SECTION PAPER 3, WEEK OF NOVEMBER 18, 2013 last four id: 5494

**Inhibition of MHC Class I Is a Virulence Factor in Herpes Simplex Virus Infection of Mice**
Orr, et al (2005) PLoS Pathogens 1(1):62-71

Instructions. READ CAREFULLY:

1. Use 1 inch margins all around.
2. Use Times 11 point font (single spaced; this page is written in Times 11 point with 1 inch margins).

   ***If you use any other font or size, you will receive 0 credit.*** It will be enforced.
3. 1½ page maximum (you can go ½ way down the second page; no more). Keep it to 1 page if you can. If you go two pages, keep the top line the same on both pages and staple them together.
4. Staple if you use two pages.
5. It is due in Section week of November 18.
6. At the top left side of the page type just as is: "SECTION PAPER 3, WEEK OF NOVEMBER 18, 2013." Then next type the last four digits of your student ID at the top right corner of the page. I have done so above as an example. ***Do not write your name on the page.***
7. It is important, encouraged, and assumed that you will read and discuss these papers in your study groups. If we could make it mandatory, we would. Write up the answers, however, in your own words and with your own thoughts. Please don't copy each other.
8. Even though you will be answering questions to a few figure panels, be sure to read the entire paper as this is essential in helping you answer the questions.

Background information for understanding the paper:

Review the sections of chapter 7 (in your textbook) on MHC Class I (including figure 7-6).

Note that "**induction**" of CD8 T cells is a preliminary event which activates naïve CD8 T cells to become cytotoxic T-lymphocytes (CTL's, or "killer T-cells"). Subsequently, they will kill infected cells which present MHC Class I + antigen (for which the T-cell is specific). The paper indicates that HSV is able to down-regulate the **killing of infected cells** by CTL's, but not affect the **initial activation** of the CD-8 cells.

**Cross-presentation** is when dendritic cells present exogenous antigen (something they phagocytose, not something that infected them) in the context of MHC Class I to activate a naïve CD8 T-cell. (Note that exogenous antigens are normally engulfed by dendritic cells and presented in the context of MHC Class II to CD4 T cells.) The intracellular pathway taken by exogenous antigens to meet up with MHC Class I is different than the pathway taken by endogenous (infecting) antigens to meet up with MHC Class I.

Reading the **"Materials and Methods"** section will help you understand the experiments.

**eGfp** = enhanced green fluorescent protein

**moi** = multiplicity of infection
This refers to the number of viruses added per cell to a cell culture.

**Rag1$^{-/-}$ mice** have no mature B or T cells.

The genes which encode the MHC proteins are known as **HLA** in humans and **H-2** in mice.

- The human **HLA complex** includes genes for three MHC Class I proteins.
  - HLA-A
  - HLA-B
  - HLA-C
- The mouse **H-2 complex** includes genes for two MHC Class I proteins
  - H-2 K
  - H-2 D

The MHC loci are highly polymorphic; many possible alleles for each gene exist in human and mouse populations.

The mouse loci, H-2 K and H-2 D, are closely linked, therefore, the alleles for H-2 K and H-2 D are usually inherited from each parent as a linked (K-D) set, known as a "haplotype."

Experimental mouse strains are inbred, and therefore homozygous at all loci. The H-2 genotypes of standard inbred strains commonly used in laboratories have been characterized. Each of these strains is arbitrarily assigned an italic, superscript letter, which describes the haplotype (K allele + D allele). Examples are:

- C57Bl/6 H-2$^b$
- BALB/c H-2$^d$

} These designations refers to particular haplotypes that were previously characterized. All the MHC alleles in these haplotypes are known.

Cell lines from more than one strain of mouse were tested in this study, because virus proteins may interact differently with the MHC Class I variants encoded by different alleles.

Figure 3B is looking at lysis of infected cells by **NK cells** (harvested from mouse spleens).

When cells are stressed, for example by virus infection, they may produce a cell surface stress protein (e.g. **Rae-1**) which binds to a receptor on NK cells. This NK cell receptor is **NKG2D**, and it activates the NK cell to kill the "stressed" cell.

**$\beta_2$m$^{-/-}$ mice** are missing a component of MHC Class I, $\beta_2$-microglobulin. Because $\beta_2$m is not synthesized, cells do not express MHC Class I on their surface. (See figure 7-4 in textbook.)

Viral infection of cells often results in dsRNA, which stimulates TLR3.
**poly I:C** is a synthetic nucleic acid (polyinosinic:polycytidylic acid), which mimics dsRNA in cells, stimulating the innate immune response.

Glycoprotein B (**gB**, gpUL55) is the major, viral antigen for the induction of neutralizing antibodies against HCMV.

Questions to answer:

In three separate paragraphs, answer the following questions regarding Figures 2C-D, 6A-B, 7B-C.

What experiment is done? Why are they doing it? How did they do it? What are they measuring? Explain the controls. What results did they see? How did they interpret the experiment? Do you agree that the data support their interpretations?

If the experimental design was already described for a previous figure, you do not have to repeat it. Just refer back to what you already explained. *(E.g. This experiment was performed like that in figure 3G, except that this time…)*