INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	15
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Before we start:

- This sheet is written from section 2 record and not in order with record
- This is the last lecture Dr.Issa gives before going abroad for 2 weeks
- Anything in double asterisk (**) was mentioned in the handout but not the lecture

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Graft vs Host Disease:

The case study discusses how transplantation from a donor will attack the host's body instead of the host's immune system reacting to the foreign antigen of the donor's organ , also known as graft rejection .

Graft versus host disease can be divided into acute and chronic depending on time of onset, if it starts in less than 100 days then it is acute and if after 100 days, it is considered chronic which is more severe and harder to cure. The symptoms that appear are petechiae (rash), watery diarrhea, pneumonia and liver damage (hepatomegaly).

To avoid such a such situation, HLA matching and panel reactive antibodies are used to see if the MHC of the donor and the recipient match but sometimes the minor histocompatibility antigens , peptides bound to the clefts of MHC molecules to increase specificity, will not match .

The test used in the past to see if the donor's T cells would react to the recipient's cells is MLR (mixed lymphocytic reaction). The recipient's APC cell (dendritic cell) is exposed to radiation or mitomyocin c to not undergo mitosis. If the donor's T cells react, they will proliferate and use the radioactive tritium (hydrogen-3) for DNA synthesis which will be detected by the sensor and prove that rejection will happen. It is important to know that handling tritium is dangerous even though it has

a low penetration (even air can block it), it has a very long half life. Now proteomics is used as it is much safer and more accurate.

The case:

7 year-old John Wells is brought by his mother to the doctor for examination due to his pale appearance and rash on his body. Blood count showed low WBC, low RBC (anemia explains why he was pale) and low platelet count (explains capillary bleeding leading to rash) all of which is called pancytopenia. Further bone marrow biopsy showed little to none of progenitor precursor cells concluding he had aplastic anemia.

He underwent bone marrow transplant taken from his 4 year-old brother after John's immune system was destroyed by radiation or the injection or radiomimetic drugs such as busulfan, and the use of immunosuppressive drugs (cyclophosphamide, fludarabine).

Even after successful surgery and prophylaxis with cyclosporine A to avoid GVHD, John had a rash and diarrhea on the 24^{th} day (acute GVHD) so was treated with corticosteroids and rabbit anti-thymocyte globulins

GvHD discovery and conditions:

First seen by Sir Peter Medawar, half-Lebanese, when he injected allogenic T cells into mice; he saw the mice developed liver necrosis and destroyed lymphoid tissue. It was first recognized in SCID patients who took blood transfusions, this is because the transfused blood still had T cells but now the purification process is much cleaner.

To develop GVHD:

1- Graft must contain immunocompetent cells (Bone marrow)
2- Recipient must express major or minor histocompatibility molecules not found in donor
3- Recipient must be incapable of rejecting the graft

GvHD can be used to attack cancer cells in leukemia patients and even be sure that the graft T cells will attack certain antigens expressed in leukemia patients (will be discussed further below)

**Mature CD4 T cells in the graft that are activated by allogeneic molecules produce a 'cytokine storm' that recruits other T cells, macrophages, and natural killer (NK) cells to create the inflammation characteristic of GVHD.

**Although B cells may also be present in GVHD inflammation, they do not have a significant role in causing or sustaining GVHD

-For the histology slides, all you need to know is that the epidermis layers are separated due to damage by inflammation and lymphocyte infiltration is shown in the liver tissues.

**Types of donors:

In the above case the donor was HLA identical... And still GVHD occurred (due to minor differences in MHC) it's not always possible to find HLA identical donor. So we may use:

1. Haploidentical (that is, half matched) donor (typically, one of the two parents) .here there is a very high risk of GVHD. For this reason, the bone marrow from haploidentical donors is manipulated to deplete the mature T lymphocytes (or to purify the stem cells only) before attempting the transplant.

2. Matched Unrelated Donors (MUDs) has also become current practice at many centers and there is also a significant risk of GVHD with this type of transplant. Some bone marrow transplant centers use T-cell depletion also for transplantation from MUDs, but this

approach is not followed by the majority of centers. Transplantation with unmanipulated bone marrow from MUDs is associated with a higher rate of engraftment and may provide a 'graft-versus leukemia' reaction, in which donor-derived mature T cells may kill the residual leukemic cells of the recipient, making relapse less likely in the case of bone marrow transplants for the treatment of leukemia.

Questions:

1) Explain “Graft-vs-Leukemia” effect?

   As mentioned earlier, we can use the T cells of the graft to attack leukemia cells , we can even specify the T cells to attack a specific antigen, for example HB-1 antigen that is expressed by lymphoblastic leukemia and transformed cells infected with EBV virus. This is done by making sure the donor’s cells do not express HB-1 so will recognize as foreign.

2) IFN-γ secreted by engrafted helper T-cells help sustains and increases GVHD, why?

   Activated macrophages will express more MHC molecules that will activate the T cells more making the disease worse.

3) Anti-Thymocyte Globulin (ATG) was given to deplete T cells and control GVHD, what other methods can be used to deplete T cells?

   Injection with IV monoclonal anti-CD3 antibodies will stop the entire immune system and increase the chance of pathogens infecting the body so using anti-CD25 and anti-CD40L that is only expressed in active T cells and not resting naïve T cells is a safer option.

4) Why are the skin and intestinal tract major sites for GVHD?
It is thought that these tissues express more MHC than other types of tissues and another possibility is that the GI is the first to interact with oral cytotoxic treatment before bone marrow transplants making more susceptible to GvHD.

s: المبادئ و الاخلاق