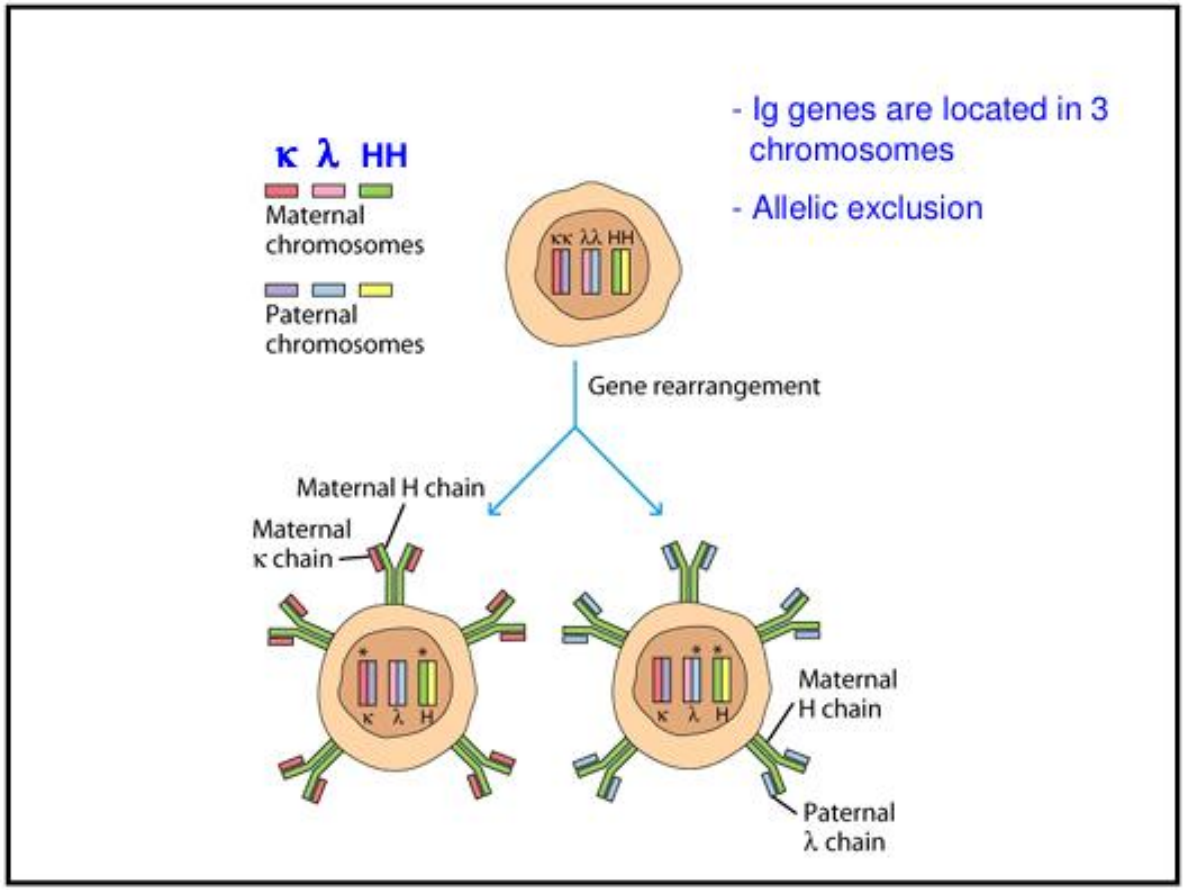
Allelic Exclusion

- We have two copies (alleles) of each Ig gene -one inherited from our father and one from our mother.
- In most cases, both genes are expressed.
- But Antibody genes are different! …. Only one heavy chain allele and one light chain allele is expressed!!!
- This is termed allelic exclusion (one allele is excluded).
- Once a productive arrangement is made, the other allele is suppressed.
- To ensure that each B cell makes antibody of a single specificity.



Allelic exclusion in B cells ensures that each B cell expresses only one type of immunoglobulin (antibody) with a unique specificity. This is achieved by silencing one of the two immunoglobulin heavy (IgH) chain alleles and one of the two immunoglobulin light (IgL) chain alleles, leading to the expression of only one functional antibody molecule per cell.

Elaboration:

The Concept:

Allelic exclusion is a fundamental mechanism in B cell development that guarantees each B cell will recognize only one specific antigen. This is crucial for the adaptive immune system's ability to respond to diverse antigens without generating self-reactive antibodies.

Mechanism:

During B cell development, the IgH and IgL genes undergo V(D)J recombination to create a unique variable region for antibody production. Allelic exclusion ensures that only one of the two possible heavy chain alleles and one of the two possible light chain alleles are rearranged and expressed in a single B cell.

Consequences:

The silencing of one allele prevents the expression of multiple antibody types on a single B cell, thus ensuring the monospecificity of B cells.

Importance:

Allelic exclusion is essential for preventing autoimmunity and maintaining the specificity of B cells in the immune response.

Allelic Exclusion Ensures a Single Antigenic Specificity

- B cells, like all somatic cells, are diploid and contain both maternal and paternal chromosomes.
- Even though a B cell is diploid, it expresses the rearranged heavy-chain genes from only one chromosome and the rearranged light-chain genes from only one chromosome.
- The process by which this is accomplished, called **allelic exclusion,** ensures that functional B cells never contain more than one VHDHJH and one VLJL unit.
- This is, of course, essential for the antigenic specificity of the B cell, because the expression of both alleles would render the B cell multispecific.
- The phenomenon of allelic exclusion suggests that once a productive VH-DH-JH rearrangement and a productive VL-JL rearrangement have occurred, the recombination machinery is turned off, so that the heavy- and light-chain genes on the homologous chromosomes are not expressed.

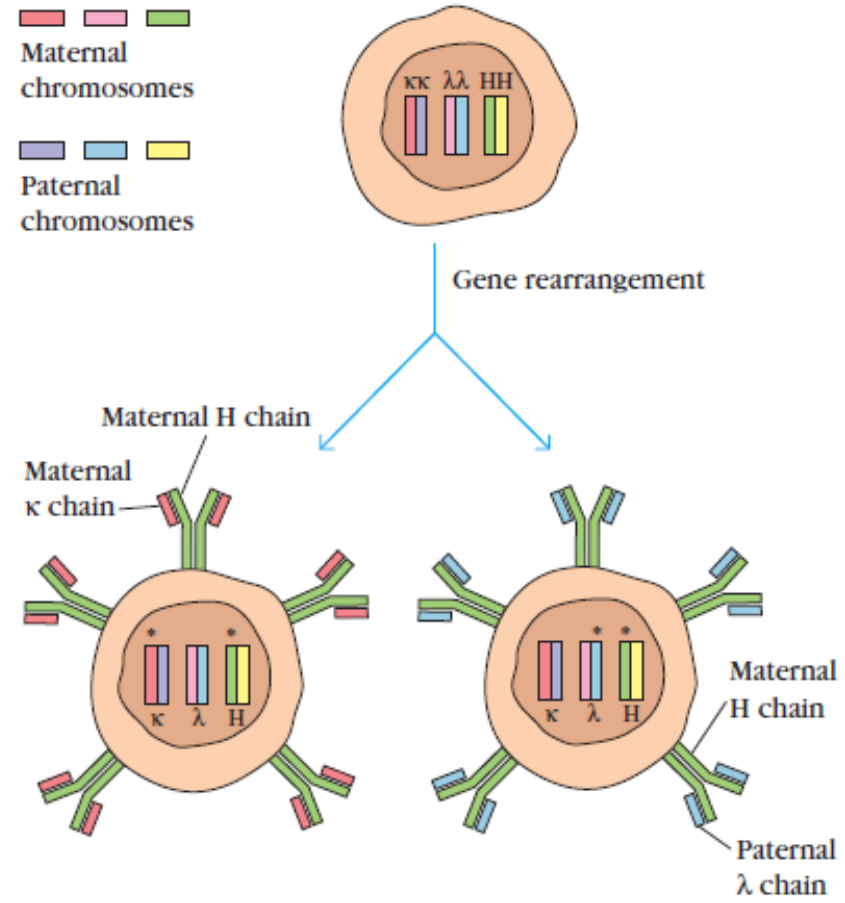


FIGURE 5-10 Because of allelic exclusion, the immunoglobulin heavy- and light-chain genes of only one parental chromosome are expressed per cell. This process ensures that B cells possess a single antigenic specificity. The allele selected for rearrangement is chosen randomly. Thus the expressed immunoglobulin may contain one maternal and one paternal chain or both chains may derive from only one parent. Only B cells and T cells exhibit allelic exclusion. Asterisks (*) indicate the expressed alleles.

- G. D. Yancopoulos and F. W. Alt have proposed a model to account for allelic exclusion.
- They suggest that once a productive rearrangement is attained, its encoded protein is expressed and the presence of this protein acts as a signal to prevent further gene rearrangement.
- According to their model, the presence of heavy chains signals the maturing B cell to turn off rearrangement of the other heavy-chain allele and to turn on rearrangement of the light-chain genes.
- If a productive rearrangement occurs, light chains are produced and then pair with heavy chains to form a complete antibody molecule.
- The presence of this antibody then turns off further light-chain rearrangement.
- If rearrangement is nonproductive for both alleles, rearrangement of the -chain genes begins.
- If neither allele rearranges productively, the B cell presumably ceases to mature and soon dies by apoptosis.

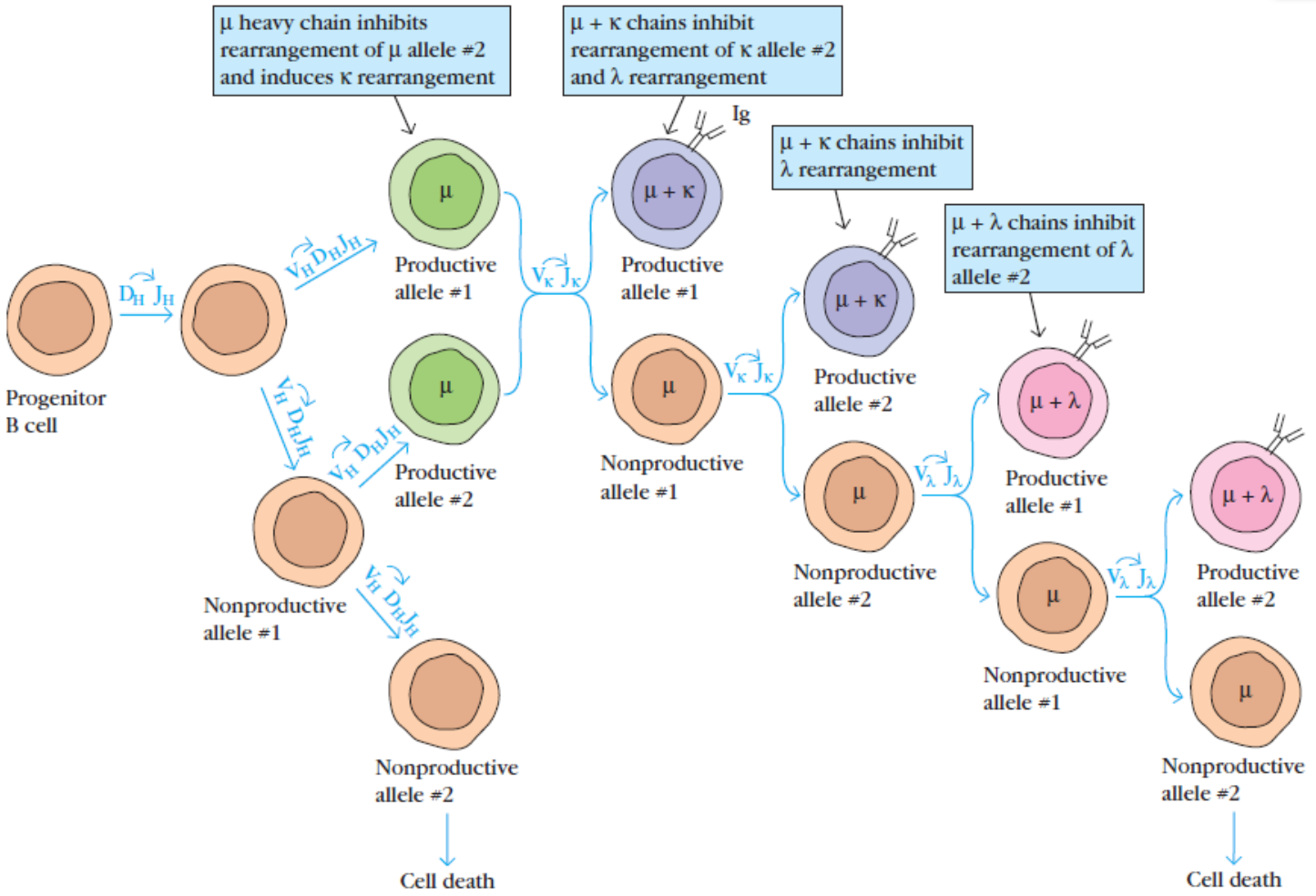


FIGURE 5-11 Model to account for allelic exclusion. Heavy-chain genes rearrange first, and once a productive heavy-chain gene rearrangement occurs, the μ protein product prevents rearrangement of the other heavy-chain allele and initiates light-chain gene rearrangement. In the mouse, rearrangement of κ light-chain genes precedes rearrangement of the λ genes, as shown here. In humans, either κ or λ rearrangement can proceed once a productive heavy-chain rearrangement has occurred. Formation of a complete immunoglobulin inhibits further light-chain gene rearrangement. If a nonproductive rearrangement occurs for one allele, then the cell attempts rearrangement of the other allele. *[Adapted from G. D. Yancopoulos and F. W. Alt, 1986,* Annu. Rev. Immunol. ***4:****339.]*