MHC II Deficiency

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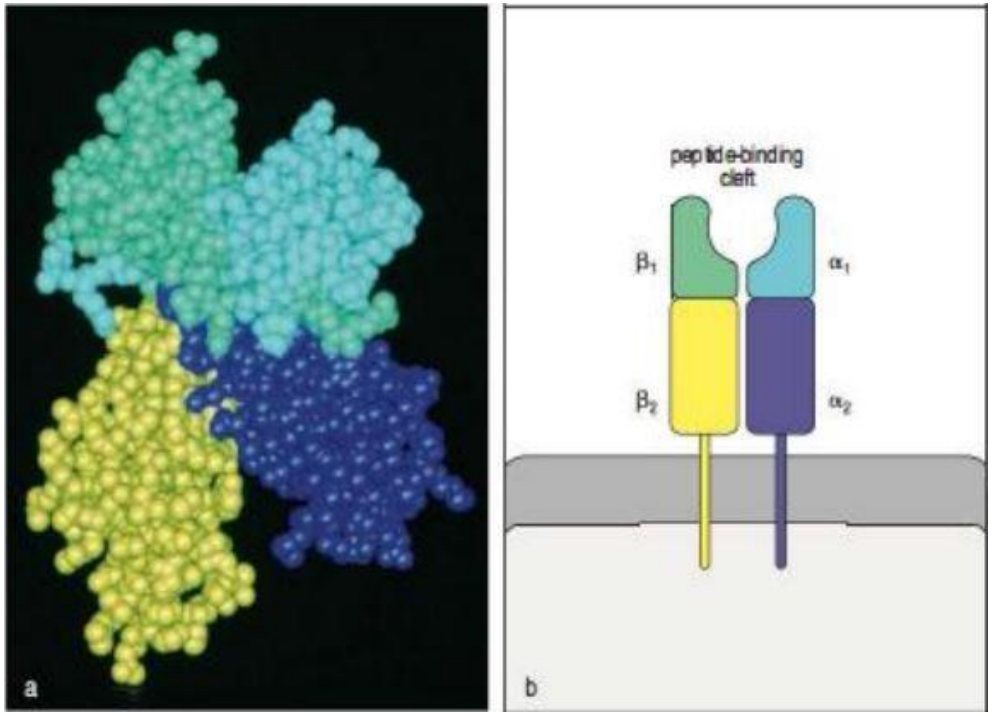
Overview

- MHC II: Structure ,Function and Expression.
- MHC II Deficiency.
- The case of Helen Burns.
- Discussion and questions.

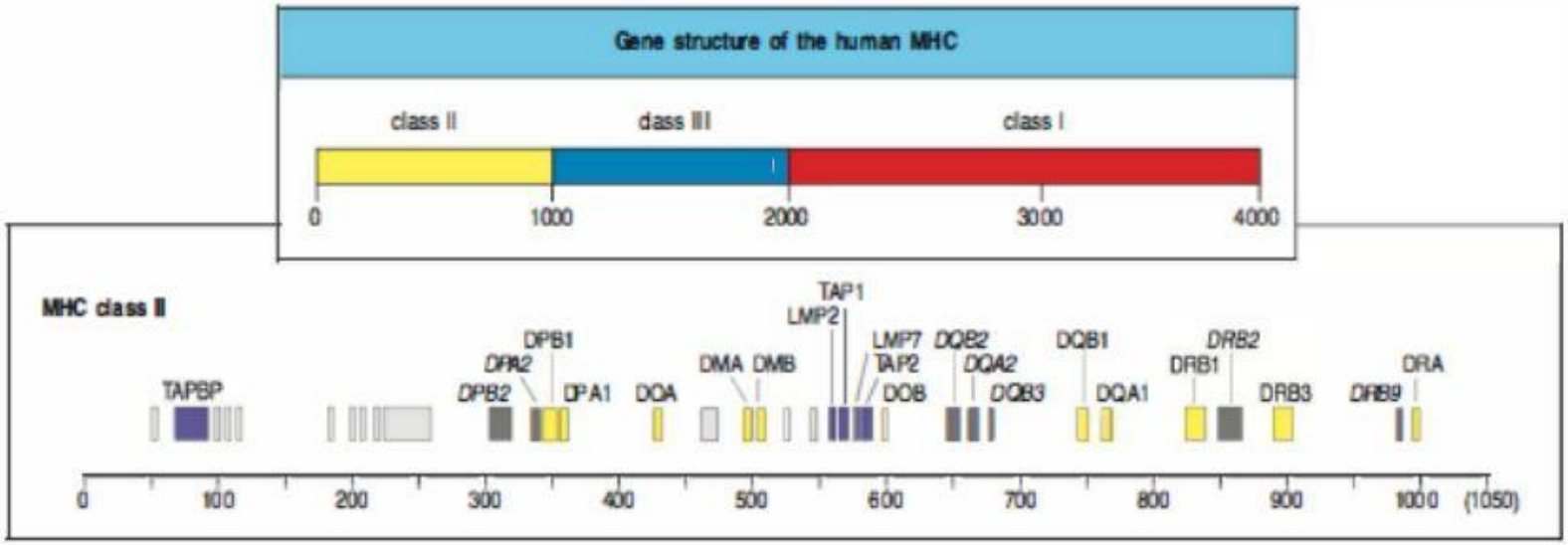
Topics bearing on this case:

- Role of MHC II molecules in antigen presentation to CD4 T cells.
- Role of the co-receptor molecule CD4 in antigen recognition by T cells.
- Lymphocyte stimulation by polyclonal mitogens.
- Mixed Lymphocyte reaction.
- Intrathymic maturation of CD4 T cells.
- FACS analysis.
- Bare lymphocyte syndrome.
- MHC class I deficiency.

MHC II: Structure, Function and Expression.



- MHC II is a heterodimer made of one α-chain and one β-chain.
- Each folded into two protein domains.
- The antigenic peptide binds in a cleft between these two chains.



- The genes encoding both chains are located in the MHC gene on the short arm of chromosome 6.
- Human MHC gene codes for Classes I,II and III proteins.

- Yellow = MHC class II genes

- MHC II = genes include DP, DQ and DR and they're highly polymorphic.

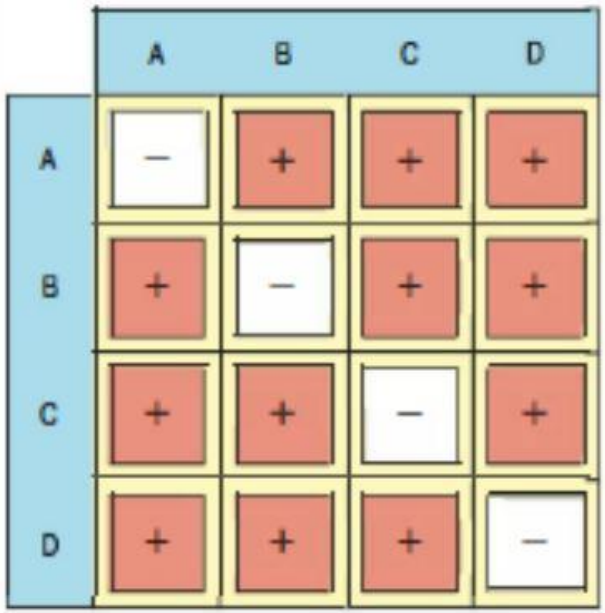
- Peptides bound to MHC II can be only recognized by **CD4** T cells and not by CD8 T cells.
- Expression of MHC must be coordinated strictly and is under complex regulatory mechanism.

MHC class II deficiency.

- AR trait.
- Mild form of SCID, susceptibility to opportunistic infections.
- SCID patients **VS.** MHC II deficiency patients.
  *T-cells and response to nonspecific T-cell mitogens (PHA) and to allogenic stimuli.
  *Graft-versus-host disease.
  *progressive infection with attenuated live vaccine strain BCG (Tb).
- Patients are deficient in CD4 T cells, in contrast to MHC I deficiency.
- Moderate to sever hypogammaglobulinemia.
- Genes encoding MHC class II on ch.6 are normal, Defect ?

Complementation groups of MHC II deficiency.

- MHC II deficiency stems from different causes in different patients.
- Fusion of B-cells taken from two affected patients corrected the defect and showed MHC class II expression.
- At least four complementation groups were found after pairwise fusions.
- The lack of MHC II molecules results from defects in the transcription factors.
- If (-) → Same genetic defect.
- If (+) → Different genetic defects.

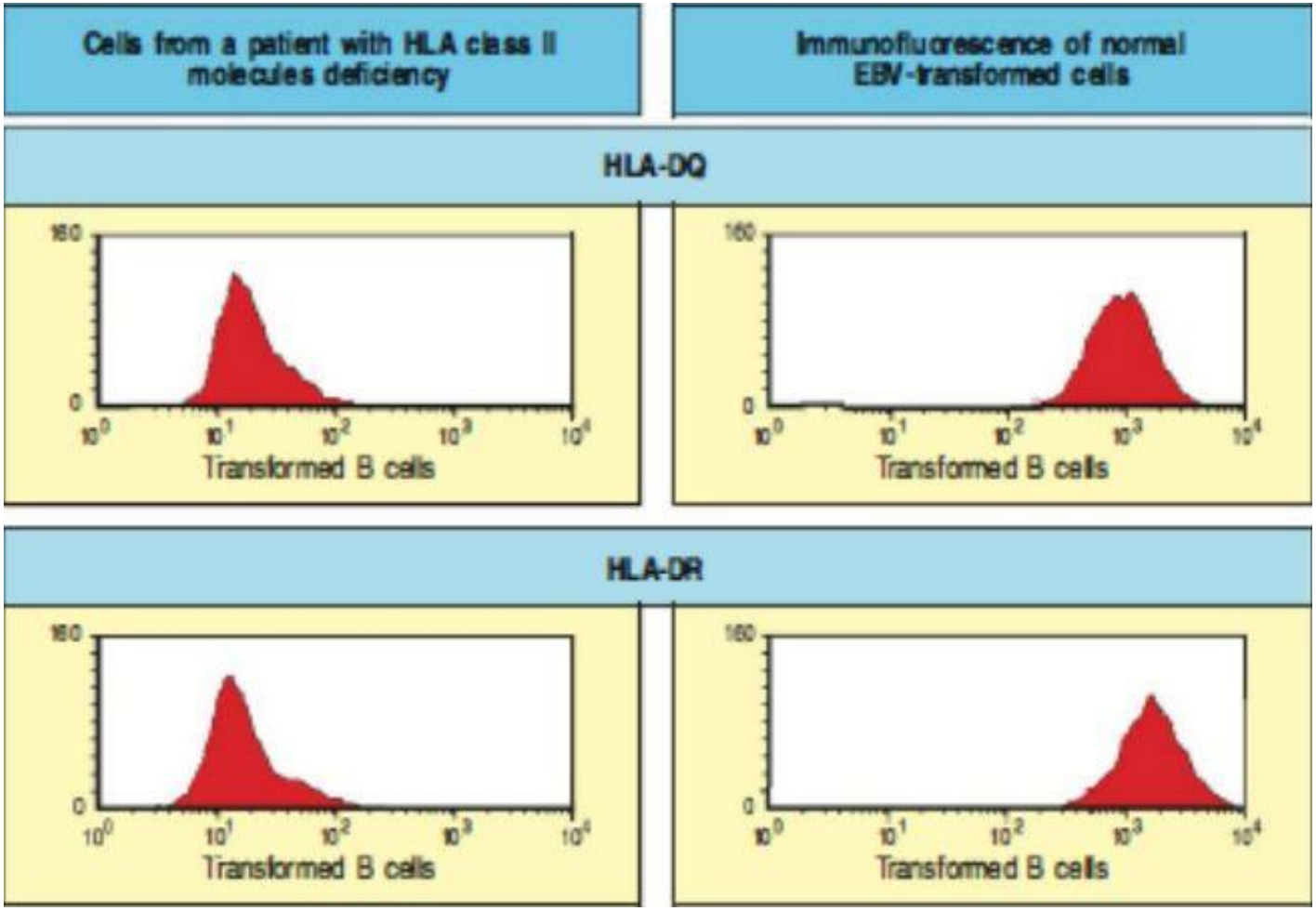


The case of Helen Burns.

- Pneumonia at 6 months, tracheal aspirate showed *Pneumocystis Carnii*, SCID ?
- Tests on peripheral blood mononuclear cells showed normal proliferative response (Lymphocyte function test)
- Her T-cells failed to respond to tetanus toxin in vitro despite the fact that she took vaccination.
- Serum Ig's → Very low (Indicates deficiency of CD4 T cells)
- **High** WBC count, **Low** Lymphocyte count, **low** CD4 +ve cells count, **Normal** CD8 +ve cells count.
- Substantial numbers of T cells and thus normal response to PHA, ruled out the diagnosis of SCID.

The case of Helen Burns.

- Bone marrow transplant indicated despite lack of diagnosis.
- HLA typing for Helen, DR type couldn't be obtained form her WBC's, The next step should be FACS analysis.
- Long term culture for her B-cells was made, by transforming them using EBV, transformed cells were examined for expression of MHC I and II with fluorescent-tagged antibodies (FACS analysis).
- Her B-cells didn't express HLA-DQ or DR, ***MHC class II deficiency was established***, and bone marrow transplant is advisable.



Helen's B-cells ***Control***

Discussion and questions.

- **Why did Helen Lack CD4 T cells in her blood?**

  → *no MHC II in thymic epithelial cells which are crucial in CD4 maturation.*

- **Why did Helen have a low level of Ig's in her blood?**

  →*lack of CD4 T-cells cytokines which are required for B-cell maturation.*

- **Explain why we ruled out SCID.**

  →*CD4 T cells count is low, however these cells are normal and able to respond to non-specific antigens(PHA) and to antigens presented by a foreign MHC.*

- **Explain why her lymphocyte failed to respond to tetanus toxin IN VITRO.**

  → *There were no cells that could present antigen on MHC II to CD4 T cells.*

- ***Would she reject a skin graft ?***

→ *Yes, her T-cells are capable of recognizing foreign MHC molecules on the grafted skin cells and would reject the graft.*

Thank you