Focus

Superantigen

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INTRODUCTION

Kappler *et al*.[1] describe a family of microbial proteins termed 'Superantigen' (SAg) that stimulates strong T-cell receptor (TCR) V_β restricted response. Superantigens are among the most potent T-cell mitogen known, with characteristic V_β signature. Previously SAg concept was limited to T cell only but recently the concept of B-cell SAg is growing. Besides classical SAg-mediated disease e.g. toxic shock syndrome (TSS), SAgs have also been proposed to contribute to the pathogenesis of several poorly understood acute and chronic inflammatory conditions including rheumatoid arthritis and psoriasis. Superantigens are not only powerful tools for the study of immunological phenomenon, but also its use is implicated in therapeutic intervention.

DEFINITION

Superantigens are microbial proteins of 22-29 Daltons in size and are potent stimulators of the immune cells in a unconventional manner produced by bacteria, virus and mycoplasma. It has two domain folding comprising of the NH_2 terminal β barrel providing the binding region for the MHC-II receptor and a long COOH terminal α barrel providing the binding site for V_β region of TCR [Table 1].

T-CELL AND B-CELL RECEPTORS

T-cell receptor (TCR) comprises of two peptide chains, either α/β or γ/δ, non-covalently associated with CD3γδε and ζ chains.[2,3] Ninety percent of peripheral blood T cells have α/β peptide chain, while γ/δ chain is present on 4% (range 1-10%) of peripheral blood and lymph node lymphocytes and 1% of thymocytes.

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α *Peptide* chain contains three regions V (variable), J (junctional) and C (constant), while β *peptide* chain in addition has a fourth region D (diversity). Each TCR complex (α/β chain) constant region interacts with CD3γδε and ζ chains and consists of immunoglobulin like, connecting peptide, transmembrane and cytoplasmic domain [Figure 1].

B-cell receptors

B-cell receptors (BCRs) comprise of membrane-bound immunoglobulin (Ig) on the surface. The C region of Ig remains inserted in the membrane of B cell, while the V region acts as the antigen-binding site (Fab). For any given Ig molecule the V region differs from every other immunoglobulin (Ig). Sequence variability is found in three segments of V region, designated as hyper-variable regions e.g. V1, V2, V3, and identified in both heavy (VH) and light (VL). The most variable part of the region V is VH3 [Figure 2].

Classical response

In classical response, after antigen processing by antigen presenting cell (APC), an epitope from a protein antigen acts as a bridge between the HLA complex of APC and TCR.[2,3] Only a small proportion of T cells become activated particularly after a co-stimulatory signal is produced by the APC. Response is highly regulated in order to limit harmful effects [Figure 3].

Superantigen response

T cell SAg binds directly to TCR and MHC-II receptor outside the conventional antigen-binding site, thus bypassing the restrictive feature of conventional antigen processing.[4,5] Superantigen binds to V_β domain of TCR, where V_β refers to a variable region of β peptide. Different SAgs have specificity for one or limited sets of V_β designation. SAg can stimulate all T cells bearing the particular V_β designation, thus SAg can stimulate 20-30% of the total T lymphocytes in an individual [Figure 3].

MHC-II positive cells are required for SAg-induced T-cell activation, but it is not MHC-II restrictive, and binding of MHC-II receptor determines the

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Table 1: Types of SAg

Exogenous	Endogenous	T-cell	B-cell
Soluble proteins secreted by bacteria and a variety of exotoxins	Cell-membrane proteins encoded by certain viruses that infect mammalian cells.	Binds directly to Vβ domain of TCR and MHC-II receptor outside the conventional antigen-binding site	B-cell SAg interacts with B-cell receptor (Ig) variable region of heavy chain/light chain outside the conventional antigen binding site

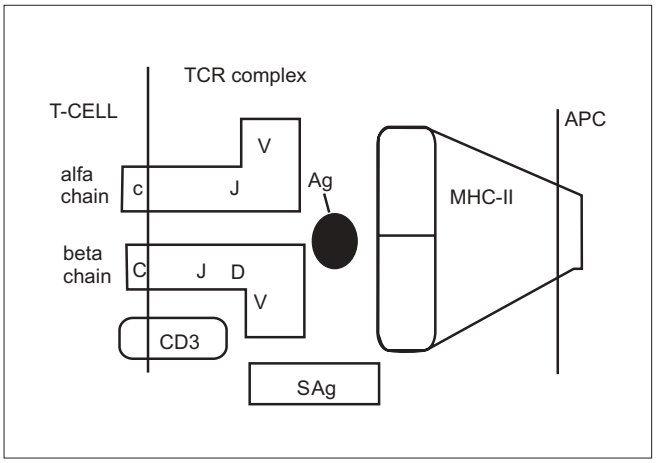

Figure 1: T cell receptor

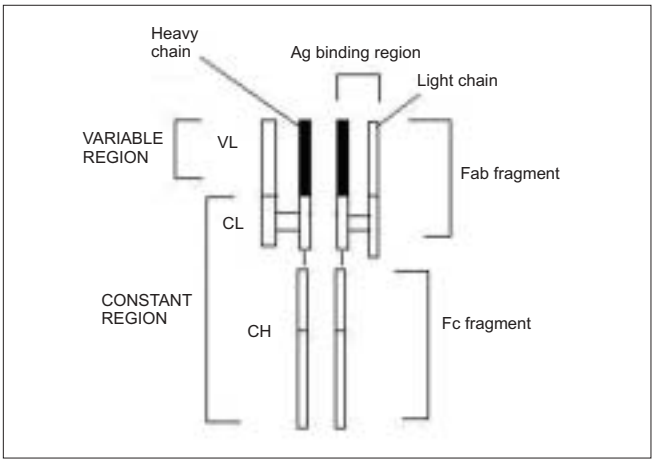

Figure 2: B cell receptor

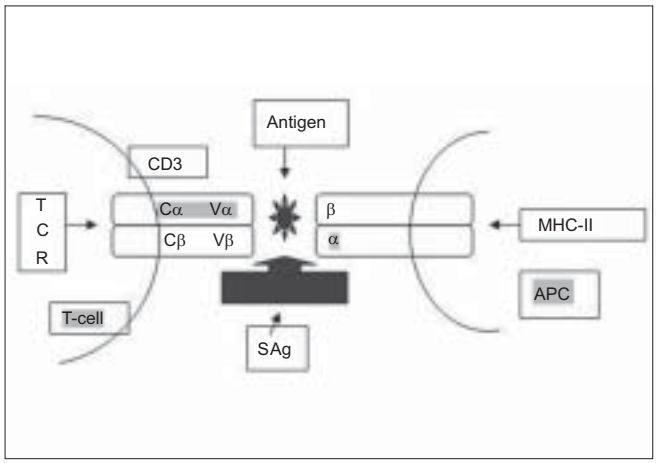

Figure 3: Superantigen interaction with TCR-MHC-II

susceptibility of an individual to the particular SAg.

Besides V_β-specific T-cell activation, certain SAgs, e.g. SEH (Staphylococcal Enterotoxin H) induces V_α-specific T-cell activation. In case of MAM (mycoplasma arthritidis associated Superantigen), interaction is intermediate between SAg and conventional peptide antigen.

B cell SAg[6] interacts with the variable region of heavy/light chain outside the conventional antigen-binding site, thus activating B cells in a VH selective manner. Most B-cell SAgs bind to the heavy chain from VH3 gene family. VH3 gene family is the largest of the seven human VH gene families and expressed by 30−60% of peripheral B cells [Table 2].

SUPERANTIGEN INTERACTION AND ITS EFFECTS

As there is no definite disease model for SAg-mediated disease, many *in vivo* and *in vitro* studies demonstrate various effects of SAg.

T-cell SAg

Massive T-cell activation and release of cytokines, e.g. TNF-α, IL-2, IL-6, INF-γ in large amount, results in capillary leak and systemic shock. There is a biphasic response after SAg stimulation of T cell, with a T-cell derived initial peak of IL-2, TNF-α, followed by second peak from macrophage-derived cytokines.[7] Proliferation of V_β-specific T cell, but not an antigen restrictive.

Deletion:[8] Initially V_β-specific T-cells expansion followed by V_β-specific clonal deletion of T cells.

Anergy:[9] Hyporesponsive state of T cell to an antigen in the absence of appropriate co-stimulatory signal.

T-cell dependent B-cell activation characterized by polyclonal IgM and IgG production, enhances humoral immunity via Ag-specific $CD4^+$ T cells[10]

Table 2: Comparison between conventional and superantigen response

Classical response	Superantigen response
Antigen requires processing by APC	Does not require processing by APC
Antigen recognition and T-cell activation is MHC-II restricted	MHC-II positive cells are required for SAg-induced T-cell activation, but it is not MHC-II restrictive
Small proportion of T-cells become activated (<0.001) and highly regulated response	Massive T-cell activation (20-30% of total T cells) and associated with adverse consequences

Cytotoxicity: (1) Cyctotoxic T-cell mediated cytotoxicity against MHC class II positive cells, known as SAg-dependent cell-mediated cytotoxicity (SDCC).[11] (2) Activation-induced cell death (AICD).[12] (3) Superantigen-dependent autokilling.[13]

Induction of autoimmune status:[14,15] Although there are no direct evidences for this SAg has been proposed as one of the etiologies for autoimmune disease. Autoimmune state may result from indiscriminate V_β-specific expansion that amplifies the clone that manifests cross reactivity towards endogenous antigen and loss of self-tolerance. This may persist even after original SAg stimuli ceases. Three different mechanisms have been proposed for induction of autoimmune status (1) In presence of SAgs and multivalent autoantigen abnormal Th-B cell interactions lead to activation, proliferation and differentiation of B-cells and production of autoantibody. (2) T-cell independent and direct activation of B cell by SAgs. (3) Superantigens may activate resting T cells that recognize autoantigens and may remain in active state in the presence of autoantigen.

Superantigens increase the expression of glucocorticoid receptor β and are associated with decreased corticosteroid response.[16]

Other effects:[5,10] Stimulates lymphocyte locomotion and neutrophilic recruitment to the site of infection, emesis and augmentation of endotoxin activity. Recruitment of T cells, B cells and APCs at the site of infection, and activation of B cells and APCs further augment the cytokine release.

B-CELL SUPERANTIGEN

B-cell SAg binds to serum Igs and leads to the formation of large amount of immune complexes. Such immune complexes activate the complement pathway and inflict tissue injury. [6,17]

B-cell SAgs bind to the surface Igs on mast cells and basophils, resulting in the release of pro-inflammatory mediators. T-cell independent VH-specific B-cell

Table 3: Immunomodulatory drugs useful for SAg-associated diseases

- Intravenous immunoglobulin (IVIg)
- Cyclosporin
- Pentoxyphylline (PF)
- Corticosteroids
- Thalidomide and its analogues
- Chinese herb: Baicalin
- STA-5236: A potent IL12/IL23 inhibitor
- TNF-α inhibitors: e.g. Adalimumab, Etanercept, Infliximab
- Monoclonal antibody and fusion protein: Alefacept, Efalizumab
- Vaccine
- Receptor antagonist: Genetically engineered proteins that interfere with binding of SAg to Vβ of TCR.

Table 4: Superantigen toxins

Staphylococcal SAg
- Staphylococcal enterotoxin A, B, C, D, E, G, H, I, J,(most studied A, B and TSST1)
- TSST-1 [staphylococcal enterotoxin F]
- Staphylococcal protein A (SpA) [B-cell Superantigen]

EB Virus
- HERV-K18 env

Peptostreptococcus magnus
- Protein L (B-cell SAg)

Streptococcal SAg
- Streptococcal pyrogenic exotoxins (SPE): SPE-A, SPE-B, SPE-C, SPE-D, SPE-F, SPE-G, SPE-H, SPE-J
- SMEZ
- Mitogenic factor (MF)
- SSA

HIV
- HIV-gp120 (B-cell SAg)

Rabies?
- ?

Mycoplasma arthritidis SAg
- MAM (mycoplasma arthritidis -derived Superantigen)

Human liver sialoprotein
- Protein Fv (B-cell SAg)

Yersinia pseudotuberculosis
- YPM

Yersinia enterocolitis?
- ?

Table 5: Diseases thought to be mediated by Superantigen

• Staphylococcal toxic shock syndrome (TSS)	• Retroviral disease- MMTV	• Rheumatoid arthritis
• Streptococcal TSS	• Infectious mononucleosis	• Chronic arthritis
• Food poisoning	• Burkitt's lymphoma	• Rheumatic fever
• Kawasaki disease	• Cytomegalovirus infection	• Sjogren's syndrome
• Scarlet fever	• HIV and AIDS?	• SLE
• Atopic dermatitis	• Rabies?	• Systemic sclerosis
• Psoriasis	• Acute juvenile PRP	• Crohn's disease
	• CTCL/Lymphomas	• Arthus reaction
		• Vasculitis
		• IDDM

Table 6: Factors affecting SAg-induced response

• MHC-II binding.	• Rechallenge: T-cell response to injected SAgs is very transient and more rapidly eliminated than primary response.	• Host-immune status: during early stages of life with developing immune system there may be immune cell tolerance to SAg. In later stages with developed immune system produce specific immune response.
• Concomitant infection.	• Type of SAg, e.g. T cell, B cell.	
• Dose: low, high: dose lower than maximum, T-cell response and dose higher than that, produce different effect.		

activation and proliferation, followed by clonal deletion, and prolonged suppression of antibody production.

ENDOGENOUS SUPERANTIGENS

Endogenous Superantigens (ESAgs) are cell membrane proteins encoded by certain viruses that infect mammalian cells. [18] In humans ESAg is encoded by env gene of human endogenous retrovirus (HERV), and all humans carry numerous copies of HERV in their genome. Exact significance of ESAg is not known in humans. Endogenous superantigen stimulates T cell in V_β in a selective manner to support viral replication and plays a role in the pathogenesis of EB virus infections, HIV infection, CMV infection and IDDM (Insulin Dependent Diabetes Mellitus).

TREATMENT STRATEGIES FOR SUPERANTIGEN-MEDIATED DISEASE

As there is no definite disease model for SAg-mediated disease and lack of controlled trials about therapeutic intervention, many drugs are claimed to be effective with different immunological properties. Following treatment strategies are proposed for the diseases associated with SAg.

1. Removal of source of SAg
   - Drain the abscess
   - Early and adequate antibacterial therapy, e.g. Clindamycin
   - Supportive care for shock
2. Immunomodulatory drugs:
   Drugs useful for various SAg-associated diseases are shown in Table 3.

Table 4 gives superantigen toxins, and Table 5 diseases thought to be mediated by superantigen, and table 6 factors affecting SAg-induced response.

REFERENCES

1. Kappler J, Kotzin B, Herron L, Gelfand EW, Bigler RD, Boylston A, Carrel S, Posnett DN, Choi Y, Marrack P. V beta-specific stimulation of human T cells by staphylococcal toxins. Science 1989;244:811-3.
2. Parish WE, Breathnach SM. Clinical Immunology and Allergy. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors. Rook Textbook of dermatology. 6th edition. Oxford: Blackwell Science 1998. p. 277-36.
3. Janeway CA, Travers P, Walport M, Shlomchik MJ, editors. Antigen recognition by B cell and T cell receptors. In: Immunobiology, The immune system in health and disease; 5th edition. London: Garland Publishing: 2001. p. 93-122.
4. Choi Y, Lafferty JA, Clements JR, Todd JK, Gelfand EW, Kappler J, Marrack P, Kotzin BL. Selective expansion of T cells expressing V beta 2 in toxic shock syndrome. J Exp Med 1990;172:981-4.
5. Llewelyn M, Cohen J. Superantigen: Microbial agents that corrupt immunity.The lancet infectious disease 2002;2:156-62.
6. Kozlowski LM, Li W, Goldschmidt M, Levinson AI. *In vivo* inflammatory response to a prototypic B cell superantigen: Elicitation of an arthus reaction by staphylococcal protein A. J Immunol 1998;160:5246-2.
7. Bette M, Schafer MK, Rooijen VN, Weihe E and Fleischer B. Distribution and kinetics of superantigen-induced cytokine gene expression in mouse spleen. J Exp Med 1993;178:1531-9.

8. Renno T, Hahne M, Tschopp J, MacDonald HR. Peripheral T Cells Undergoing Superantigen-induced Apoptosis *In vivo* Express B220 and Upregulate Fas and Fas ligand. J Exp Med 1996;183:431-7.
9. Kawabe Y, Ochi A. Selective anergy of V β 8+, CD4Tcells in staphylococcus enterotoxin B-primed mice. J Exp Med 1990;172:1065-70.
10. Torres BA, Perrin GQ, Mujtaba MG, Subramaniam PS, PS, Anderson AK, Johnson HM. Superantigen enhancement of specific immunity:antibody production and signaling pathway. J Immunol 2002;169:2907-4.
11. Holzer U, Orlikowsky T, Zehrer C, Bethge W, Dohlsten M, Kalland T; *et al*. T-cell stimulation and cytokines release induced by staphylococcal enterotoxin A (SEA) and SEAD227A mutant. Immunol 1997;90:74-80.
12. Tchilian EZ, Anderson G, Moore NC, Owen JJ, Jenkinson EJ. Involvement of LFA/ICAM-2 adhesive interaction and PKC in activation induced cell death following SEB rechallange. J Immunol 1996;87:566-72.
13. Koning F, Rust C. Staphylococcal enterotoxin mediated human T-T cell interaction. J Immunol 1992;149:317-2.
14. Friedman SM, Posnett DN, Tumang JR, Cole BC, Crow MK. A potential role for microbial superantigens in the pathogenesis of systemic autoimmune disease. Arthritis Rheum 1991;34:468-80.
15. Crow MK. Connective tissue disorders-systemic lupus erythematosus, cellular immunology. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH editors. Rheumatology 3rd edition. Philadelphia: MOSBY (Elsevier Science); 2003 p.1347-1358.
16. Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. J Allergy Clin Immunol 2000;105:782-7.
17. Anderson AL, Sporici R, Lambris J, Larosa D, Levision AI. Pathogenesis of B cell Superantigen induced immune complex mediated inflammation. Infection and Immunity 2006; 74:1196-1203.
18. Pousnett DN, Yarilina AA. Sleeping with enemy-Endogenous superantigen in humans. Immunity 2001;15:503-6.