MCB 150 Problem Set Infectious Disease

ANSWERS

Q1.  *Staphylococcus aureus* is a very common extracellular bacterial pathogen that causes a wide range of diseases ranging from strep throat to rheumatic fever and toxic shock.

A.  What would be the primary *adaptive* immune response to these bacteria?

Antibodies and Th2 cytokines.

B.  *S. aureus* infection can occasionally cause a systemic inflammatory response that can result in shock and organ failure.  How could this bacteria cause this serious disease consequence?

The *S. aureus* has an exotoxin that can act as a superantigen and bind to TCR and MHC causing non-specific T cell activation.  The release of cytokines by T cells can cause systemic macrophage activation/inflammation (probably through the acute phase response) leading to toxic shock.

Q2.  *Leishmania* are protozoan parasites that cause skin diseases and potentially systemic infections that can be lethal.  *Leishmania* primarily infect macrophages and live endosomally.  It has been well-documented that certain strains of mice, such as BALB/c, are more susceptible to *Leishmania* infection whereas other strains of mice, such as C57Bl/6, are more resistant to infection.

A.  Would you expect the resistant C57Bl/6 mice to mount a Th1 or Th2 response?  Why would a targeted cytokine bias be beneficial in response to this parasite?

Th1

Th1 responses are very good at activating macrophages and stimulating a cellular immune response.  However, an *intracellular pathogen* spends the majority of its life within a cell where these mechanisms cannot penetrate.  A Th1 response would mount a more robust CMI.

B.  Propose an immune genetic difference that could help explain why BALB/c mice are more likely to mount an immune response that is less able to resolve *Leishmania* infection?

A difference in the promoter region of IL-4 that allows higher transcription.  A stronger affinity IL-4R.  Many other possibilities including MHC, inflammation genes, IFN-γ, IL-12, GATA-3, T-bet, MyD88, TLR etc.

C.  A new vaccine for humans has been developed using a recombinant fusion protein combining three antigens identified from the mouse model of *Leishmania*.  This vaccine is a single recombinant polyprotein comprising the sequences of all three open reading frames genetically linked in tandem.  The resulting molecule comprises an open reading frame that codes for a 111kDa polypeptide.

Would this vaccine require an adjuvant and what type of immune response would you expect this vaccine to elicit?

Yes.  It would require an adjuvant because the untreated protein will not initiate inflammation on its own.  (okay to say no PRR recognition/TLR activation, no inflammation from tissue injury etc.)

This would primarily elicit ab and Th responses.  It might elicit both Th1 and Th2, but not CTL.
Q3. Influenza virus infects the respiratory epithelial cells.
A. Before the adaptive immune response is activated which innate immune responses will be most effective against spreading of Influenza virus infection? List 2.
   α and β Interferons and NK cells.
B. For resolution of Influenza virus infection the adaptive immune response is usually required, what 2 arms of the adaptive immune response are most effective at preventing spread of viral infection? CTLs and neutralizing antibodies IgGs.
C. What immune evasion mechanism does Influenza virus have to help avoid the adaptive immune responses? Please explain.
   Antigenic drift is the primary immune evasion mechanism to evade neutralizing antibodies. This occurs through mutations in the viral envelope proteins (Hemagglutinin and Neuraminidase) especially in the areas of neutralizing epitopes. Antigenic shift can also happen but with less frequency.

Q4. Why are enveloped viruses susceptible to complement-mediated lysis whereas non-enveloped viruses are resistant to complement-mediated lysis?
   Complement-mediated lysis acts through the membrane attack complex. The MAC complex is initiated when C5b6 binds C7 which causes the complex to undergo a conformational change in which hydrophobic regions are exposed and can insert within the membrane phospholipid. C8 then helps create a pore to which multiple C9 fragments are added eventually forming a circular pore. This would not be possible without a lipid membrane.

Q5. Trypanosoma brucei are unicellular protozoan parasites which live extracellularly in your bloodstream and can cause the disease sleeping sickness. Infection with T. brucei is transmitted by tsetse flies.
A. If you have a systemic infection with Trypanosomes, in which lymphoid organ will these parasites be filtered out by phagocytic cells to get activation of the adaptive immune response? (4 pts)
   Spleen
B. What are two factors that will help determine if T. brucei will make a good immunogen (in other words that it will be seen by the adaptive immune response)?
   1. Complexity based on amino acid composition (Foreignness)
   2. Size
   3. Dose
C. What type of adaptive immune response will be most effective for eliminating these parasites and why?
   Antibodies (requiring Th2 and B cells activation) are most effective against eliminating extracellular parasites.
D. Will the T. brucei antigens be presented by dendritic cells through the exogenous antigen processing pathway or the endogenous antigen processing pathway? Explain your answer. Exogenous ag processing pathway because they live extracellularly and therefore must be taken up by APCs through phagocytosis or receptor mediated endocytosis.
Q6. You wish to make a vaccine against a pathogenic virus whose normal route of infection is through the gastrointestinal tract.

A. Which adaptive immune defenses might be useful against the virus after it has penetrated the lining of the intestine but before it has entered a cell?

**Antibody (IgG, IgM) – neutralization, opsonization, complement-mediated lysis**

B. Why might an inactivated vaccine prepared from killed virus and injected intramuscularly give relatively poor protection in field tests?

**Since vaccine is killed, antigen would be cleared relatively quickly and would not give lasting immunity without booster shots. Adjuvant would probably be required to elicit any type of immune response. Vaccine injected intramuscularly would elicit primarily IgG and IgM, which are less effective than secreted IgA for mucosal immunity.**

C. What alternative approach would you want to try to make a more effective vaccine against this pathogen? Why should it be more effective?

**Live attenuated vaccine, or protective epitope cloned into viral vector such as attenuated polio virus that can be given orally. A live vaccine which can be given orally can mimic natural infection and elicit IgA.**

Q7. Poliovirus infects epithelial cells and neurons. Poliovirus infection can lead to paralysis and death. Polio is transmitted fecal-orally.

A. What type of adaptive immune response activated which secondary lymphoid tissue will help prevent poliovirus from leaving the intestines and entering the bloodstream?

**Secretory IgA from Mucosal Assoc. Lymphoid tissue MALT or GALT. Peyer's patches okay.**

B. Fill in the chart below advantage in giving the Sabin polio vaccine (live attenuated virus administered orally) or the Salk polio vaccine (killed virus injected intravenously).

<table>
<thead>
<tr>
<th>Type of Vaccine Route</th>
<th>Sabin polio vaccine</th>
<th>Salk polio vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live attenuated</td>
<td>Inactivated virus</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Injected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Live, elicits stronger immunity, slgA protection</th>
<th>No revirulence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disadvantage</td>
<td>Possible revirulence</td>
<td>No replication. No oral protection.</td>
</tr>
</tbody>
</table>