Major Histocompatibility Complex

PART- 4

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# Pathways for processing antigen

Two pathways are proposed-

1. Cytosolic or Endogenous pathway

2. Exogenous pathway

Cytosolic or Endogenous Pathway

- **Antigenic peptides for class I MHC molecule are processed through cytosolic or endogenous pathway.**

- **For this pathway, antigen are generated within cell.**

- **Proteasome (A proteolytic system): degraded irregular/ antigenic intracellular proteins into short peptide.**

Overview of endogenous and exogenous pathways for processing the antigenic peptides

Reference: Kuby – Immunology; 7th Edition by Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones; Chapter-8: The Major Histocompatibility Complex and Antigen Presentation; Page: 284
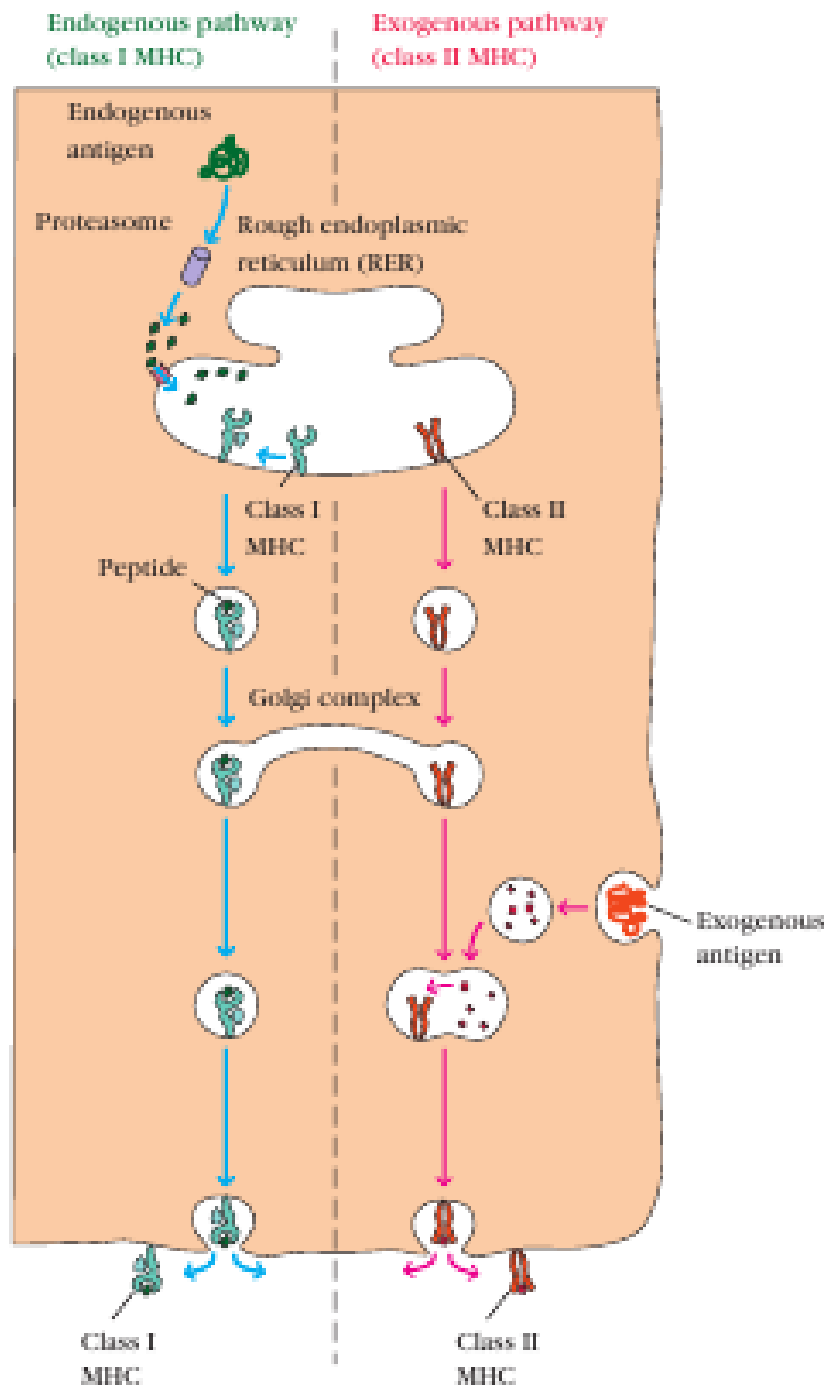
General pathway of protein degradation

PROTEASOME

- Found in all eukaryotic cell
- Degrade proteins into short peptides
- Size- 20S
- Composed of 14 subunits
- Structure: barrel like symmetrical ring
- Target protein degrade in proteasome when ubiquitin (small protein) attached.

- **Proteasome complex consists of**
  - **20S base**
  - **19S regulatory component**
- **Central hollow of proteasome degrade ubiquitin-protein complex.**
- **Cleavage of peptide bond- ATP dependent.**
- **Break down of protein through proteasome complex is also utilize by the immune system.**
- **Degraded antigenic peptides are displayed by APCs through class I MHC molecules.**

Specific pathway of protein degradation

IMMUNOPROTEASOME

- **Found in infected APCs**
- **Size equal to proteasome**
- **Its unique components are induced by**
  - **Interferon-γ and**
  - **TNF-α**
- **Interferon-γ and TNF-α act as signal molecule for LMP2 and LMP7 genes**
- **Product of LMP2 and LMP7 genes (replacement catalytic protein subunit) convert standard proteasome into immunoproteasomes.**
- **Immunoproteasomes work more efficiently than standard proteasome.**
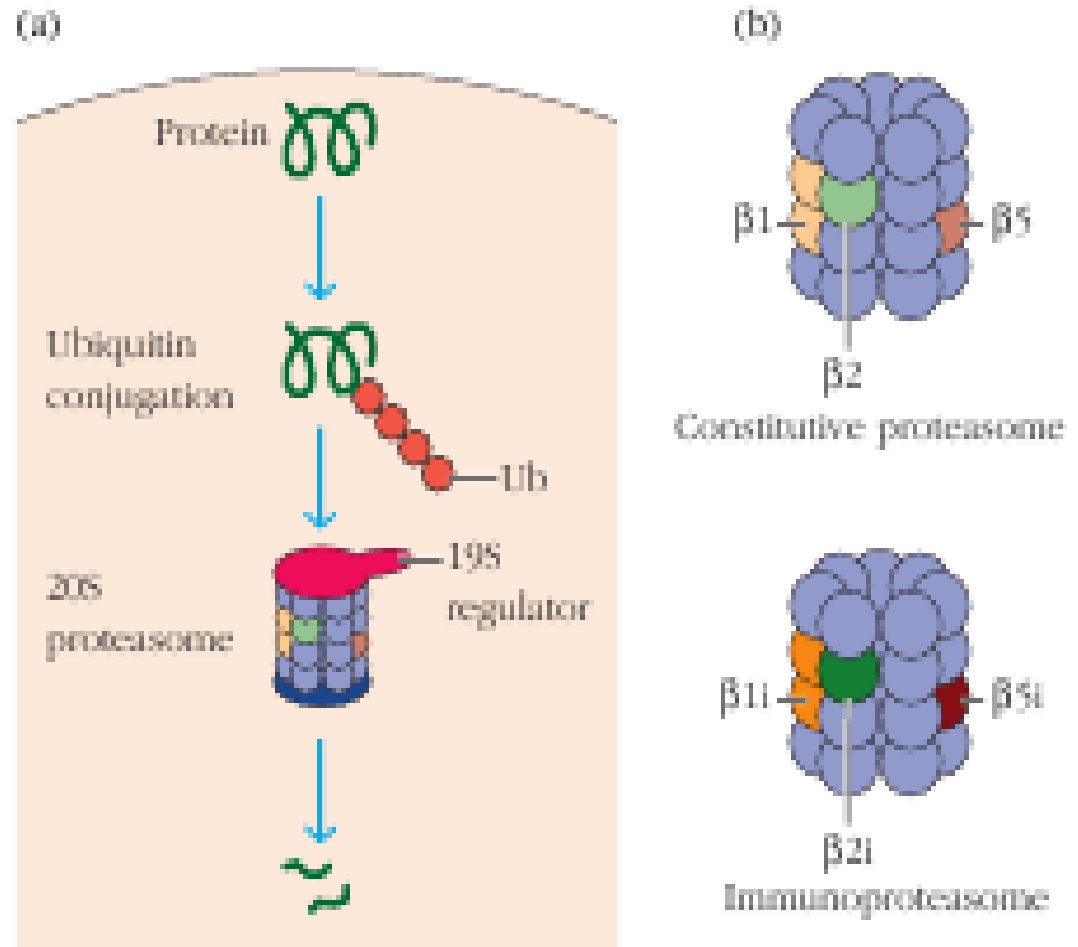
Reference: Kuby –Immunology; 7th Edition by Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones; Chapter-8: The Major Histocompatibility Complex and Antigen Presentation; Page: 285

Transporter Protein- TAP

- **TAP-membrane spanning heterodimer**
- **Consists of two protein**
  - ➢**TAP1 and**
  - ➢**TAP2**
- **Have two domain**
  - ➢**RER lumen domain**
  - ➢**Cytosolic domain-ATP binding**
- **Antigenic peptides formed by proteasome are translocated by TAP into RER lumen.**
- **Hydrolysis of ATP required during transportation.**

- **TAP show affinity for antigenic peptide (8-16 AAs).**
- **ERAP (Endoplasmic reticulum aminopeptidase)**
  - **Found in ER lumen**
  - **Trimmed longer peptide**
- **TAP1 and TAP2 protein synthesized by**
  - **TAP1 and TAP2 gene**
  - **Mapped within class II MHC region**
  - **Allelic form exist in population**
- **Deficiency of TAP leads to disease syndrome.**

Transporter Protein-TAP and processing of antigenic peptides

Reference: Kuby –Immunology; 7th Edition by Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones; Chapter-8: The Major Histocompatibility Complex and Antigen Presentation; Page: 286
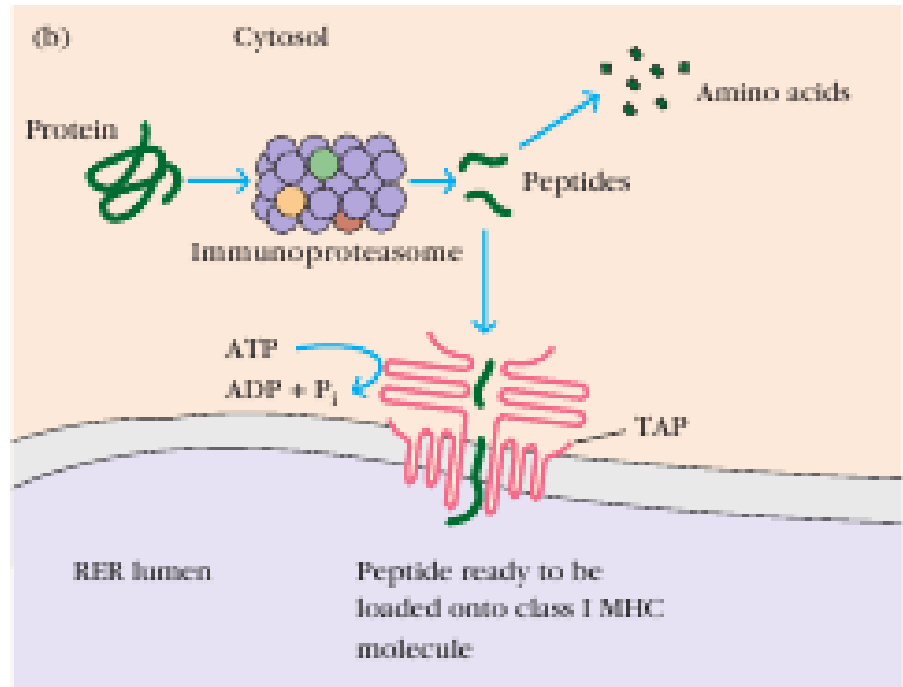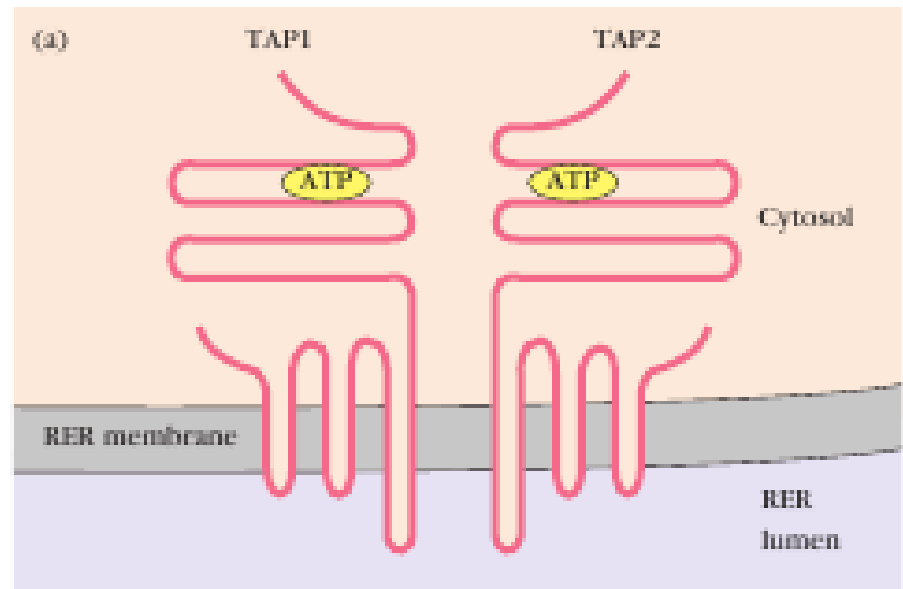
Deficiencies in TAP Can Lead to Bare Lymphocyte Syndrome

Reference: Kuby –Immunology; 7th Edition by Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones; Chapter-8: The Major Histocompatibility Complex and Antigen Presentation; Page: 287

Role of molecular chaperone in assembly of Class I MHC Molecule

- **Molecular Chaperones are-**

- **Calnexin**

  - **found in ER membrane**

  - **Help in folding of class I α chain withERp57 protein (enzymatic activity)**

- **Calnexin release after assembling of α chain and β microglobulin.**

- **Molecular chaperone-**
  - **Calreticulin and**
  - **Tapasin**

  immediately associated with class I MHC molecule after release calnexin
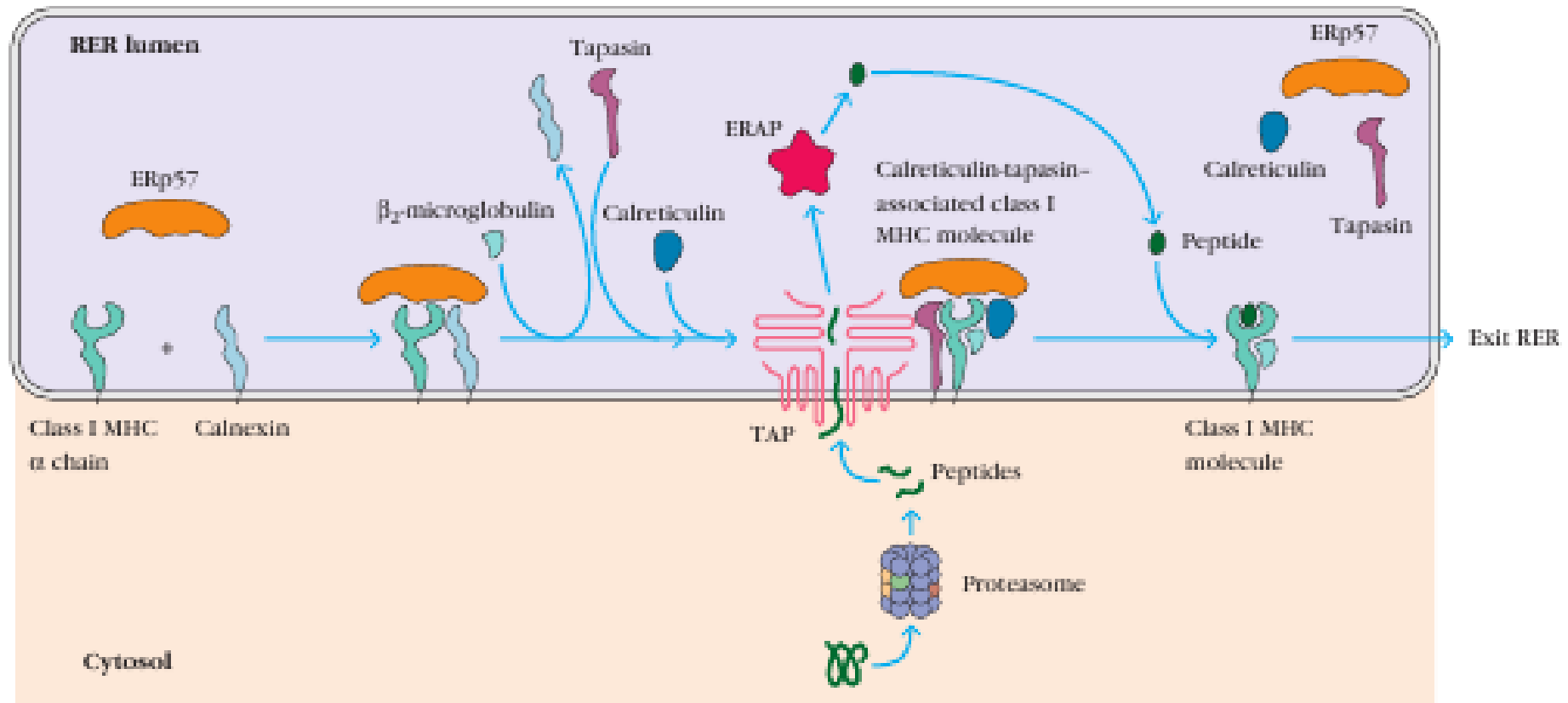
- **Tapasin (TAP associated protein)-**
  - ✓ **Bring transporter in proximity with class I MHC molecule**
  - ✓ **Allow acquiring of antigenic peptide with class I MHC molecule.**

- **ERAP1**
  - ✓ **Help in removing residue from amino-terminal of peptide to enhance the binding capability with class I molecule.**

Assembly and stabilization of class I MHC molecules

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Thanks