

Cytokine Small group Master Answers

Master Answer to Case 1

Orchestrators of the Immune Response

Leprosy can incite either a Th1 (helper) or Th2 subset dominant response. The dominant subset is influenced by route and dose of antigens (*M. Leprae*), status of the patient, especially nutritional (malnutrition is associated with depressed Th function), and MHC/TLR dictation of the immune response. HIV infection or other diseases (cancer for example) that could affect the patients' immune system could also play a role. The expression of the tuberculoid form of leprosy can be further influenced by any drug that inhibits macrophage activation. Thus cyclosporine (an immunosuppressant drug) or corticosteroids (potent anti-inflammatory drug) can convert tuberculoid leprosy to the more lethal form. Conversely, if the activated macrophage in a granulomatous (Th-1) lesion in a patient with tuberculoid leprosy is threatening vital structures (for example: here the brachial plexus) it may be therapeutically advantageous to suppress the dominant Th1 subset while treating the actual infection with antibiotics to attenuate the granulomas and prevent irreversible destruction. Corticosteroids that suppress IL-1, IL-6 and TNF- γ ; and anti-TNF monoclonal antibodies, have been used clinically to suppress destructive TH-1 responses. The genes that would be considered in a vaccine would be Th1, including IL-12, IL-12R; IFN- γ and IFN- γ R; IL21 and IL21R and/or any other in the Th1 sequence that you think are critical to an effective response. Genes that produce Th1 TLR activation via DC or Toll like receptors could also be possibilities.

Master Answer for Case 2

Orchestrators of the Immune Response

Here the pathogenic mediator is a soluble protein elaborated in extracellular fluid by proliferating bacteria. The response needs to be rapid and one mediated by antibodies that neutralize the toxin. In order to develop a vaccine, the antigen needs to be a toxoid type of protein that mimics the real toxin and stimulates Th2 responses that will promote antibody formation. IL-4 (could be combined with IL-6 and 10, and/or 21) would be the most logical cytokine needed as an effective vaccine promoter and one that could be linked either to a toxoid type derivative of the toxin or to inserted into a microbe that has been engineered to produce a toxoid antigen. Using the concept of passive immunity, an effective and life saving treatment strategy in patients with heart involvement would be the use of intravenous anti-toxin IgG to block the effects of the neurotoxin that has not irreversibly bound to the conducting system. The source of this blocking antibody could be from recombinant synthesis, removal from a survivor of the disease or a previously vaccinated patient.

Master Answer to Case 3

Orchestrators of the Immune Response

The setting of this unusual outbreak of disseminated lethal infection by a usually quite benign attenuated tuberculosis vaccine suggests that there was clustering of a genetic defect causing a unique immunodeficiency state characterized by susceptibility to mycobacterial illness. There is a high degree of intermarriage in many of these villages and genes with lethal consequences can emerge. In this particular instance, the genetic defect being passed through the interbred families could either, but not limited to, be a defect in Th-1 cytokine production, defective Th-1 cytokine receptor synthesis or loss of function

mutations of Th1 activating TLR. The most likely defect is either in IL-12, IL-18 or INF γ . There have already been families (and recently a patient at Loyola) documented with interferon receptor defects that are highly susceptible to tuberculous type infections. For the purposes of our discussion, IL-12R receptor deficiency could be just as likely and this experimental deficiency in mice is also characterized by high susceptibility to mycobacterial infections. The simplest way to begin tracking the possible genetic defect would be to extensive haplotyping of the affected children, their parents and the unaffected siblings. In this case, the recessive defect was found on chromosome 6. The in vitro testing that would document the deficiency employs assays of the mononuclear cells of the affected siblings parents and normal sibs. One possibility would be to probe mononuclear leucocytes isolated from these subjects with antibodies to the receptors that could be involved. Since it appears that the ultimate lethal defect in these patients is their inability to upregulate TNF- α because of a deficiency in interferon- γ , assays can be devised to measure whether their mononuclear cells could indeed do so. If a patient with (or without) an INF γ mutation developed a disease caused by IL-23

driven Th17 inflammation, treatment with recombinant INF γ would theoretically have a beneficial effect because of the strong suppression of Th17 activation by INF γ .

Master Answer to Case 4

Orchestrators of the Immune Response

The polymorphism of MHC in the outbred human population makes it highly likely that there will be a wide range in the intensity of an immune response to a given antigen and it follows that there will be a parallel diverse spectrum of disease expression ranging from no clinical symptoms at all to death. The variance in reactivity to antigens is due, in large part, to differences in how they are presented by the varying MHC Class I and II determinants to immune effector cells and /or the type of TLR that is activated on DC. The resultant response can range from literally none at all to potent cytotoxicity and granuloma formation to exuberant antibody formation with all possible combinations in between. In the cases presented, one unfortunate model plane enthusiast either was exposed to a markedly greater amount of fungus and/or couldn't generate an effective killing response to the fungus because of the way his DC presented the antigen to T cells-the end result is fulminant respiratory failure. The remainder of the group had the capability to generate adequate antifungal responses and maintain normal respiratory function. Their symptoms remained those of cytokine activation only- fatigue etc. In the drug abuser group, at least 2 individuals could not generate any effective cytotoxicity to the virus-presumably based on polymorphic TLR and DC- and died from liver necrosis secondary to viral destruction while 6 had normal immune responses to a viral infection. The twin offered a rare opportunity to be the source of histo-compatible CD8 cytotoxic cells directed against the virus that is killing his brother. CD8 cells could be removed from the twin and expanded ex vivo by exposure to hepatitis virus antigens and then re-infused into the dying twin.