

The Major Histocompatibility Complex: Class II

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What is the Major Histocompatibility Complex?

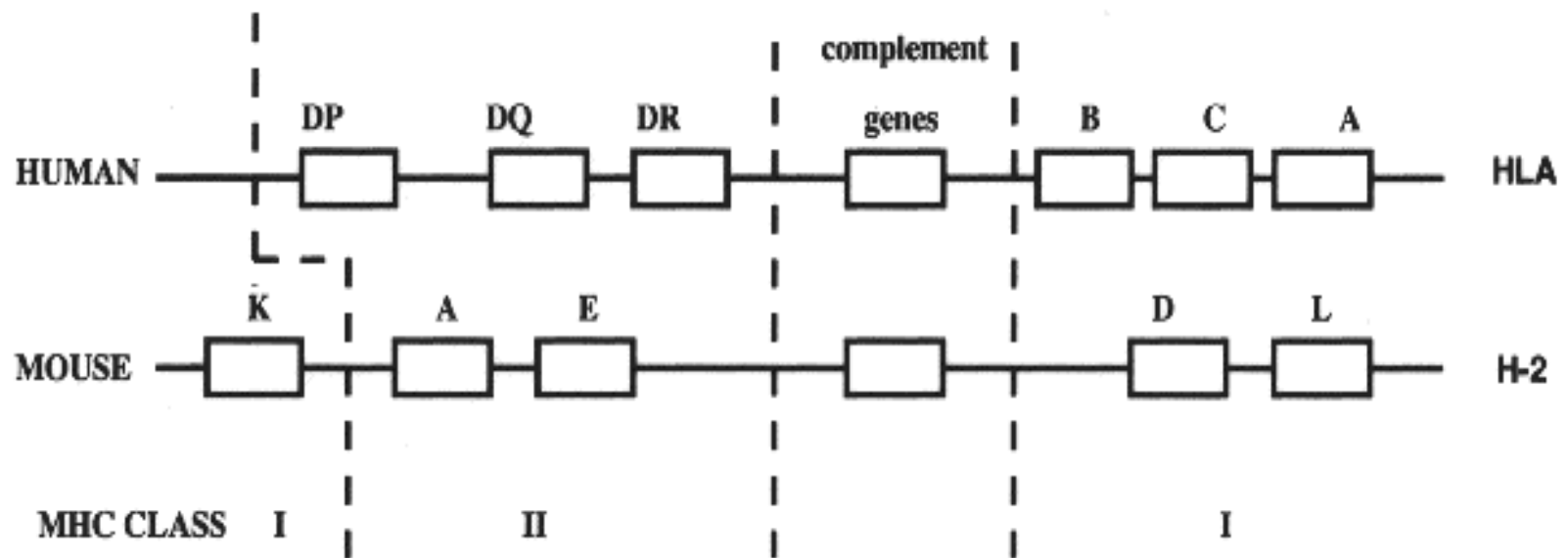
- The Major Histocompatibility Complex (MHC) is an integral component of the immune system
- A genetic complex responsible for encoding several cell surface proteins important in antigen presentation; also glycoprotein encoding and immune response initiation
- Composed of genes which encode Class I and Class II molecules

MHC Function

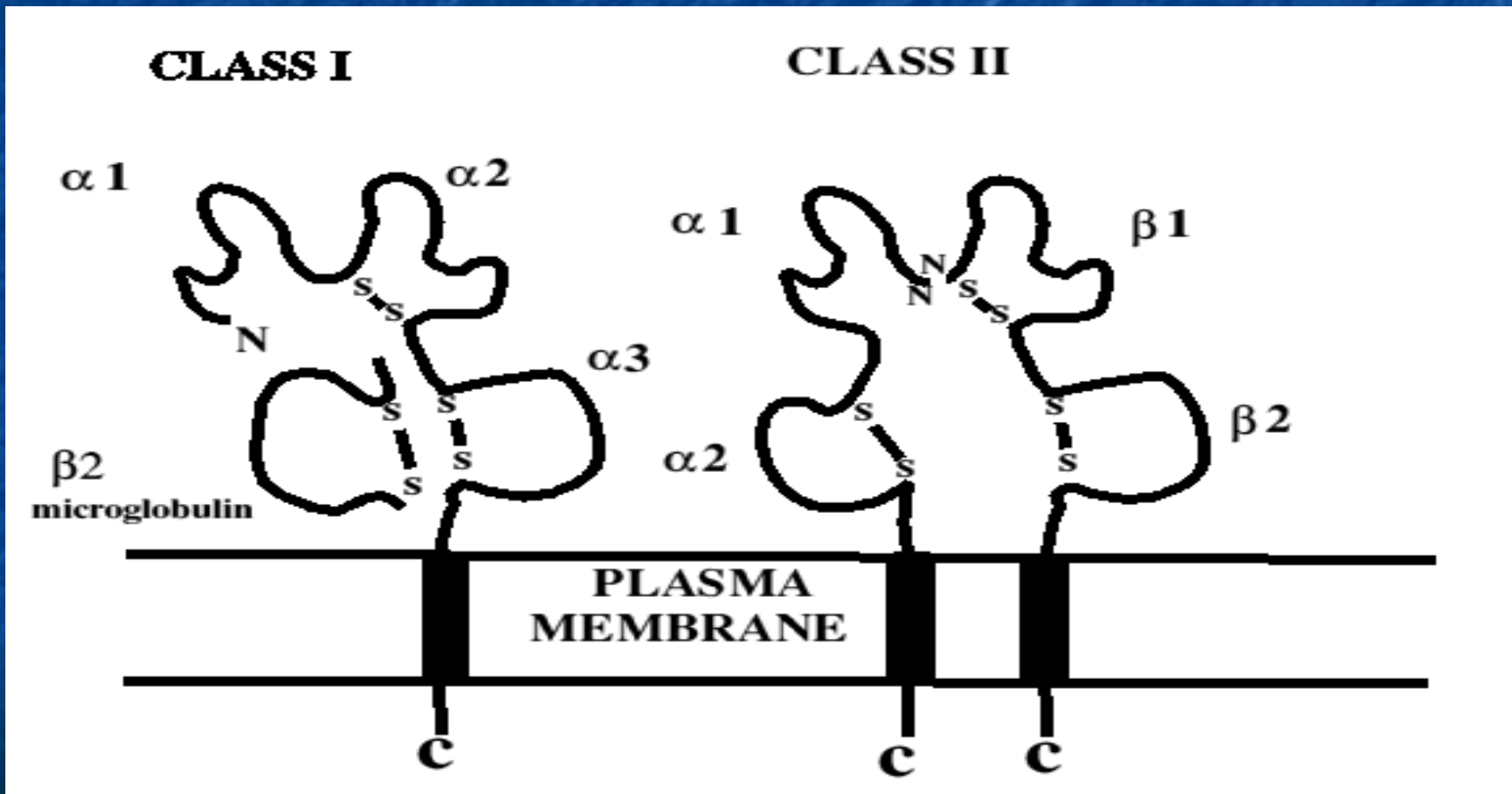
- Gene transcription regulation
- Class I—membrane glycoproteins which are widely expressed on cells throughout the body
- Class II—focus of presentation; generally restricted to antigen-presenting cells (APCs) such as macrophages, dendritic cells, and B cells; also thymic epithelium

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MHC Gene Structure



MHC Protein Structure

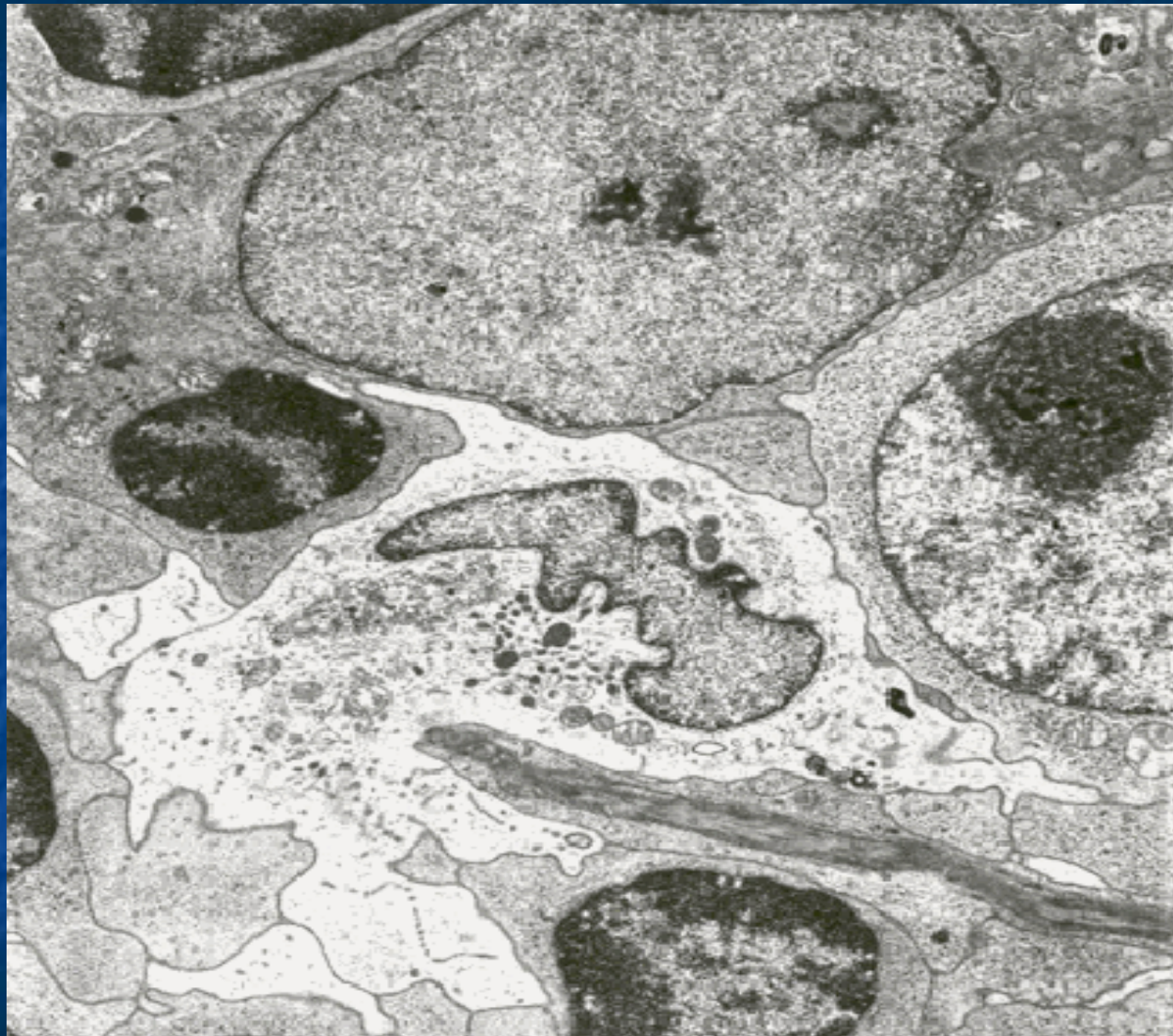


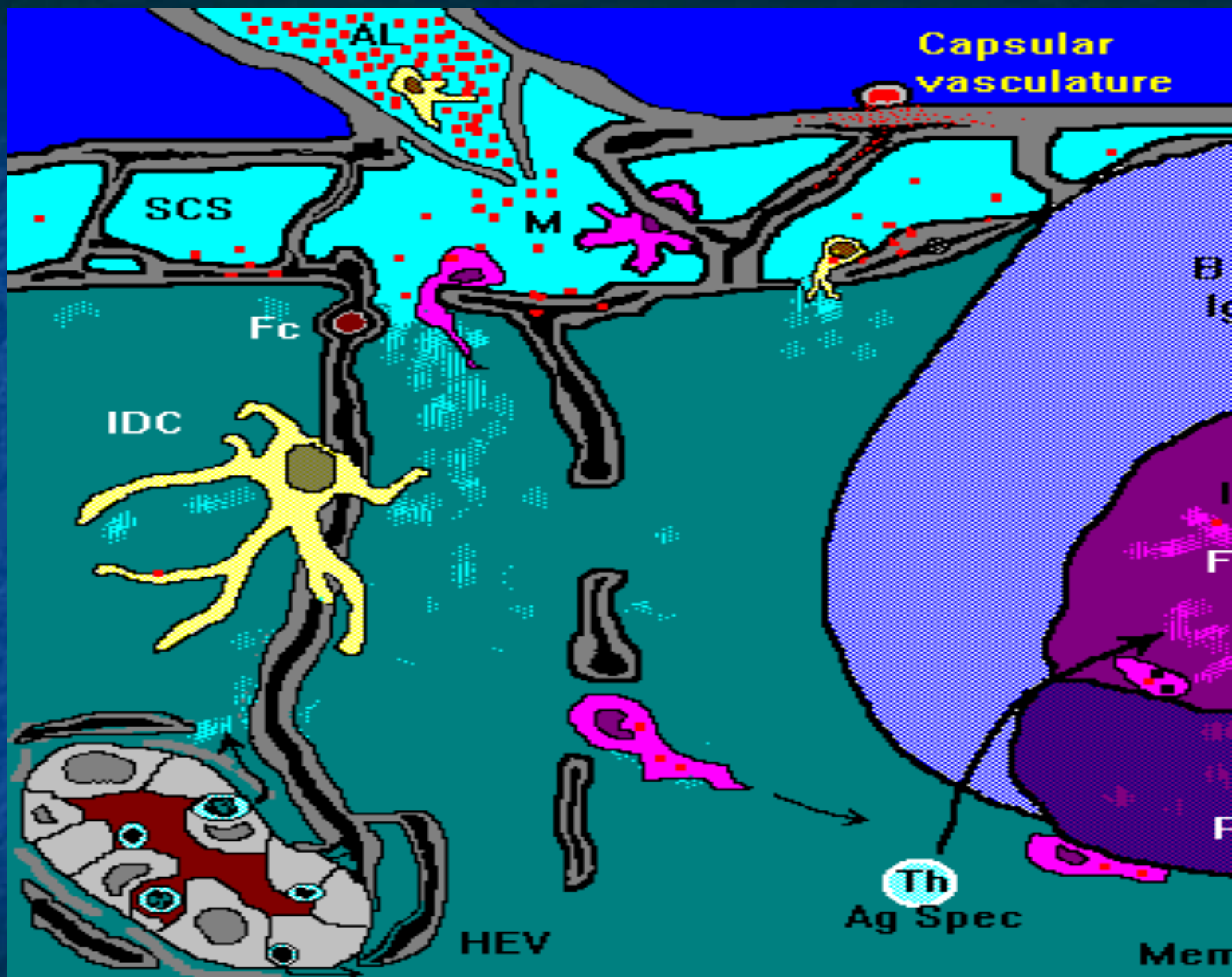
MHC Class II Function

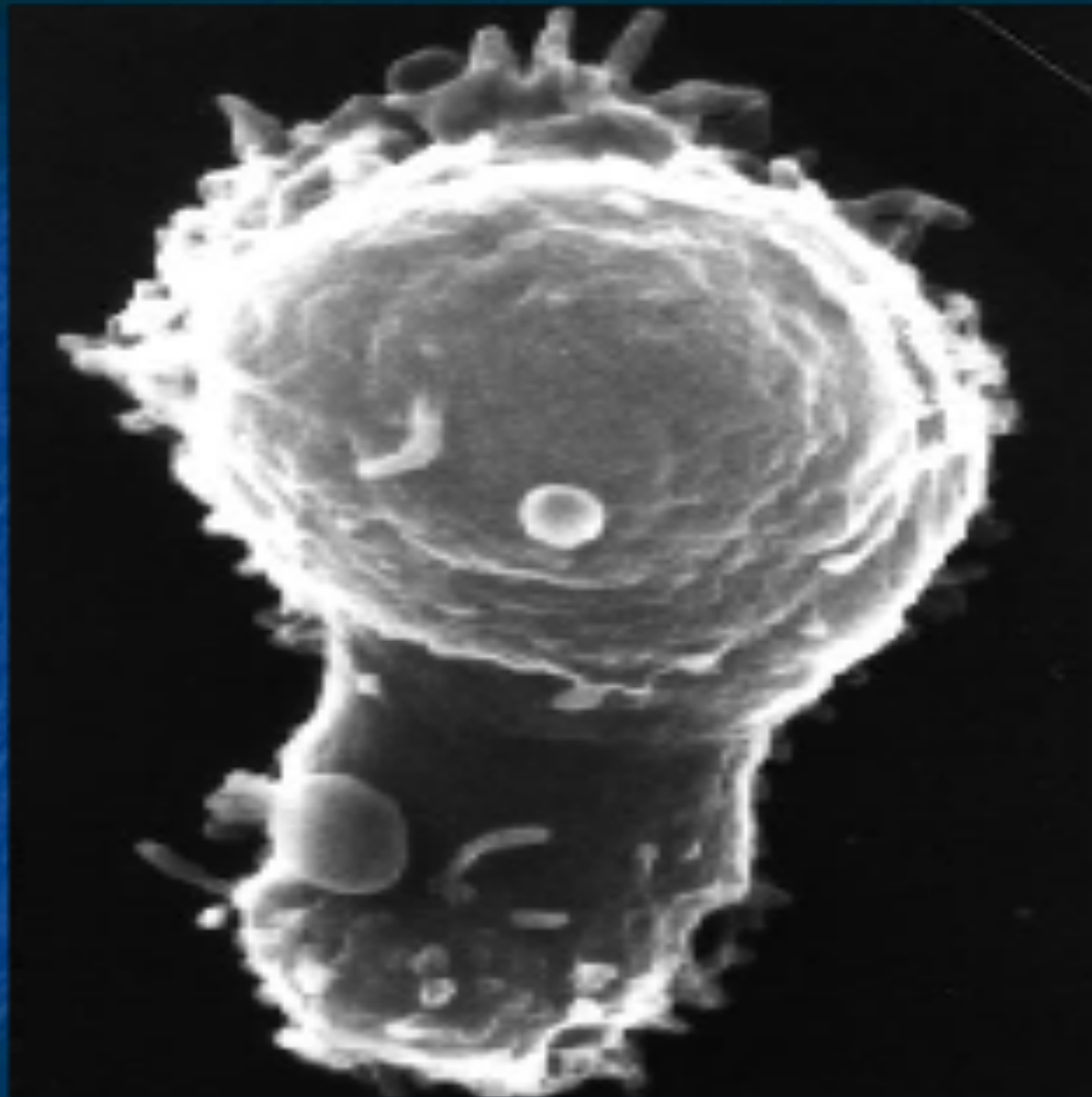
- Regulation of MHC class II expression is essential to control of immune response
- Critically important to specific recognition of antigens by immune system
- Class II genes encode heterodimeric glycoproteins that present antigens to CD4+ T lymphocytes
- Three classical class II molecules (histocompatibility leukocyte antigens) in humans: HLA-DP, HLA-DQ, and HLA-DR

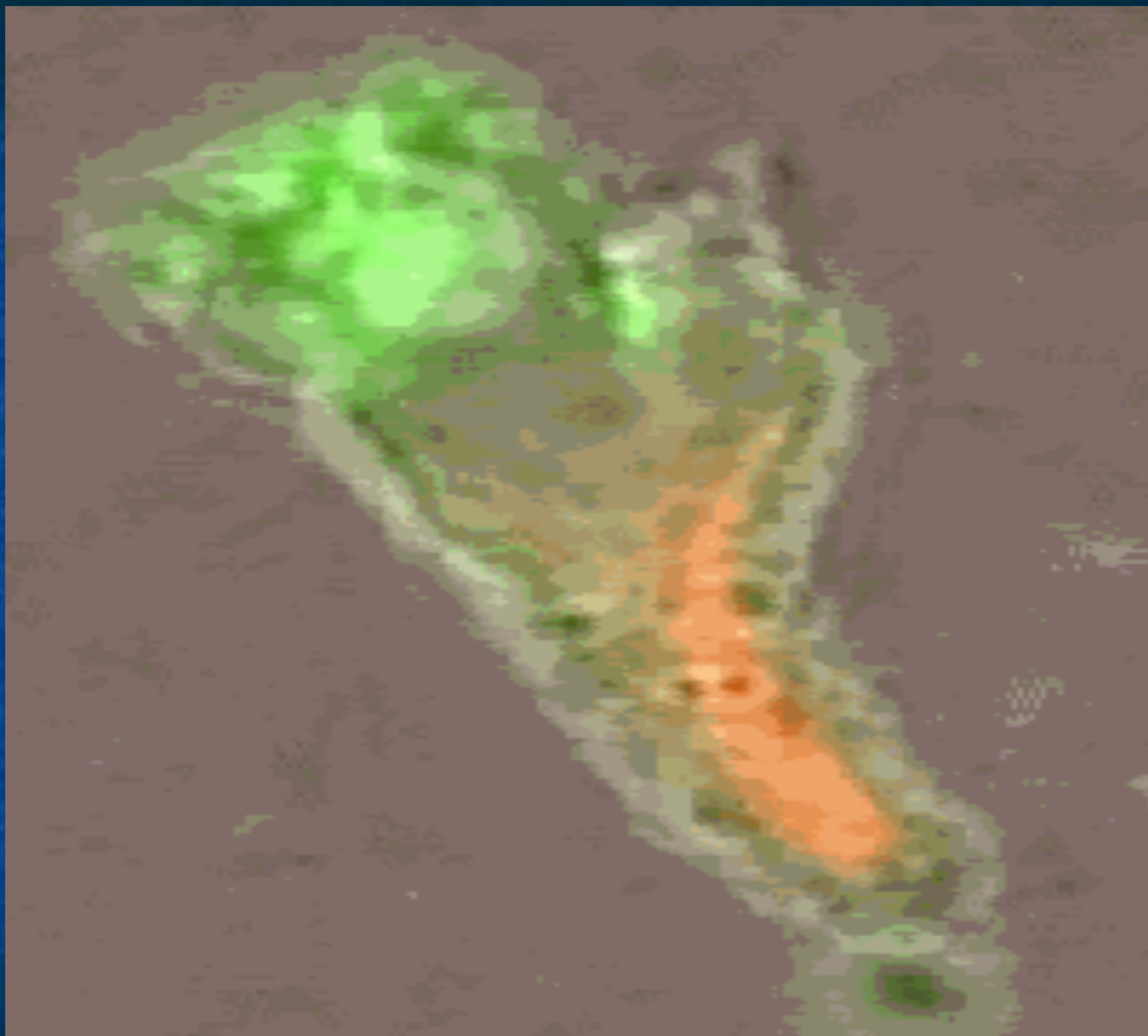
MHC Class II Mechanisms

- Genes involved in activation of MHC—essential and highly specific for MHC II
 - Class II Transactivator (CIITA)
 - Non-DNA binding transactivator that functions as a molecular switch, controlling both constitutive and inducible MHC-II expression
 - Regulatory Factor X (RFX)
 - Three subunits: RFXANK, RFX5, AND RFXAP
 - Transcription factors which bind the conserved X1 box (cis-acting sequence) of MHC class II promoters
 - Subunits of the nuclear RFX complex; DNA binding dependent on RFX complex formation
 - Transactivation dependent on region of RFX5





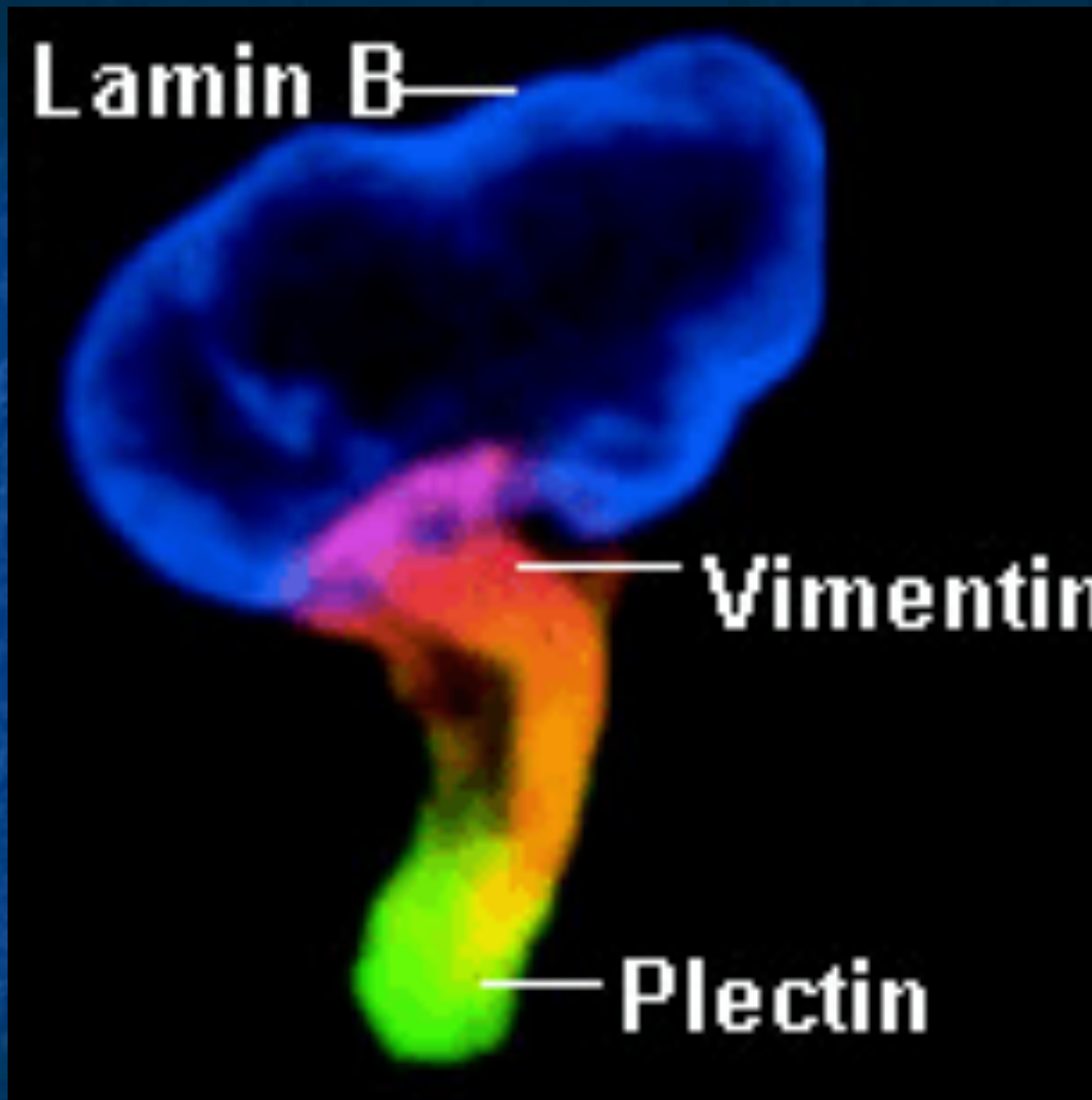


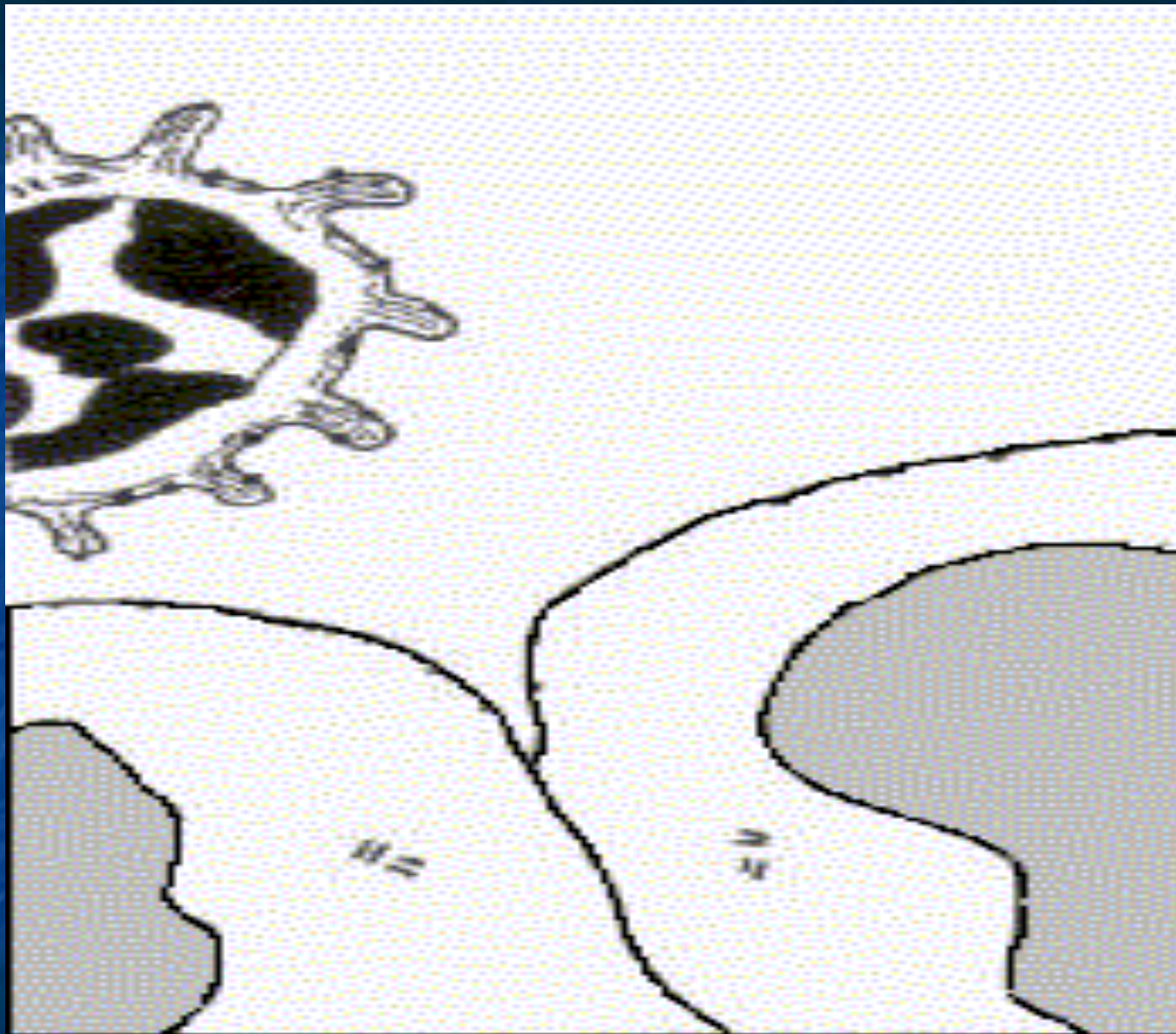


Lamin B

Vimentin

Plectin





MHC Class II Deficiency

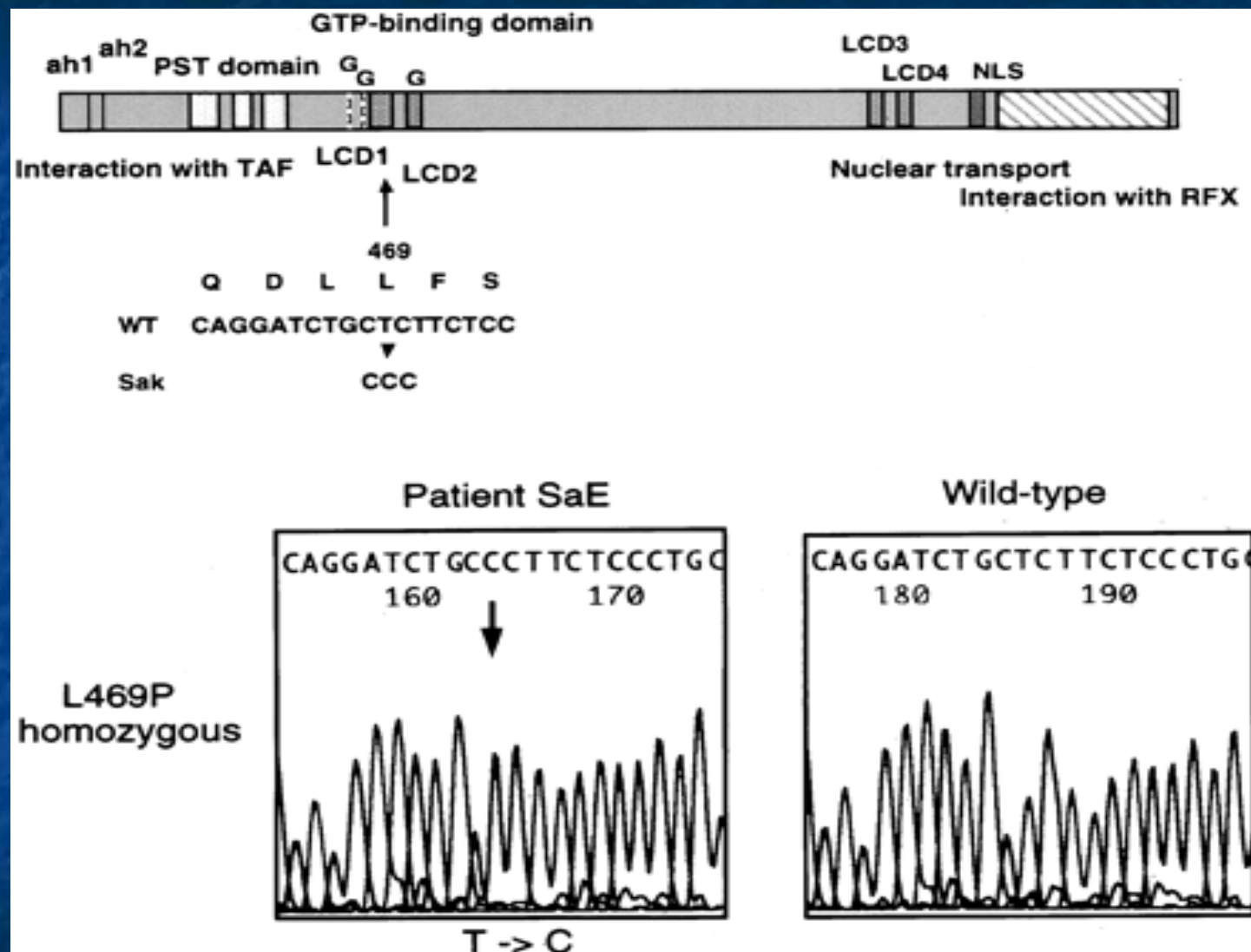
- An autosomal recessive primary immunodeficiency disease where MHC Class II molecules may be completely absent ("bare lymphocyte syndrome")
- Two distinct patterns:
 - Mutations in CIITA gene
 - Defects in RFX binding
- May result from mutations in four different transcription factors
- Mutations classified according to complementation group (A,B,C,D)

MHC Class II Deficiency

- Primary deficiency
 - RFX5-regulatory gene responsible
 - Defect in binding of the nuclear complex (RFX) to the X box motif of class II promoters; also defect may result from inability to assemble the RFX complex
 - Binding repaired via transfection of patient's cells with RFX5 cDNA

MHC Class II Deficiency

- Abnormal expression of MHC class II genes associated with autoimmunity, tumor growth, and failure to mount an immune response
- BLS is a severe combined immunodeficiency
 - similarities to AIDS



MHC Class II Studies

- Retrovirus-mediated gene transfer used to restore expression to MHC class II-negative patient cells from complementation group A of MHC class II immunodeficiency
 - Cocultivation with the virus producer line was consistently shown to be the optimal method for infection of all cell types

MHC and Disease

- Deficiency or mutation of MHC components
- Many autoimmune diseases are polygenic (no single gene is either necessary or sufficient for disease development)
- However, the MHC has been implicated as part of many such diseases
 - Type I (insulin-dependent) diabetes mellitus
 - Rheumatoid and juvenile chronic arthritis
 - Multiple sclerosis
 - Graves' disease
 - Systemic lupus erythematosus.....etc.

MHC and Disease

- To confirm genetic linkages, family-based association studies are being increasingly used
- The MHC has also been completely sequenced; this has aided in improved disease diagnosis and organ/tissue transplantation
- Currently, diagnostic tests are being developed which involve actual gene sequences; this method of accurate and rapid diagnosis would allow better control of disease progression

Did you know?

- Recent perfume studies indicate MHC involved in reasons for preference
- Forty-four men were given a t-shirt to wear for two nights in a row, without using any perfumed cosmetics or soaps; t-shirts were then rated by women
- Results indicated that women were most attracted to smells of men whose MHC differed from their own

Did you know?

- One significant subgroup among the women:
 - Those who were on the contraceptive pill preferred the odor of men whose MHC genes were similar to their own
 - Why? Contraceptive pill mimics pregnancy; biological advantage in being close to family members who will have a greater investment in the survival of the offspring

Did you know?

- More recent research from the University of Bern suggests that in choice of perfumes to wear, humans are attracted to scents that enhance their own scents; this reflects MHC genetic make-up, which then alerts potential mates to MHC compatibility.

To Sum It All Up...

- The major histocompatibility complex (MHC) is a vital component of the immune system
 - Aids in identification of self vs. non-self
 - Class II Presents non-self particles to immune cells
 - Deficiency and mutation in MHC Class II genes has been implicated in various diseases; current research on autoimmune diseases largely involves MHC
 - The MHC also affects other aspects of everyday life: the choice of scent you wear as well as the scents you find attractive