Systems Biology of Antigen Processing: From Structures to Mechanisms

Alistair Bailey[1,2], Tim Elliott[2], Andrew Phillips[3] and Jörn Werner[1]

[1]School of Biological Sciences, University of Southampton, Boldrewood Campus, Southampton , SO16 7PX
[2]Cancer Sciences Division, Somers Cancer Research Building, MP824, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD
[3]Microsoft Research Cambridge, Roger Needham Building, 7 J J Thomson Ave, Cambridge CB3 0FB

UNIVERSITY OF Southampton School of Medicine

email: ab604@soton.ac.uk

Microsoft Research

The Challenge

Cells present fragments of proteins called antigens to other cells using MHC Class I proteins. These protein complexes present the antigen from within cells at the surface and act as displays for the immune system to survey the inside of cells for diseases, viruses and other pathogens. However some antigens, such as those in cancer cells, are not presented as strongly as others and these antigens may go unseen by the immune system. This is believed to be due to a process of 'editing' of the antigen peptides involving another protein, Tapasin. Antigens are selected according to the stability of the complexes formed so that only a few of the many possible antigens dominate in presentation[1].
A deeper understanding of the processing of antigens is necessary for the development of therapies that could use our immune systems to fight diseases such as cancer.

Three modelling strategies

- Modelling the structures of proteins involved in antigen processing to try and identify functional features[2].
- Protein-Protein docking simulations to investigate structural interactions[6].
- Modelling processes with the Stochastic Pi-Calculus Machine developed by Microsoft Research[7] to investigate high-level protein interaction mechanisms .

Antigen Peptides

Proteins are made from 20 different Amino Acids (AA). Protein fragments of 8 to 10 AA in length form antigen peptides. This provides over 5 billion permutations for possible antigens of 8 AA in length alone.

MHC Class I proteins are assembled in the endoplasmic reticulum (ER) of cells. They are unstable in this empty 'open' conformation.

MHC Class I form a stable 'closed' conformation when bound to an antigen peptide and can travel to the cell surface.

Tapasin, the key protein involved in antigen 'editing' of MHC Class I molecules. This occurs in the peptide loading complex (PLC).

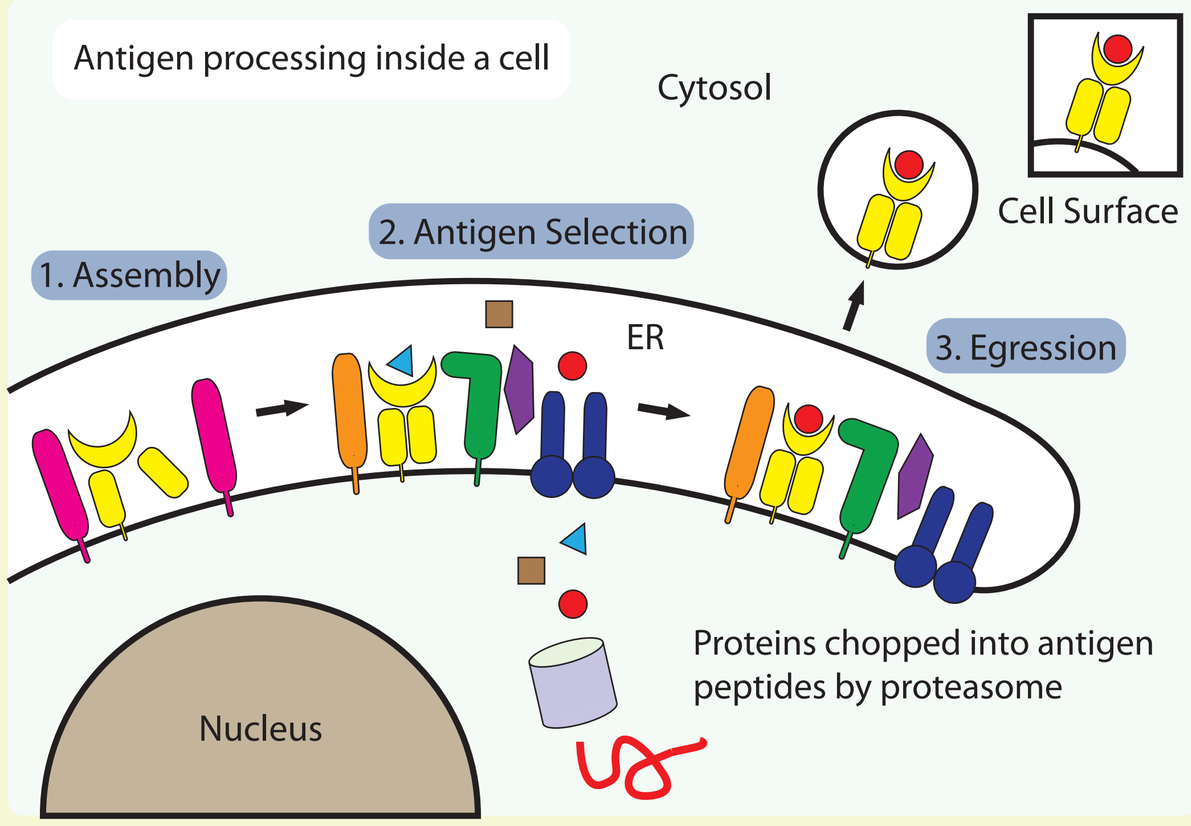
Calnexin binds to MHC Class I during early protein assembly.

It is replaced by Calreticulin in the PLC.

Erp57 is a protein bound to Tapasin in the PLC. It is also thought to assist in MHC Class I assembly

The transporter associated with antigen processing (TAP) delivers a supply of antigen peptides to the ER.

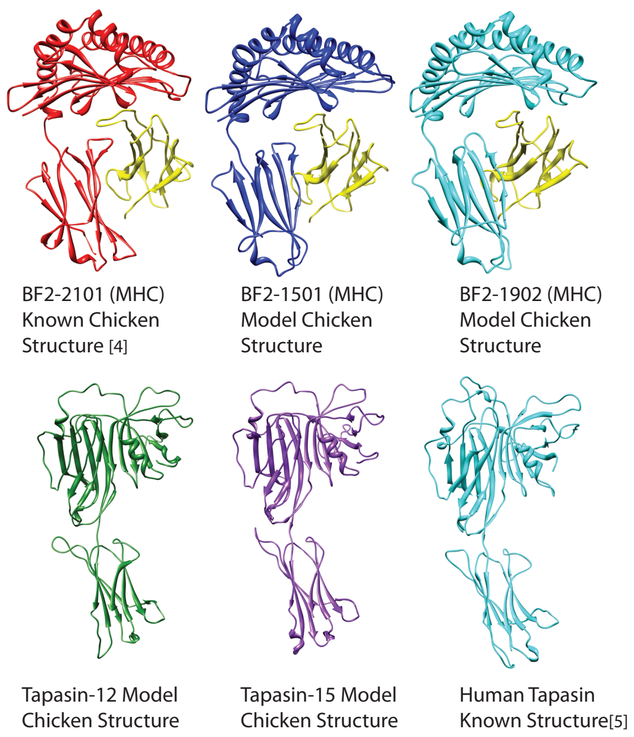
Antigen processing inside a cell



Comparative Structural Modelling

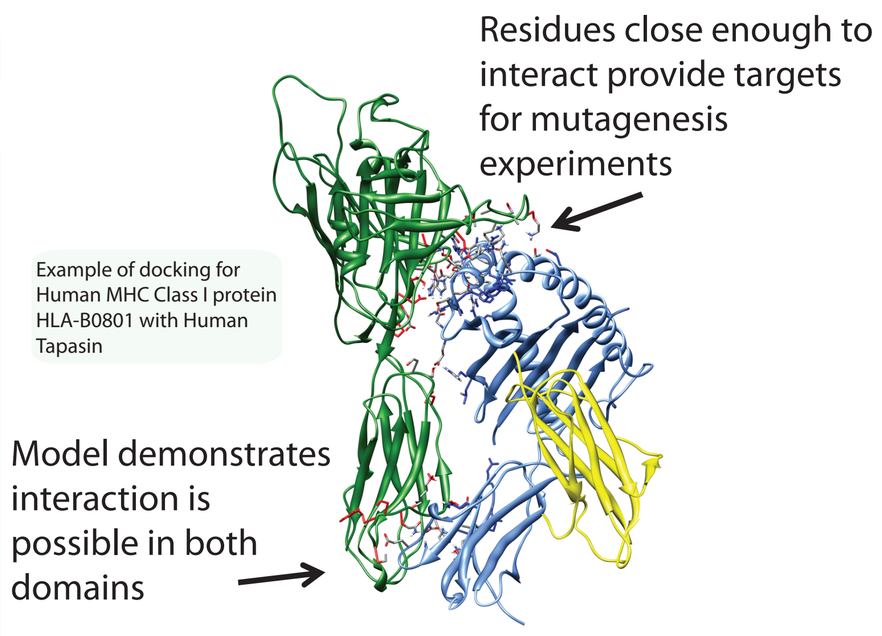
Genes expressing human MHC Class I proteins and Tapasin are distant on the genome unlike in the chicken genome. Identification of co-evolved structural differences [3] may indicate sites of interaction between the chicken proteins and thus genomic sites important in the 'editing' process for both humans and chickens.

Models are built by comparing known structures with protein sequence code [2,4,5].



Protein Docking[6]

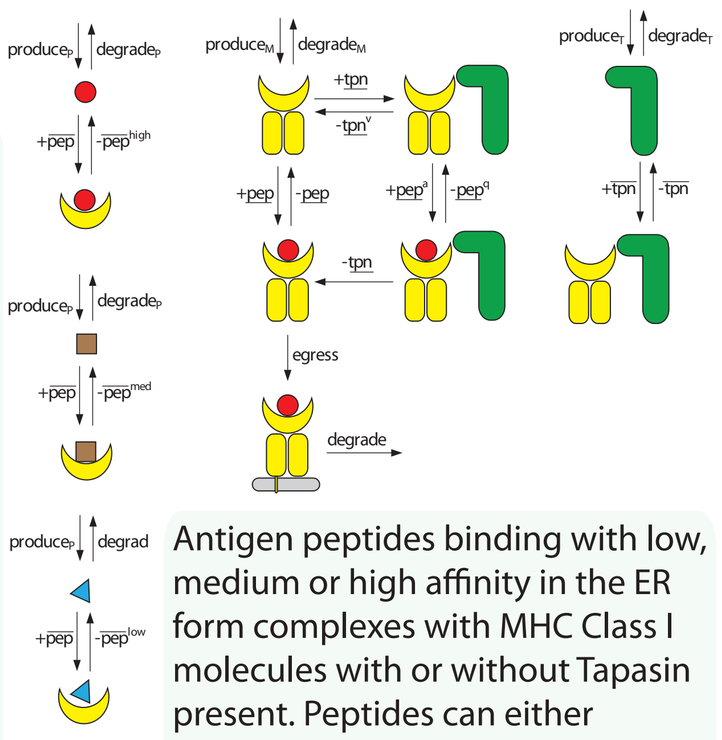
Structures are presently being docked *in silico* to examine how they may bind & to identify interacting protein residues that can be mutated for *in vitro* mutagenesis experiments with real proteins.



Note: These MHC structures are 'closed' surface structures. Future work may use molecular dynamics to create 'open' conformations for docking as may exist in the ER.

Stochastic Pi-Calculus model for antigen processing [7]

Using the Stochastic Pi-Calculus Machine (SPiM) proteins can be modelled as a network of concurrent processes. Messages sent in parallel replicate binding and unbinding reactions of the proteins.
Tapasin has been shown to improve 'editing', but the mechanism is unclear.
Future work combining the structural model information with SPiM may further reveal this mechanism.

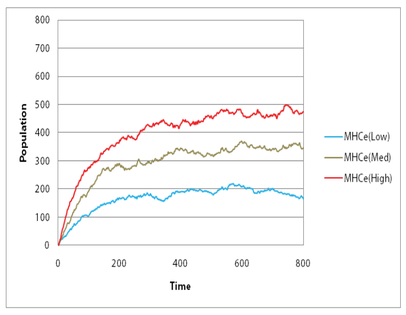


Antigen peptides binding with low, medium or high affinity in the ER form complexes with MHC Class I molecules with or without Tapasin present. Peptides can either unbind or loaded MHC Class I molecules egress from the ER.

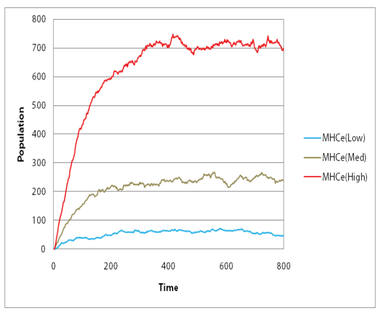
SPiM Model Results

Tapasin improves antigen 'editing'. Plots show populations of MHC with Low, Medium & High Affinity Antigen.

Without Tapasin



With Tapasin



Summary

Insights gained from structural models inform the process models which improves our understanding of exactly which regions of the genome give rise to improved 'editing' of antigen.

References

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