Immunology 6

Specificity 8
Specificity

- of immunoglobulin molecule on B cell – BCR
- of receptor on T cell – TCR

is defined and produced before their exposition to antigen

Number of specificities of BCR and TCR overpasses the number of genes on human chromosomes

*Limited amount of genes can generate almost unlimited amount of specific BCR and TCR molecules*
- monomer of immunoglobulin
- light and heavy chains
- light – $\lambda,\kappa$
- heavy – $\varepsilon,\mu,\delta,\gamma,\alpha$
- variable part – constant part
• structurally like immunoglobulin
• heterodimer consisting of $\alpha\beta$ or $\delta\gamma$ pair of chains.
• $\alpha\gamma$ - light
• $\delta\beta$ - heavy
• Variable and constant part
Genetic base of specificity

- Individual inherited set of genes from parents (maternal and paternal)
- in one individual there exist maternal or paternal forms of alleles on different molecules of receptors or Ig (allotypes)
Exclusion of alleles

- only kappa or lambda light chains from father of mother
- maternal or paternal heavy chain

- For genes encoding TCR αβ or γδ
  (α or γ pre light β or δ for heavy)
Exclusion of alleles

Each B cell and plasma cell has four light chain gene clusters. Only a single (chromosome) or (chromosome 22) gene cluster derived from the either the maternal (M) or paternal (P) chromosome pair is expressed.

Each B cell and plasma cell has both maternally and paternally derived heavy chain gene clusters (chromosome 14)

Gene cluster

Maternally derived κ chain cluster and maternally derived heavy chain cluster expressed.

Paternally derived λ chain cluster and paternally derived heavy chain cluster expressed.

Paternally derived κ chain cluster and paternally derived heavy chain cluster expressed.

Paternally derived λ chain cluster and maternally derived heavy chain cluster expressed.
Antigen specific receptors on lymphocytes

- Domains - **NH ends** of **variable parts** of heavy and light chains on **B lymphocytes** differs in different sequencies of aminoacids

- Domains - **C ends** – of **constant parts** have **limited variability** in the same isotype produced by different B or plasma cells
Genetic base of specificity

- **Sequence of aminoacids** is encoded by genes od DNA localised on *chromosomes* – *overload of genes* =>

- Aminoacids are encoded on several chromosomes: 2, 22, 14 for BCR
  14 and 7 for TCR

- In chromosomal locuses V, J, C – for light
  V, D, J, C – for heavy
Genetic base of specificity

- Genes are rearranged,
- transcribed to mRNA
- translated to the single light and single heavy chain polypeptide
Gene rearrangement, deletion, mutation

- Every individual is able to produce $10^{15}$ epitope-specific receptors

Rearrangement is responsible for enormous variability of epitope-specific part on variable domains of heavy and light chains $V_L V_H$ on BCR and TCR

- It arises by deletion of existing nucleotides genes in a segment of DNA on chromosome encoding this individual receptor molecule
Genotype of TCR – V(D)J chromosome 14 and 7

- **TCR:** V, D, J gens: - for $\alpha = 45V/L \times 55J$
  
  - for $\beta = 50V/L \times 2D \times 12J$

  $1200 \times 2475 = 3 \times 10^6$

  - for $\gamma = 5V/L \times 5J$

  - for $\delta = 2V/L \times 3D \times 4J$

  $24 \times 25 = 600$

+ constant part coding + 20 junction part
Genotype of BCR chromosomes

2 (κL), 22 (λL) a 14 (H)

Rearrangement of genes for Ig
- happens in early stages of B lymphocyte evolution
- leads to formation of variable parts, that can recognise majority of antigenic structures ever present

• 1 B cell = 1 isotype, 1 specificity (constant)

class switch
Genes encoding BCR

- Chromosome 2 – κ light – 40V x 5J x 1C = 200
- Chromosome 22 – λ light – 30V x 6J(C) = 80
- Chromosome 14 – heavy - 200V x 20D x 6J = 24000 = 9,1 x 10^6

• encoding of constant parts 9C (α1, α2, γ1, γ2, γ3, γ4, μ, δ, ε) 10^8
BCR
Rearrangement of genes for heavy chains - isotype
Class switch

- can happen suddenly or by exposition of the same type of antigens repeatedly to memory B cells
- Memory B cells – not every B cell that is exposed to the antigen change to plasma cell and start to produce Ig (IgM) at once. Some change to B memory cells and produce Ig after the next challenge (IgM, IgG)
Somatic hypermutation
Affinity maturation
APC