bind to non-processed antigen because they polymerize and form TABM. The soluble immunoregulatory protein may differ somewhat from the membrane-associated TCR because of post-synthetic modification. Simple amino acid substitutions of TCR α-chains could result in a soluble molecule (34).

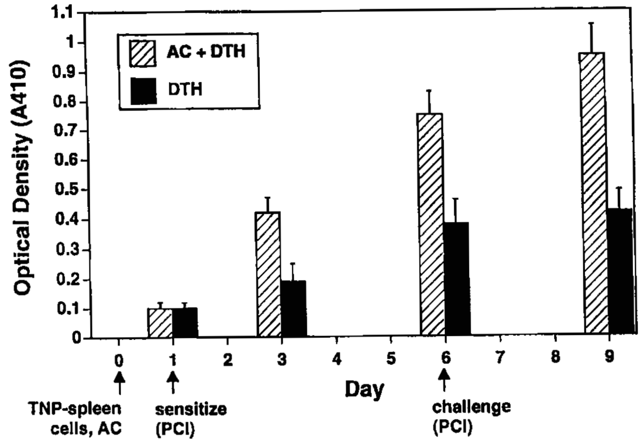

Figure 2. Injection of antigen into the anterior chamber of an eye of naïve mice potentiates the appearance in serum of TABM specific for the antigen after sensitization. The anterior chamber of an eye of naïve BALB/c mice received BALB/c TNP-spleen cells, and the mice were sensitized by epicutaneous application of picrylchloride (PCI) to the shaved abdomen. Five days after application of PCI, one ear was challenged by epicutaneous application of PCI. Mice were bled as indicated, and TNP-specific TABM quantified by antigen capture ELISA with TNP-BSA. (From Ref. 35.)

In Vivo Activity

TCR $C\alpha^-$, β^- TsFi that transfer inhibition of delayed-type hypersensitivity (DTH) has been demonstrated in the sera of mice receiving an injection of antigen into the anterior chamber (AC) of the eye (18). AC injection of naïve mice with trinitrophenylated spleen cells (Fig. 2) (35) or ovalbumin (OVA)-primed mice with OVA (36) potentiated or induced, respectively, the appearance in serum of TABM. TNP-specific TCR $C\alpha^+$, $C\beta^+$ serum TABM induced by AC injection of TNP-sensitized mice with trinitrophenylated bovine albumin (TNP-BSA) were found to specificially inhibit DTH when injected intravenously into mice primed to TNP-BSA (37). Moreover, injection of mice with cyclophosphamide prevents the production of serum TABM and the suppression of DTH induced by AC injection

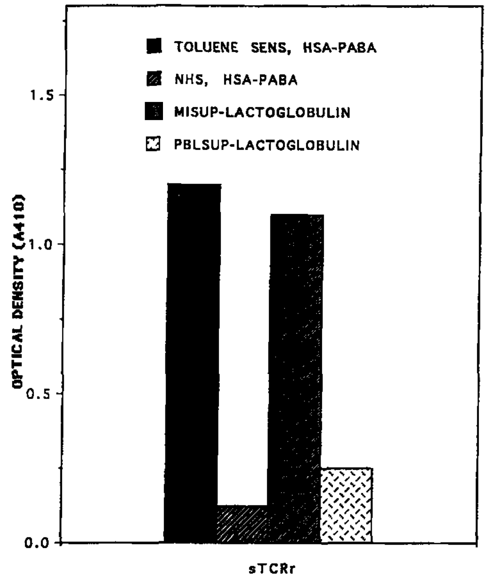

Figure 3. Detection of human sTCRr (TABM) *in vivo* and *in vitro.* Sera of individuals with a sensitivity to toluene or healthy controls were diluted and added to microtiter trays coated with *p*-aminobenzoic acid-human serum albumin (PABA-HSA) or HSA. After incubation and washing to detect "captured" sTCRr (TABM), rabbit anti-sTCRr (TABM) was added, followed by peroxidase-labeled goat anti-rabbit IgG followed in turn by tetramethybenzidine (TMB) liquid substrate. The optical density (O.D.) represents the mean of four replicates. The O.D. of binding to HSA (0.35 toluene-sensitive, 0.18 healthy controls) has been subtracted. TOLUENE SENS, serum from toluene-sensitive individuals; NHS, normal human serum.

Peripheral blood lymphocytes from individuals with milk intolerance or nonsensitive individuals were first cultured with β-lactoglobulin for 2–3 hr. The cells were then washed and cultured in serum-free medium for 5 days. The culture medium was then concentrated by precipitation with $(NH_4)SO_4$ and resuspended and dialyzed into phosphate buffered saline. One hundred microliters of dialyzed cell culture proteins were added to microtiter trays coated with 1 μg/well β-lactoglobulin. After incubation, anti-sTCRr (TABM) was added, followed by peroxidase-labeled goat anti-rabbit IgG and TMB substrate. The sTCRr (TABM) binding detected is O.D. ± SEM of four replicate samples. MISUP, culture supernatant from peripheral blood lymphocytes of milk intolerant individuals; PBLSUP, culture supernatant from control peripheral blood lymphocytes. (Data provided by C. Little and G. Georgiou, Department of Immunology, Royal Children's Hospital, Melbourne, Australia.)

of antigen (38). Since monoclonal TABM are recognized by monoclonal anti-TsFi (28), it is likely that serum TABM induced by intracameral injection of antigen are TsFi.

Our laboratory has also identified TABM in human sera that are also identified by polyclonal antibodies to a TCR Vβ framework epitope (39). C. Little and G. Georgiou (Royal Children's Hospital, Melbourne, Australia; personal communication) used this anti-TABM antiserum in antigen capture ELISA to demonstrate that individuals with milk intolerance have high titers of serum TABM specific for β-lactoglobulin. As shown in Figure 3, peripheral blood lymphocytes from these individuals produce TABM specific for β-lactoglobulin. The sera from patients sensitive to toluene contain TABM specific for *p*-aminobenzoic acid (Fig. 3). In addition, patients symptomatic with AIDS have elevated serum levels of TABM (Fig. 4), some of which bind specifically to a peptide recognized by antibodies to HIV-1 (Cone RE, Guha A, Kohler H, unpublished observation). It is tempting to speculate that these immunoproteins contribute to the pathogenesis of AIDS by suppressing DTH reactions that could eliminate HIV-1.

The emerging picture of the role of soluble antigen-specific T-cell immunoproteins is that these molecules amplify, focus, and extend T-cell immunoregulatory function (5). As such, quantitation of these proteins in sera may provide a useful prognostic tool to monitor and/or understand T-lymphocyte activity. TsFi and TsFe may be antigenically distinct isoforms of immunoproteins that are made by CD4$^+$ or CD8$^+$ cells. The regulatory function of the molecule may depend on lymphokines made by the cell producing the antigen-specific immunoregulatory "factor." Thus, a CD4$^+$, Th2 cell could produce an antigen-specific TsFi associated with IL-10, IL-4, or IL-6. Other T cells may produce antigen-specific molecules associated with other cytokines such as TGFβ.

Are soluble antigen-specific T-cell immunoproteins extracellular TCR? Molecular genetics should provide an answer to this question. Amino acid sequence of TABM suggests similarity, but not identity, to TCR α-chains. A distinct gene for soluble antigen-specific T-cell immunoproteins could be derived from TCR

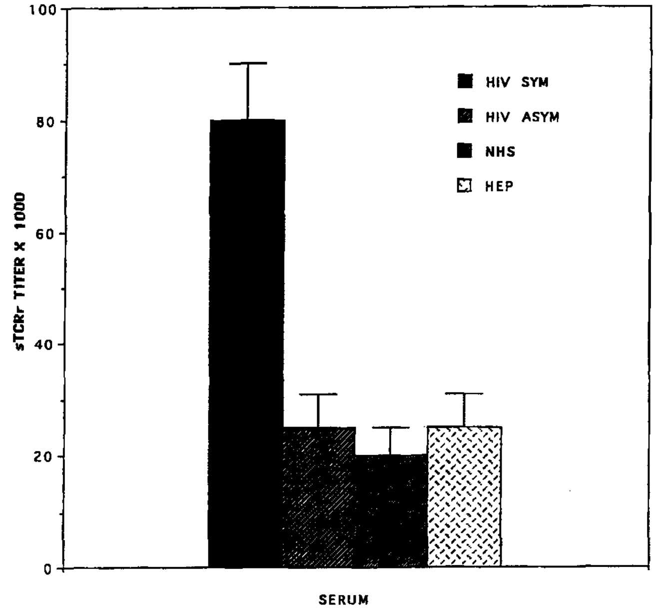

Figure 4. Elevation of sTCRr (TABM) in the sera of symptomatic HIV$^+$ (HIV SYM) individuals. Sera from asymptomatic HIV$^+$ (HIV ASYM) or healthy (NHS) individuals or from individuals with hepatitis B (HEP) were diluted 1:5,000–1:320,000, and 100 μl aliquots coated to microtiter trays. Anti-sTCRr (TABM) was added followed by alkaline phosphatase-conjugated goat anti-rabbit IgG and *p*-nitrophenyl phosphate substrate. The sTCRr (TABM) titer is the highest dilution of coated serum, giving an O.D. (A410) with anti-sTCRr (TABM) two times larger than that obtained with normal rabbit serum.

genes by gene duplication and mutation. Alternatively, TCR chains have undergone post-synthetic modification. Soluble α, β recombinant TCR have been shown to bind unprocessed antigen and inhibit the immunosuppressive activity of a TsFe by competing for macrophage receptors for TsFe (21). Until definitive molecular/genetic information concerning TSF/TABM is available, it has been suggested (4) that these molecules be termed soluble (s) TCR-related (r), or sTCRr. Perhaps sTCRr represent the early evolutionary development of antibodies before the advent of B lymphocytes and immunoglobulins.

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