**MICROBIOLOGY 4**

**VIRAL EVASION OF HOST IMMUNITY**

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The outcome of virus infection is the result of a ‘battle’ between the virus’s ability to replicate and the host immune response that attempts to control and eliminate virus.

**Outline, using examples from named viruses, how viruses escape innate immunity by subversion of host innate immune responses**

**Innate immunity** comprises:

1 Barriers: epithelial surfaces are major points of entry for virus into host. They are covered with protective secretions that contain mucus and collectins which can act as decoy receptors.

Influenza virus neuraminidase can enzymatically remove the decoy receptors from mucus allowing virus to gain access to the ‘real’ receptor at the cell surface.

2. Interferon response: All cells can make and respond to type I interferons, IFN alpha and IFN beta. These are soluble cytokines that are secreted when the cell detects a foreign pattern. IFN lambda acts at epithelial cells in the same way.

Detection of the virus or other invading pathogens is by pattern recognition receptors, **PRR**s. These can be at the cell surface, for example Toll Like receptors **TLR**s

Or they can be intracellular, for example RIG-I.

The PRRs detect unusual nucleic acids that are nonself because they are different to those made by the host or they are in the wrong place. These are the pathogen associated molecular patterns or **PAMP**s.

When the PAMP is detected, a signaling cascade is set in motion that results in the transcription of the IFN genes.

Newly transcribed and translated IFN is secreted from the infected cells and acts on specific receptors on the surface of the infected cell or neighbouring cells and signals the synthesis of hundreds of new genes that have antiviral effects.

For example:

PKR will shut down protein translation, a host function on which viruses are absolutely dependent.

Mx will bind and nullify incoming virus genomes.

IFITM3 will prevent the entry of enveloped viruses.

Tetherin will prevent the budding of many enveloped viruses.

In addition IFN will recruit other arms of the immune response such as dendritic cells and NK cells.

Because this IFN response is so powerful, many viruses have had to evolve strategies to antagonize it.

For example:

Hepatitis C virus encodes a protease that targets and destroys MAVS, a key protein in the detection pathway.

Influenza A virus NS1 protein binds to RIG-I and stops it seeing the PAMP.

Poxviruses secrete soluble cytokine receptors, vaccinia virus B18, that mop up IFN and stop it from reaching its own receptor.

Interferon can be used as an antiviral treatment. However it stimulates so many aspects of a cytokine and chemokine response that it is associated with side effects like fever and aching. Pegylated IFN is used as a treatment for hepatitis C virus infection.

**Describe, with named examples of viruses, how antigenic variation may lead to viral evasion of host immunity**

Viruses that cause acute infections are susceptible to **neutralization** by virus specific antibodies which protect against reinfection. Many such viruses escape antibody recognition for example:

Human rhinoviruses that cause the common cold exist as multiple antigenically distinct serotypes

HIV exists as multiple clades

Influenza viruses mutate and evolve to change year on year, **antigenic drift**

**Describe with named examples how viruses escape host cellular immune responses**

Infected cells can be recognized and destroyed by antigen specific T cells when viral peptides are processed and presented by MHC class I. To avoid this many viruses encode products that intervene with **MHC processing and presentation**. For example

Herpes Simplex Virus HSV ICP47 prevents the loading of peptides in to the transporter protein complex **TAP**.

Human cytomegalovirus US3 binds to MHC class I and prevents it transport to teh cell surface

HCMV US2, US11 and adenovirus E3 gp19 proteins stimulate the MHC to recycle from the cell surface to the cytosol

Although stopping MHC getting to the cell surface is good, it creates another problem for the virus because cells that lack MHC expression are targets for **NK** cell killing.

HCMV encodes an MHC mimic UL18, to stop this.

When viruses lose the proteins that normally control the host immune response, either by passage through cell culture many times (for example strains of HCMV or poxviruses like MVA) or by deliberate genetic engineering (for examples GM strains of influenza virus that lack NS1 protein) they become attenuated and thus suitable for use as vaccines.