Activity 3 - Why is the Major Histocompatibility Complex so important?

We saw in resource 2 that fetal trophoblast cells are perilously exposed to the maternal blood and immune system. So why are they not attacked as a foreign invader?

Half of the genes a fetus inherits came from its father, so why are these not recognised as alien by the mother – and rejected like a tissue transplant?

To answer this question, we need to think about what proteins cause rejection of tissues and organs when transplantation surgery goes wrong.

Remarkably, most tissue graft rejection reactions occur when the recipient's immune system attacks one of a very small number of proteins – the product of one of maybe just six different genes.

Because of this phenomenon, these rejection-inducing proteins are called the 'Major Histocompatibility' proteins ('histo-' means 'tissue'). The genes which encode them are all bunched together on one chromosome – as the 'Major Histocompatibility Complex', or MHC.

In humans this is on chromosome 6 (below), and you inherit one of these chromosomes from each parent. In other species, the MHC is on different chromosomes.

(Public Domain: https://en.wikipedia.org/wiki/Chromosome_6_(human)#/media/File:Human_male_karyotpe_high_resolution_-_Chromosome_6_cropped.png)

To find out more about the MHC, see:

http://www.biology.arizona.edu/immunology/tutorials/immunology/10t.html

https://www.ebi.ac.uk/interpro/potm/2005_2/Page1.htm

http://www.ncbi.nlm.nih.gov/books/NBK27156/

Why does the MHC stimulate such strong immune responses?

We believe there are good reasons why the few proteins encoded by the MHC are so effective at causing immune rejection.

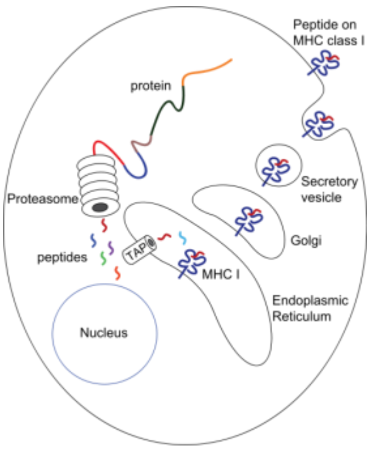
1. Almost every nucleated cell in the mammalian body has MHC proteins on its surface. Because of this, almost any transplanted organ (or, potentially, developing embryo) can express these proteins to activate the recipient (or maternal) immune system.

In fact, if you look back at Resource 1, you will see there are two subsets of MHC proteins, and it is MHC ‘Class I’ which is expressed on almost every cell type. Because of this pregnancy biologists are particularly interested in MHC Class I.

https://en.wikibooks.org/wiki/Structural_Biochemistry/Protein_function/Major_Histocompatibility_Complex_(MHC)/MHC_Class_I

2. MHC proteins play an important role in ‘serving up’ fragments of protein antigens to lymphocytes, as you saw in resource 2. Thus, the MHC is involved in almost every immune interaction which takes place – so any MHC proteins on a transplanted organ (or fetus) is potentially open to rapid examination by the recipient (or maternal) immune system. This is why any ‘foreignness’ in the MHC proteins rapidly elicits an immune rejection reaction.

This is a diagram of how proteins are chopped up, and their peptide fragments ‘served up’ on MHC class I molecules:



(Creative Commons: https://en.wikipedia.org/wiki/MHC_class_I#/media/File:MHC_Class_I_processing.svg)

3. Finally, the MHC genes are exceptionally variable within most mammalian populations. While most genes exists in just one, two, or maybe three different allelic forms, some MHC genes have more than a *hundred* different alleles. Because of this

- members of a population produce a diverse array of different MHC proteins
- most individuals are heterozygous for each MHC gene
- there is strong natural selection to maintain this variation
- an organ donor’s MHC (or father’s MHC) will almost certainly be different, or ‘foreign’, to that of the organ recipient’s MHC (or mother’s MHC)

There are a few strange exceptions to this diversity, such as the cheetah:

www.ncbi.nlm.nih.gov/pubmed/21183613

Thus, MHC proteins are dangerous drivers of graft rejection, so pregnancy biologists worry that it is these which can potentially lead to fetuses being rejected like organ transplants.

Does the MHC have any other roles in biology?

The main function of the MHC is indeed to 'serve up' antigen peptides to T-lymphocytes, but the weird features of the MHC mean it has been used for some other things, too.

1. Because the alleles vary so much, if animals can work out a way to detect MHC, they can use it to work out which individuals share MHC alleles with them, and thus are close relatives.

For example, rats and mice can 'smell' the MHC alleles of other individuals, and even humans – although we do not know how.

Female rodents use this system to avoid mating with closely-related males. Remarkably, there is also evidence that humans select their partners on this basis!

http://ndt.oxfordjournals.org/content/15/9/1269.full

https://www.theguardian.com/lifeandstyle/2013/sep/08/can-you-smell-perfect-partner

http://www.pbs.org/wgbh/evolution/library/01/6/l_016_08.html

2. We are not certain, but it is possible 'natal homing' – the ability of adult salmon to swim back up the river of their infancy to spawn – is aided by the fishes' ability to detect MHC-related odours released by their kin into the water flowing downstream.

http://www.nature.com/articles/srep02800

(Creative Commons: https://en.wikipedia.org/wiki/Salmon#/media/File:Cub_with_trophy.jpg)