Master Answers for Lymphocytotoxic Small group

Master Answer for Case 1
LYMPHOCYTE CYTOTOXICITY

This patient, a female with multiple exposures to two sets of paternal MHC antigens, is at high risk for rejection after transplant because she may be reactive with multiple donor alloantigens. Some females with prior exposure to alloantigens have a precarious situation because they must receive a completely unmatched cadaver graft (cannot match hearts or lungs since they have to be used within a short time interval and few if any would match anyway). Thus a biopsy showing rejection 14 days after transplant would not be unusual. Recruitment of cells would reflect not only the mechanisms of standard T-cell cytotoxicity and TMMI (delayed hypersensitivity) but large numbers of T-cells that can react in a 'direct' way to the presentation of alloantigens ("immune heresy"). The latter phenomenon, though observed, is not understood. The cells in the biopsy would be a mix of CD3, CD4+, CD3 CD8+cells intermingled with activated macrophages which CD4 cells had recruited and Th17 cell (It is highly likely that it will soon be found that Th17 cells are the most important cell mediating rejection). A critical addition to biopsy analysis is now looking for CD4,25 FoxP3 cells to assess whether the recipient is trying to suppress rejection or becoming tolerant. .Mini-microarray biopsy analysis will likely supercede classical histology methods in the very near future. Experimental array analysis of renal transplant biopsies has already provided the surprise that B cells predict severe rejection and that there is a specific array "signature" that even tells the clinician whether drugs are causing renal dysfunction or it is true rejection that is the problem!

In terms of monoclonal antibody therapy, the transplant community has been very creative. An anti CD3 monoclonal was the first developed and is somewhat effective under certain situations, many other monoclonal antibodies directed against epitopes that include CD-4, CD-8, IL2 and IL2 receptors, and CTLA-4 are in clinical or experimental trials. You might predict that the broad blocking power of the anti CD-3 monoclonal has potentially lethal side effects and you would be correct. The other anti-cytokine monoclonals are not working well because of the redundancy of the cytokine network. Monoclonals that could mimic CTLA-4 however show promise because they may induce CD4, 25, FoxP3 regulator cells in the graft that will suppress graft specific cytotoxic responses. The most current interest is developing methods of expanding T regs ex vivo and infusing them back into the patient to enhance tolerance (method shown in lecture).

The xeno- transplant presents a formidable array of hurdles. First, for ethical and technical reasons, apes and chimps are not a realistic source of organs. Humans, great apes and old world monkeys are the only mammals without α-GT epitopes on their cell surfaces. They make huge amounts of antibody to this determinant which is present on many bacteria in their gut so hyperacute rejection is the first problem. These antibodies will react immediately with any organ transplanted with the epitope on its cells. Even if this form of rejection can be prevented by developing α-GT deficient pigs, the standard forms of MHC disparity driven acute and chronic rejection will still occur.

Master Answer for Case 2

Timing is what matters. Here timing is unfortunate because the niece has varicella (chicken pox) and it is still in its infectious phase. She infected the uncle via his respiratory route. The uncle has few effective immune responses as he recovers from chemotherapy. She had a typical course of the disease with small skin vesicles ***without*** *significant viral proliferation in the lungs because she had normal CD-4 and CD-8 T-cell responses that generated a highly effective population of viral specific CD-8 cells. Thus, areas of infection in her were typically manifested as small blisters resulting from contained clusters of viral infected epidermal cells surrounded by anti-varicella CD8 cells. If she had been vaccinated previously, she would have had almost no clinical manifestations because varicella specific memory T cells would be patrolling and would be capable of rapidly mounting a secondary response to the virus in tissue sites while varicella antibody generated by the vaccination would suppress widespread dissemination of the virus. The uncle, in contrast, cannot respond in the same way and the virus proliferates, causing significant cellular damage, neutrophil infiltration, blood vessel destruction and hemorrhage into the skin. The unchecked virus disseminates and grows within the lung causing impaired oxygenation. The treatment currently available is acyclovir (an anti viral drug that you will learn about next year) and provision of passive immunity by infusion of varicella specific IgG to prevent further systemic dissemination of live virus.*

Master Answer for Case 3

LYMPHOCYTE CYTOTOXICITY

This patient (organ recipient) was unfortunate in that he received lungs from an EBV (infectious mononucleosis) positive (B-cell virus) donor. EBV was carried over in the donor peribronchial lymphoid tissue and infected the non-immune host. The virus flourished because the patient's T-cell defense mechanisms- especially CD4 helper functions- had to be suppressed to allow the grafted lungs to survive. EBV infected B-cells will normally display EBV antigen in their Class I MHC just like any other viral infected cell but, in this instance, are not eliminated because there are insufficient EBV specific CD8 cells generated in the absence of CD4 help. The cumulative effect is unregulated B-cell growth stimulated by the virus and, ultimately the development of B cell tumors. The best way to prevent this is to not use EBV positive donors for EBV negative recipients whenever possible. In this case, a source of MHC compatible T-cells was available from the twin. The transplant physicians immediately tested the twin to determine whether he had had infectious mononucleosis. He was seropositive, meaning he had had EBV in the past. The twin's T-cells were isolated from his peripheral blood and stimulated with EBV and expanded in vitro. They were then infused into his brother and the CD8 EBV reactive cells then controlled the virus. The hazard of this type of therapy is that the presence of any cells in the infusion that could react with the graft itself would cause rejection. Thus, very careful preparation of the infused cells is mandatory. The bone marrow transplant patient presents a completely different situation.

*The recipient, whose immune system in large part has been eliminated before transplant, assumes major characteristics of the immune system **of the donor**. Thus, an identical twin of the donor, who had EBV previously, would be the source of expanded CD8 EBV specific T cells.*

Master Answer for Case 4

LYMPHOCYTE CYTOTOXICITY

Case 4 represents the future of oncology in several ways. You might predict that lymphocytes infiltrating a tumor were most likely NK and CD3, 8 positive T cells. NK would be induced to infiltrate a tumor based on possible alterations of the tumor cell MHC Class I structure and/or anti-tumor antibody coating of the tumor cells. If tumor antigens were displayed by the tumor MHC class I then generation of tumor specific CD3,8 T cells should occur. As a rule, effector cells, especially T cells, found in a tumor are usually a good thing and are linked to better clinical outcomes.

However, T cells are a very heterogeneous group of cells. As noted above, if the T cells are tumor antigen specific CD8s, that is a very good thing. However, if they are CD4,25, FoxP3 T cells that is NOT necessarily a good thing. The Journal of Immunology article and the Perspective in the New England Journal of Medicine posted for this Small Group provide evidence that, at least in some metastatic melanomas, T regulatory cells may actually be protecting the tumor, not the patient. Tumor cells are actually secreting chemotactic signals that recruit and convert T cells to T regs protective of the tumor! The lack of an effective intra-tumoral immune response in these patients is associated with early metastases. The neighborhood the tumor is in is also important. Some neighborhoods are better than others and arrays can identify those that predict better survival.

If you weren't a fan of array technology before, you should be after reading the assigned articles because it is clear that arrays, in some form, will supplant conventional histology and provide much more interactive gene information that can be applied to treatment of tumors in the very near future.

As technology and basic immunology increase understanding of how tumors interact with the patient's immune system and surrounding tissue , you will be able to enhance the immune response to tumors (activated DC, vaccines, and who knows what else) and improve patient survival.