

(1) Describe a possible theory as to why a mother does not reject a fetus (which is essentially an allograft with paternal alleles).

Trophoblast cells are the ones in direct contact with maternal tissue and vasculature and are responsible for nutrient exchange. Fetal survival may be explained by the observation that trophoblast cells fail to express paternal MHC. MHC class II molecules have not been observed on trophoblast cells. These cells only express a nonpolymorphic class I molecule (HLA-G), which may provide protection from NK cells. These trophoblastic cells also seem to lack the necessary costimulatory molecules needed for activation of an immune response.

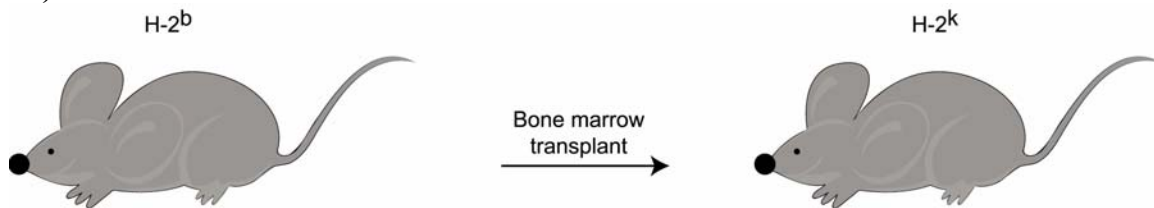
Another theory is that the uterus is an immunologically privileged site (such as the brain, eye, and testis). This may occur via the constitutive secretion of inhibitory cytokines (i.e., TGF- β). IL-4 and IL-10 may also be expressed to inhibit a Th1 response.

(2) Why is a co-stimulatory signal from CD28 on T cells necessary for full transcriptional activation of the IL-2 gene?

Co-stimulatory signal from CD28 leads to AP-1 activation. NFAT and AP-1 are required for full transcription of the IL-2 gene due to binding sites for both transcription factors in the IL-2 promoter.

(3) Answer the questions regarding the chimeric mice described below:

A mouse denoted strain B (H-2b) is irradiated (which destroys bone marrow cells and BM derived cells) and transplanted with bone marrow from Strain A mice (H-2k).



These mice are noticed to be very vulnerable to infectious illnesses of all kinds and a few of them die before they can be transferred to a germ-free environment. *Why do these mice get sick so easily?*

The thymocytes derived from the transplanted bone marrow undergo positive selection on the thymic epithelial cells in the cortex of the thymus of the recipient mouse (H-2b haplotype). Thus, the mature T cells that leave this thymus will bear TCRs restricted to the H-2b haplotype. All of the APCs, however, will be derived from the donor bone marrow and thus will express MHC molecules of the H-2k haplotype. The new, H-2b restricted T cells will be unable to interact with the MHC molecules of the APCs, and since these are the only APCs in the mouse, no T cells will be activated or experience clonal expansion.

Peripheral blood lymphocytes are isolated from these chimeric mice and FACS analysis obtained the following results:

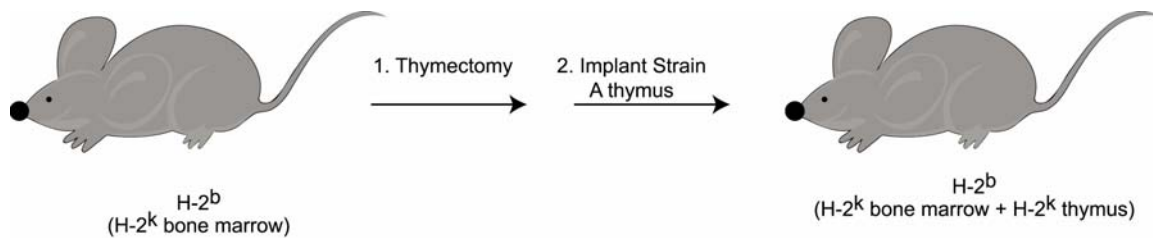


B-52=an antibody that binds to T-cell receptors which are restricted to D^b
K-20=an antibody that binds to T-cell receptors which are restricted to IA^k

Do these results agree with your theory? Explain.

These results do agree. According to these results, T cells are undergoing maturation in the thymus and establishing themselves in the periphery. The presence of B52 binding to CD8 cells suggests in general that the T cells are being restricted to the H-2b MHC molecules. The CD8+B52- T cells represent CD8 T cells restricted to other class I MHC loci of the H-2b haplotype (i.e. Kb, or Lb). The absence of K20 binding CD4 T cells suggest that, in general, these T cells do not bear TCRs that bind MHC molecules of the H-2k haplotype. The population of CD4+K20- T cells most likely represents T cells restricted to class II MHC loci of the H-2b haplotype (i.e. IAb, or IEb). Again, these T cells should be incapable of having a classical TCR-MHC interaction with the donor derived APCs.

Next, the thymii of the chimeric mice are removed and replaced with thymii from strain A mice.



These mice still exhibit a propensity to get sick, but they are now particularly susceptible to viral infections, while many bacterial infections are cleared. *How do you explain these new findings?*

The H-2k bone marrow derived thymocytes are now educated in an H-2k thymus. This means that the T cells leaving this thymus (having been both positively and negatively selected on cells from H-2k haplotype MHC molecules) will be restricted to H-2k MHC molecules and will be competent to recognize foreign antigen presented by the donor-derived APCs. This is just as one would expect in a normal H-2k mouse. The difference, however, is that the class I MHC molecules expressed on the non-BM, non-thymic tissue cells of the transplant recipient mouse will be of the H-2b haplotype. If this mouse experiences a viral infection, CD8 T cells may be activated on virus-infected professional APCs and via APCs that acquire viral antigens (i.e., via endocytosis/phagocytosis and cross-priming), but the resulting CTLs will be incapable of killing other virus-infected tissue cells because their TCRs will be unable to recognize viral antigen in the context of these cells' H-2b class I molecules.