INTRODUCTION

Kappler et al.[1] describe a family of microbial proteins termed ‘Superantigen’ (SAg) that stimulates strong T-cell receptor (TCR) Vβ restricted response. Superantigens are among the most potent T-cell mitogen known, with characteristic Vβ 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), SAg s 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 NH2 terminal β barrel providing the binding region for the MHC-II receptor and a long COOH terminal α barrel providing the binding site for Vβ region of TCR [Table 1].

T-CELL AND B-CELL RECEPTORS

T-cell receptor (TCR) comprises of two peptide chains, either α/β or γδ, non-covalently associated with CD3γδζ and ζ chains.[2,3] Ninety percent of peripheral blood T cells have α/β peptide chain, while γδ chain is present on 4% (range 1-10%) of peripheral blood and lymph node lymphocytes and 1% of thymocytes.

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 CD3γδζ 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 Vβ domain of TCR, where Vβ refers to a variable region of β peptide. Different SAg s have specificity for one or limited sets of Vβ designation. SAg can stimulate all T cells bearing the particular Vβ 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
susceptibility of an individual to the particular SAg.

Besides Vβ-specific T-cell activation, certain SAgS, e.g. SEH (Staphylococcal Enterotoxin H) induces Vβ-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 Vβ-specific T cell, but not an antigen restrictive.

Deletion:[8] Initially Vβ-specific T-cells expansion followed by Vβ-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]
Cytotoxicity: (1) Cytotoxic 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 Vβ-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 2: Comparison between conventional and superantigen response**

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

**Table 3: Immunomodulatory drugs useful for SAg-associated diseases**

- Intravenous immunoglobulin (IVIg)
- Cyclosporin
- Pentoxylhyline (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**

<table>
<thead>
<tr>
<th>Staphylococcal SAg</th>
<th>Streptococcal SAg</th>
<th>Mycoplasma arthritidis SAg</th>
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<tbody>
<tr>
<td>TSST-1 [staphylococcal enterotoxin F]</td>
<td>SMEZ</td>
<td>Human liver sialoprotein</td>
</tr>
<tr>
<td>Staphylococcal protein A (SpA) [B-cell Superantigen]</td>
<td>Mitogenic factor (MF)</td>
<td>Protein Fv (B-cell SAg)</td>
</tr>
<tr>
<td>EB Virus</td>
<td>SSA</td>
<td>Protein L (B-cell SAg)</td>
</tr>
<tr>
<td>HERV-K18 env</td>
<td>HIV</td>
<td>Peptostreptococcus magnus</td>
</tr>
<tr>
<td>Peptostreptococcus magnus</td>
<td>HIV-gp120 (B-cell SAg)</td>
<td>Rabies?</td>
</tr>
<tr>
<td>Protein L (B-cell SAg)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Yersinia pseudotuberculosis</td>
<td>YPM</td>
<td>Yersinia enterocolitidis?</td>
</tr>
</tbody>
</table>
activation and proliferation, followed by clonal deletion, and prolonged suppression of antibody production.

**ENDOGENOUS SUPERANTIGENS**

Endogenous Superantigens (ESAs) 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\(_{\beta}\) 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**


