

T cell receptor and the b cell receptor: comparison



**ASSIGN
BUSTER**

The entire world is full of pathogens which we need to fight off to leave a normal life. Due to this, we have an immune system that helps us fight off and prevent/manage subsequent infections. Our immune system can be classified into two, the innate and acquired immune responses. The innate immune response is broadly specific and provides the first defensive action against any infection. Their response to any subsequent infection stays the same as the initial infection. In contrast, the acquired immune response is highly specific such that it provides defence by generating antibodies specific to an antigen. They also have the capacity of keeping infection memory such that there will be a more powerful response to future infections. Innate immune response is mostly provided by macrophages, dendritic cells, polymorphonuclear leukocytes, mast cells, natural killer cells, erythrocytes and platelets. The acquired immune response is provided by lymphocytes, the T (T cells) and B lymphocytes (B cells).

The lymphocytes are derived from hematopoietic stem cells (HSC) in the bone marrow. That form MLPs (myeloid-lymphoid progenitors). If the HSC and MLP stay in the bone marrow they form B cells and if they migrate (via blood) to the thymus they form T cells (see figure below).

Initiation of immune response by the lymphocytes first requires recognition of the antigens and this is achieved by cell surface receptors called BCRs (B cell receptor) and TCRs (T cell receptor). These two receptors have great similarities and differences in their structure complexes, antigen recognition, cell activation and genetic recombination.

A) STRUCTURE OF BCRs AND TCRs

Both the BCR and TCR have great similarities and differences in the structure. They both exist as multi-chain complexes as seen in the diagrams below:

i) Antigen recognition components

In the figure above, section A shows the structure of a BCR. The BCR antigen recognition medium is an immunoglobulin (Ig) molecule (a transmembrane antibody). The antibody is modified via alternative splicing that adds a hydrophobic transmembrane domain and a short cytoplasmic domain (~3 aminoacids) at the C terminus of the immunoglobulin heavy chain (Wall & Kuehl 1983). All naïve B cells only express both IgM and IgD classes of immunoglobulin but do switch to other classes upon activation by antigens (Goding, 1978). The antibody (figure 2C) is a highly specific Ig that can adopt any one of the 5 immunoglobulin isotopes, IgG, IgA, IgM, IgD and IgE. The antibody has 3 regions of which 2 regions (FAB) vary from antibody to antibody and bind to antigens and 1 region (FC) that binds to effector molecules. The antibody is composed of 2 light and 2 heavy chains held together by inter and intra disulphide bonds. The heavy chains depending on the Ig isotypes can be any one of $\hat{\Gamma}^3$, μ , $\hat{\Gamma}^\pm$, $\hat{\Gamma}^\prime$ or \hat{E}^\times chains. The variable domains (VH and VL) bind to antigen and also bring about variability and antigen recognition specificity. This specificity is mainly due to the presence of 3 hypervariable regions (Complementary Determining Regions), namely CDR1, CDR2 and CDR3 in the variable regions.

Similar to BCR, the antigen recognition medium in TCR is an immunoglobulin heterodimer made from $\hat{\Gamma}^\pm$ and $\hat{\Gamma}^2$ Ig chains (in most T cells) or $\hat{\Gamma}^3$ and $\hat{\Gamma}^\prime$ Ig

chains. Unlike in BCRs where the Ig can be of 5 types, in TCRs the Ig heterodimers are only of 2 types. The two Ig chains in TCRs are (also like BCRs) held together by intra and inter disulphide bonds. As seen in section C, each Ig chain folds into 2 domains, the variable and the constant domain. This folding greatly resembles the FAB region of the antibody in BCRs. Likewise antibodies, the $\alpha\beta$ and $\beta\delta$ heterodimers also have hypervariable regions (CDR1, CDR2 and CDR3) in variable domains. The variable regions in both BCRs and TCRs bring about specificity and diversity

The BCR antibodies have a hinge joint (connecting FAB and FC) that makes the Ig molecule very flexible. Unlike antibodies, the flexibility of the TCR Ig molecule is very limited at the elbow region (junction of constant and variable region) (Degano et al, 1996).

ii) ACCESSORY PROTEINS

Both the BCR and TCR have very short cytoplasmic domains that restrict the binding of any signal transduction factors to the receptors. Due to this the receptors are unable to transduce signals into cells upon antigen recognition. Signal transduction is achieved via the accessory proteins. BCRs (figure 2 section A) accessory proteins consists of one or more dimers of one each of α and β chains held together in the cell membrane by a pair of disulphide bonds. The cytoplasmic domains of these chains have phosphorylation sites called ITAMS. Unlike BCR accessory protein, the TCR accessory proteins (figure 2, section C) is composed of a complex known as CD3. It consists of 3 types of invariant chains, namely ζ , η and ϵ . A ζ or η chain couples up with one ϵ chain (by formation of disulphide bonds) each to form two dimers ($\zeta\epsilon$ and $\eta\epsilon$). In addition to this, a dimer of 2 zeta

($\hat{I}\eta$) chains is also present. Together, these 3 dimers make up the CD3 complex. The $\hat{I}\eta$ chains have a much longer cytoplasmic tail than the \hat{I}^{β} , \hat{I}^{γ} and \hat{E}^{δ} chains and have 3 ITAMs as compared to one in the \hat{I}^{β} , \hat{I}^{γ} and \hat{E}^{δ} chains. Therefore for both BCR and TCR accessory proteins are dimers that all contain ITAMs.

B) GENERATION OF RECEPTOR DIVERSITY

There are millions antigens and we need to produce millions of antibodies against them. However, we do not have millions of Ig genes so how are we able to produce all these different antibodies? The answer is antibodies are produced in developing B cells via genetic recombination of genes encoding the immunoglobulins (Hozumi and Tonegawa, 1976). The figure below shows the gene segments coding immunoglobulins.

Figure legend: The human heavy chain locus as shown in the last row, consists of about 38-46 functional VH genes, 27 DH and 6 JH genes. The light chain can be either made of $\hat{I}\kappa$ or $\hat{I}\lambda$ chains. The $\hat{I}\kappa$ locus consists of about 30 functional $V\hat{I}\kappa$ genes and 5 $J\hat{I}\kappa$ genes each separated by a J segments. The Kappa locus has about 34-40 functional $V\hat{I}\lambda$ genes and 5 $J\hat{I}\lambda$ genes.

The variable heavy chain region of the antibody is made from the joining of the V (variable), D (diversity) and J (joint) gene segments and the variable light chain (which can be either $\hat{I}\lambda$ or $\hat{I}\kappa$) is formed from the joining of V and J segments only. A process called $V(D)J$ recombination involves joining different gene segments and as a result bringing about antibody diversity. At the heavy chain locus, any one of the 27 D and 6 J gene segments are first joined together and then any one of 46 V gene segment is joined to this DJ

segment. This rearranged DNA is then transcribed to form a primary mRNA. This mRNA then undergoes splicing to bring the VDJ segment close to the constant gene segment. Additional diversity is achieved as any 1 of the two types of light chains can be formed. Random insertion of nucleotides either side of D segments also creates N-nucleotide diversity. In total about 10^6 possible immunoglobulin gene combinations can be formed. This recombination process is driven by recombination signal sequences that flank the coding gene segments. Certain enzymes (RAG-1 and RAG-2) help mediate this somatic recombination process. The antibodies produced undergo a process of clonal selection where only the antibody specific to the antigen preferentially proliferates to make many antibodies.

Binding affinity of BCR is greatly increased after antigen recognition where the variable regions of both heavy and light chain undergo somatic hypermutations. This is where point mutations are put in the variable regions of rapidly proliferating B cells. These mutations produce antibodies that may have good, moderate or poor affinity for the antigens. The antibody with good affinity will have a selective advantage during clonal selection.

The gene segments encoding TCR β chain follow the similar V, D, J and C arrangement of BCRs. The recombination process involves one of the two $D\beta$ genes rearranges next to one of $J\beta$ genes. Then one of the ~ 50 V genes arranges next to the preformed $D\beta J\beta$ genes. As seen, this is also similar to the B cells where a DJ segment forms first and then joins up with a V segment. There is also random insertion, just like in B cells, of nucleotides either side of D segments to create N-nucleotide diversity. Unlike in B cells, there is no somatic hypermutation in T cells after antigen recognition. If this

<https://assignbuster.com/t-cell-receptor-and-the-b-cell-receptor-comparison/>

occurs, the TCR will lose its ability to recognise MHC and the peptide it presents.

C) ANTIGEN BINDING/RECOGNITION

BCR and TCR have similar immunoglobulin antigen recognition receptors but the types of antigens they recognise are very different. BCR can recognise native (as a whole) antigens and TCR can only recognise a single antigen peptide sequence presented onto cell surfaces by MHC (Major histocompatibility complex) molecules. The antigens recognised by B cells are native and therefore the antibody in BCR mostly recognise discontinuous epitopes on the antigen and antigens recognised by the TCR is in form of linear peptide sequences and therefore they mostly recognise continuous or linear epitopes.

Antigen recognition by BCR is very simple where the antibody variable region simply recognises specific epitopes on antigen and bind to it. The BCR can recognise 3 types of antigens, Type 1 thymus independent antigens (where bacterial lipoproteins can bind to mitogenic bypass molecules on B cells surface and this allows non-specific antigen B cell activation), Type 2 thymus independent antigens (applies to antigens that have well spaced and repetitive polysaccharides that bind to multiple antibodies in BCR and activate the B cell) and Thymus dependent antigens (require helper T cells). Thymus dependent antigens when bind to TCR, instead of causing activation normally cause anergy. Due to this, once the binding has occurred, the whole antigen+TCR complex is endocytosed, the antigen is hydrolysed by enzymes and processed to small linear peptides and then presented onto the B cell surface via MHC2 molecules. Helper T cells then recognise this

<https://assignbuster.com/t-cell-receptor-and-the-b-cell-receptor-comparison/>

peptide-MHC complex. B cells have loads of CD40 on their surface that binds to CD40L present on Th helper cells. In response to this Th cells secrete IL-4, 5, 6 that also help activate other costimulatory molecules in the BCR coreceptor complex. All these events provide costimulation of the B cells and it is activated.

$\alpha\beta$ heterodimer TCRs in comparison can recognise any type of antigen that is processed and presented as a single peptide on MHC1 on target cells and MHC2 on B cells, macrophages and dendritic cells (all professional antigen presenting cells). The non-covalent forces that help TCR bind to the peptide-MHC complex are similar to the forces that enable the antibody bond to the antigen i. e. noncovalent.

Unlike BCR that only have to recognise epitopes on antigens, the TCR has to both recognise the presence of both MHC molecule and antigen peptide. The TCR $V\alpha$ (variable alpha region) overlays $\alpha 2$ helix of MHC1 or $\beta 1$ helix of MHC2 and the $V\beta$ domain overlays $\alpha 1$ helix in both MHC1/2. The CDR1 and CDR2 bind to α helices of MHC and the CDR3 (which is more variable), binds to the antigen peptide on MHC. This concept is summarised in the picture below:

Figure legend: The picture shows how the TCR variable complementarity determining regions (CDR) which are the binding sites interact with peptide-MHC complex. The CDR1 and CDR2 bind to the MHC alpha helices and CFR3 binds to the peptide.

The $\gamma\delta$ TCRs are more similar to BCR antibody as they can recognise native antigens without the requirement of processed antigen presentation.

<https://assignbuster.com/t-cell-receptor-and-the-b-cell-receptor-comparison/>

Another similarity of BCR and $\hat{\beta}\hat{\gamma}$ TCRs is that in the antibodies of BCRs, the CDR3 regions on heavy chain are shorter than the CDR3 in heavy chains and also the same in $\hat{\beta}\hat{\gamma}$ TCRs is seen where the $\hat{\beta}$ are shorter than the $\hat{\gamma}$ CD3.

COSTIMULATIONS

Both lymphocytes do not get activated (but undergo anergy) once they recognise and bind to an antigen. They require costimulatory signals that will eventually lead to the activation of the lymphocytes. The B cells have BCR co-receptor complex consisting of CD19 and CD21 (complement receptor), CD81 and LEU13 (interferon induced transmembrane protein 1). All these molecules are stimulated in presence of interferons and complements that give a costimulatory signal to B cells and activate it when it has recognised an antigen. The precise details of how these costimulatory molecules stimulate B cell signalling are still under investigation.

In contrast to the 4 main costimulatory molecules in B cells, the primary costimulatory molecule in T cells is CD28 (figure besides)

The binding of peptide-MHC to TCR causes up-regulation of certain molecules (e. g. CD28). T cells, like B cells can be costimulated by either cytokines or costimulatory molecule interactions.

APC have surface molecules such as the B7. 1 and B7. 2 (or the CD80 and CD86) that recognise and bind to a molecule on the surface of the T cells called CD28 found on CD. This interacting provides co stimulation. The CTLA4 molecule is highly expressed after proliferation of the T cells. Once it binds to B7, instead of co stimulating T cells, it turns the T cells " off". This is

helpful in preventing excessive immune responses. No such regulatory mechanism is seen in B cells.

A unique feature of T cells is that they have co receptors (CD4 and CD8) that help recognise the MHC molecules. CD4 molecules act as co receptors for MHC2 and are found on helper T cells and CD8 molecules present on cytotoxic T cells help recognise MHC1 molecules.

ACTIVATION OF B AND T CELLS

The activation of B and T cells following antigen recognition is somehow similar as it involves the phosphorylation of the ITAMS of accessory proteins. In B cells, antigen binding and co stimulation recruits the BCR+antigen to lipid rafts that brings protein tyrosine kinase Lyn close to the ITAMs of the cytoplasmic tails of the BCR associated proteins. Lyn phosphorylates ITAMs and triggers a signal cascade that results in increase of cytoplasmic calcium levels that activate transcription factors that control the entry of B cells into cell cycle. Eventually activate the B cells which then form plasma cells (that make loads of clones of antibodies to the antigen) and memory cells that will help manage subsequent infections. The initial proliferation of the activated B cell is accompanied by somatic hypermutation of the rearranged antibody variable genes that lead to the production of antibodies that may have poor, moderate or good binding capacity to the antigen. The good binding antibodies will be preferentially selected during clonal selection and they will further undergo proliferation to produce plasma and memory cells.

A similar situation also occurs in T cells where there is activation of lipid rafts that bring the zeta chain ITAMS close to Lck (a protein tyrosine kinase) that

phosphorylates the ITAMs and therefore create opportunity for other factors to bind to it and eventually cause mobilization of calcium that causes proliferation of T cell into Helper T cells, Regulatory T cells and Cytotoxic T cells.