Activity 4 - How might the mammalian fetus avoid immune attack?

If you have read the other three resources for this topic, you will now be aware of the potential problem facing the embryo/fetus. Its trophoblast cells, presumably bearing graft-rejection-inducing paternally-inherited MHC proteins, are exposed to a maternal immune system evolved to destroy 'foreign' cells.

So how does it survive?

It seems there are three main strategies the fetus can use – but how important each one is, and in which mammalian species, remains unclear – an active area of research!

1. The placenta acts as a simple barrier

In resource 2 we saw that there is no dramatic mixing of maternal and fetal blood in the placenta – for physiological purposes, the two are separate.

So, in a simple sense, the placenta is acting as a barrier. However, there are complications to this simple view.

First, the placenta may block the passage of any anti-fetus antibodies which the mother forms. For example, many mares make antibodies to their foals' proteins. This can happen due to leakage of foal blood into the mother at birth, which causes a potentially fatal disease called 'neonatal isoerythrolysis'…

http://www.thehorse.com/articles/28659/neonatal-isoerythrolysis-in-foals

…but most mares also make antibodies to their foals' MHC proteins long before birth. However, remarkably, these anti-foal-MHC antibodies do not seem to cause any problems (this reference is quite complex, even for a degree student!):

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4641323/

It seems that, as these anti-foal antibodies enter the placenta, they bind to MHC proteins on cells 'on their way in', and this stops them getting as far as the foal itself.

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

Another issue is that the placental 'barrier' is not complete, and cells from the fetus leak into the mother…

http://www.smithsonianmag.com/science-nature/babys-cells-can-manipulate-moms-body-decades-180956493/?no-ist

…and vice versa:

http://www.nytimes.com/2009/02/03/health/research/03immu.html?_r=0

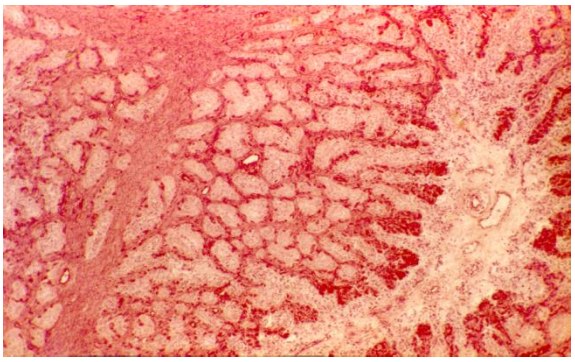
Obviously, this cell leakage could have all sorts of complicated effects, but we have no idea what those are! Certainly, it does not seem to lead to the immune rejection of many pregnancies.

How do you think leakage of fetal cells into the mother might be useful for clinicians?

2. The fetus 'switches off' MHC protein production in trophoblast cells exposed to the mother

If MHC proteins are so liable to cause graft rejection, surely it makes sense for the fetal trophoblast to switch them off?

Well, to some extent this *is* what happens. In most mammals studied, MHC Class I expression is suppressed in trophoblast cells. This is a microscopic view of ox placenta stained pink for MHC Class I.

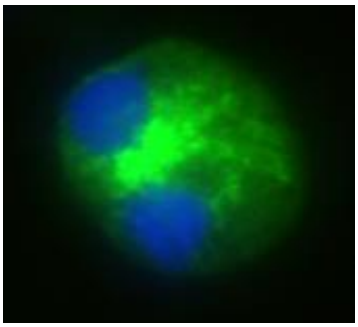


The red/pink areas are the mother's cells, and the paler areas are the calf's trophoblast cells – clear evidence that the trophoblast has 'turned its MHC down'.

However, switching off MHC presents a problem. As we saw in resources 1 and 3, MHC proteins have a valuable function – they 'serve up' antigen fragments to the immune system to allow pathogens to be attacked. Switching them off completely would make trophoblast cells prime targets for infection.

Indeed, trophoblast cells do get infected – and often by pathogens extremely important for animal and human health. Do an internet search and see if you can find out which pathogens.

This problem may explain why, in cattle, horses and humans, MHC is, perhaps unexpectedly, *switched on again* in trophoblast cells particularly exposed to the mother's immune system. In cattle, trophoblast 'binucleate cells' switch on MHC Class I, green-stained in this picture:



(image by the author)

And human 'extravillous cytotrophoblast' cells make a weird MHC molecule, not seen elsewhere in the body:

https://en.wikipedia.org/wiki/HLA-G

As you can imagine, this is all very confusing to scientists, who are desperately trying to find out what's going on!

3. The fetus may alter the mother's immune system to prevent attack

Finally, there is now evidence that the fetus alters its mother's immune system to protect itself. Obviously, it can't just 'switch it off', or mother and baby would both die from an infection, but it may subtly alter it…

First of all, there is evidence that fetuses of sheep and cattle suppress the local uterine immune system, partly because of the effects of progesterone produced during pregnancy:

http://www.ncbi.nlm.nih.gov/pubmed/17322123

What is progesterone? When is it produced? What tissues produce it?

(Creative Commons: https://upload.wikimedia.org/wikipedia/commons/d/d2/Veau_nouveau-n%C3%A9bis.jpg)

Second, there is also surprising evidence that being pregnant can suppress a mother's body-wide cellular immune response, while increasing her humoral immune response (see resource 1). This may be because most graft rejection responses are cellular rather than humoral.

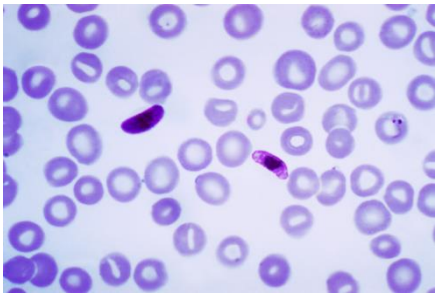
https://www.merckmanuals.com/home/women-s-health-issues/pregnancy-complicated-by-disease/autoimmune-disorders-during-pregnancy

https://www.youtube.com/watch?v=6C2o79isHT0

For example, some women find that a pre-existing autoimmune disease (see resource 1) gets completely better when they are pregnant. Others find that it gets worse.

Most alarmingly, there is good evidence that women are more likely to contract certain infectious diseases, including major killers such as malaria, when they are pregnant. Considering that more people have died of malaria over human history than *any other cause*, this seems a bizarre weakness in our immune system!

http://www.who.int/features/2003/04b/en/



(Public domain: https://en.wikipedia.org/wiki/Plasmodium_falciparum#/media/File:Plasmodium_falciparum_01.png)