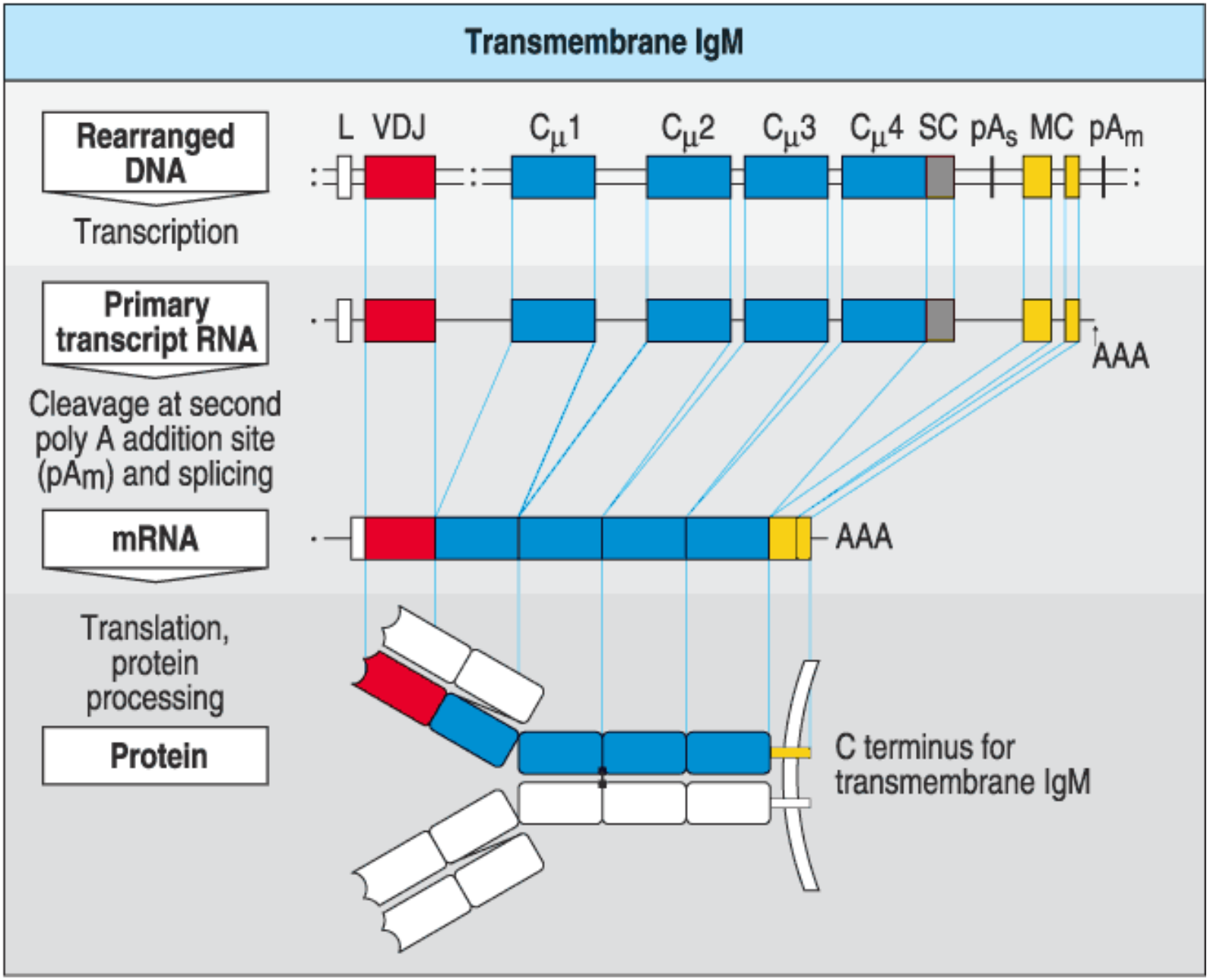
Lecture 6.
Learning Objectives and Summary



6. Maturation of antigen receptors and generation of antibody diversity

Learning objectives:

1. Learn the nature, mechanism and function of VDJ recombination of Ig and TCR genes.
2. Learn the mechanisms by which mRNA encoding different heavy chain classes are expressed and how membrane vs. secreted heavy chain mRNAs are formed.
3. Apply this knowledge to understand the pathogenesis of inherited human diseases in which gene rearrangement is defective.

SUMMARY

1. During lymphocyte development, random V, D and J gene segments are joined at the DNA level, with loss of the intervening DNA. VDJ joining is unique for Ig (κ, λ and heavy) and TCR (α, β, γ, δ) loci.

2. Both lymphocyte-specific mechanisms and enzymes involved in general repair of double-strand DNA breaks are necessary for VDJ recombination.

3. VDJ recombination has the following functions: I) generation of combinatorial diversity, ii) generation of junctional diversity, iii) activation of V gene promoters, and iv) provide the opportunity for receptor editing.

4. Ig heavy chains undergo a second DNA rearrangement, termed “class switch recombination” (CSR). This allows expression of γ, ε, and α heavy chains. CSR requires instruction by T cell cytokines.

5. mRNAs encoding the μ and δ heavy chains as well as membrane (BCR) vs. secreted (Ig) forms of the B cell antigen receptor are generated by differential RNA processing.