COURSE: Medical Microbiology, MBIM 650 – Fall 2009

TOPIC: Immunoregulation Lecture #15

FACULTY: Dr. Jennifer Nyland
Office: Bldg #1, Room B10
Phone: 733-1586
Email: jnyland@uscmed.sc.edu

TEACHING OBJECTIVES:

1. To discuss regulation of immune responses including regulation by antibody, Tregs, and cytokines
2. To discuss some genetic factors influencing immunoregulation

REQUIRED READING:

Male, *et al*. Immunology, 7th Ed., Cpt 11.

KEY WORDS:

Treg, Tr1, CTL2, Foxp3.

IMMUNOREGULATION

1) The magnitude of an immune response is determined by the balance between antigen-driven activation of lymphocytes and negative regulatory influences that prevent or dampen the response. Regulatory mechanisms can act at the recognition, activation or effector phases of an immune response.

2) Regulation in response to Ag has been discussed previously.

   a) Recognition of antigen in the absence of co-stimulation resulting in anergy,

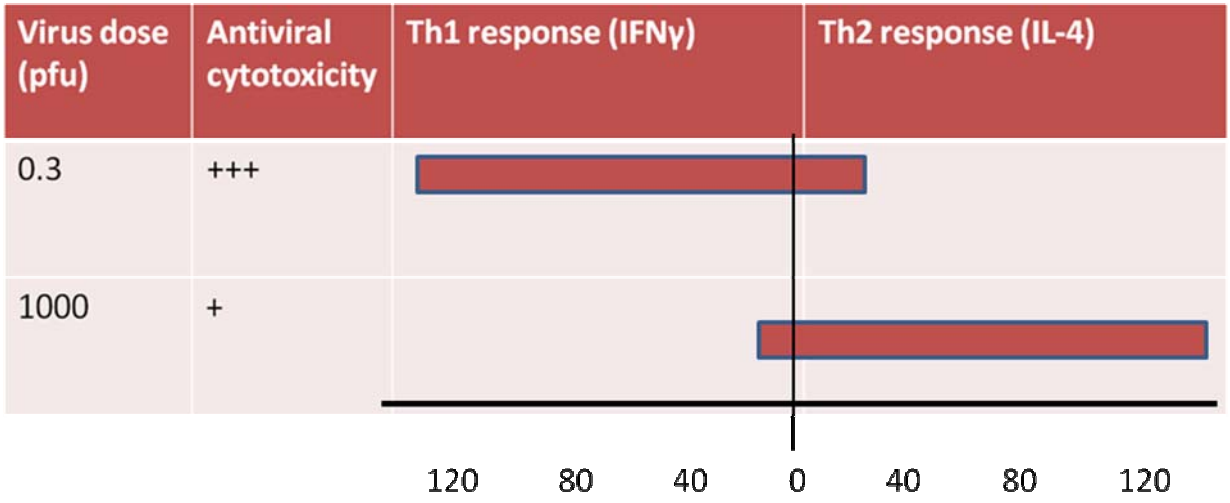
   b) Recognition of antigen with CTLA-4 engagement of B7 resulting in down regulation of T cell activation,

   c) Cytokines with stimulatory or inhibitory activities on immune cells,

   d) Idiotype/anti-idiotype interactions leading to stimulation or inhibition of immune responses.

   e) Dose and route of Ag exposure can induce differential Th responses (Figure 1) which in one case can protect and in another can tolerize.

Figure1.



3) Regulation by antibody

a) Soluble antibody can compete with antigen receptors on B cells and block or prevent B cell activation (Figure 2A). In this case the regulation is occurring at the recognition level.

b) In addition antigen antibody complexes can bind to Fc receptors on B cells, sending an inhibitory signal to B cells (Figure 2B). Here regulation occurs at the activation level.

c) Antibody can also regulate activation (enhance) by maintaining a source of antigen for APC. In this case, Ab binds Ag forming an immune complex which binds and activated the complement system. Complement activation allows for ligation to the complement receptor on the APC (Figure 2C).

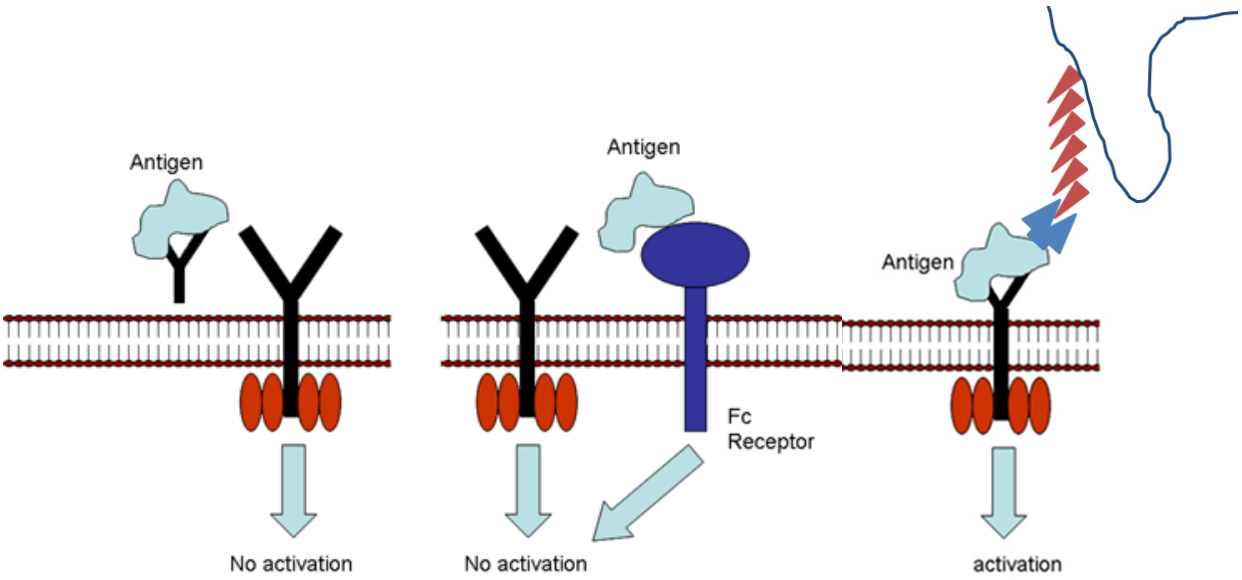


Figure 2A **Figure 2B** **Figure 2C**

4) Regulation by cytokines

   a) Cytokines are positive or negative regulators. They act at many stages of the immune response, but their activity is dependent upon the other cytokines present in the microenvironment as well as receptor expression on effector cells. Cytokines regulate the type and extent of the immune response generated.

5) Regulation by regulatory T cells (Tregs): Regulatory T cells (Tregs) are recently described populations of cells that can regulate immune responses. They do not prevent initial T cell activation; rather, they inhibit a sustained response and prevent chronic and potentially damaging responses. They do not have characteristics of Th1, Th2, or Th17 cells but they can suppress both Th1 and Th2 responses.

   a) Naturally occurring Tregs – The thymus gives rise to CD4+/CD25+/Foxp3+ cells that function as Tregs. These Tregs suppress immune responses in a cell contact-dependent manner but the mechanism of suppression has not been established.

   b) Induced Tregs – In the periphery some T cells are induced to become Tregs by antigen and either IL-10 or TGF-β. Tregs induced by IL-10 are CD4+/CD25+/Foxp3- and are referred to as Tr1 cells. These cells suppress immune responses by secretion of IL10. Tregs induced by TGF-β are CD4+/CD25+/Foxp3+ and are referred to as induced Tregs. These cells suppress by secretion of TGF-β.

   c) CD8+ Tregs – Some CD8+ cells can also be induced by antigen and IL-10 to become a Treg cell. These cells are CD8+/Foxp3+ and they suppress by a cell contact-dependent mechanism or by secretion of cytokines. These cells have been demonstrated *in vitro* but it is not known whether they exist *in vivo*.

6) Genetic factors influencing immunoregulation

   a) MHC-linked genes help control response to infection. Certain HLA haplotypes are associated with individuals who are responders or nonresponder, those who are susceptible or resistant.

   b) Non-MHC genes are also involved in immunoregulation. An example is a gene related to macrophage activity encoding a transporter protein involved in transport of nitrite (NO_2^-) into the phagolysosome, natural resistance-associated macrophage protein-1 (Nramp1). Polymorphisms in this gene could change the activity of macrophages.

   c) Cytokine, chemokine, and their receptors are involved in immunoregulation as discussed previously. Polymorphisms in the genes encoding these, in particular the receptors, have been shown to correlate to susceptibility to infection or generation of autoimmune disease.