Regulatory mechanisms in Specific Immune Responses.

Regulatory mechanisms in Specific Immune Responses: Based on:

- i). Prior exposure to ag
  Nature and concentration of ag (see lecture on antigens: Immunogenicity and antigenicity)
- ii). Sequestration of antigens in immune privileged sites
- iii). Circulating ab
- iv). Cytokines
- v). Anti-idiotypic ab: Network theory
- vi). T suppressor cells?

- i). Prior exposure to ag

Q. What is the overall result of primary exposure to antigen?

A. Primary exposure to ag can lead to

1) responsiveness (where primary and secondary responses differ) and production of memory T and B cells (with class switching)

2) induction of tolerance

Q. Tolerance is often mentioned in light of transplantation. But mechanisms for inducing tolerance couldn't have evolved in anticipation of medical technology. So, what is the evolutionary advantage to tolerance?

- **A.** Tolerance (induction of anergy) may simply be a reflection of the mechanisms for negative selection against self-reacting B and T cells. Tolerance may be necessary so the immune system doesn't respond to "self"-antigens to which it is not exposed during maturation.

- **Q.** When does the body naturally contain tissues which are genetically dissimilar (besides the rearranged B and T cells leading to idiotopes on ab and TCR — see later).
- **A.** During sperm and egg cell production and pregnancy.

- ii). Ag sequestration - hiding self antigen from the immune system - e.g. lens of the eye, developing sperm cells, to some extent a developing fetus in the uterus.

- These are considered immune "privileged sites". (Note that this is not really "tolerance" since it is a passive process rather than an active one of inducing anergy or apoptosis in potential responding cells.)

- **Q** What is the basis for antigen competition that may occur when recent exposure to one antigen limits response to another.
- e.g. A mouse will develop a given response when infected with horse red blood cells (HRBC). However, if it is first primed a few days before by an injection of sheep RBC, the later response to HRBC is less than if the SRBC had not been injected.
- Thus, prior exposure to an unrelated antigen and priming of an ab response reduced the subsequent ab response.

- **A** This may result from interference by the first ag utilizing much of the APC capacity so the second ag is not as effectively presented and/or by the presence of down-regulating cytokines in the process of reducing the response to the first ag.

- **Circulating ab**
- Circulating ab may invoke a sort of negative feedback mechanism. For example, circulating maternal ab interferes with childhood vaccinations in kids under a year -- the MMR vaccine for measles, mumps and rubella is not given until 1 year since it is not likely to elicit an immune response prior to that.
- **Q** Why?
- **A** One way this might occur is by the circulating ab binding to the ag and promoting clearance before any naive B cells can bind and become activated.

- Consider the following:
- A primary immune response to a carrier + hapten A generates circulating ab to hapten A.
- Next, a carrier with hapten A and a second hapten B is introduced to elicit a secondary response to hapten A. If the earlier statement is true, you would expect the circulating ab to bind to the hapten A epitopes and assist clearance of the whole carrier + hapten A + hapten B complex before an immune response to the hapten B could be elicited.

- However, it turns out that this doesn't happen and a response to the second hapten does develop.
- Therefore, it is likely that circulating ab inhibits immune response in an epitope-specific fashion by competing for ag with the ab on naive B cells. If the circ. ab. binds all the epitopes, then the naive B cells, which are in low concentration, may never see the ag.
- However, other exposed epitopes such as those of hapten B in the example could be responded to.

- **Cytokine-mediated regulation.**
- Two classes of T helper cells have been identified that secrete different sets of lymphokines and lead to different responses.
- TH1 cells secrete interferon gamma and IL-2, thus stimulating cytotoxic cells. These cells are also involved in delayed type (Type IV) hypersensitivity
- TH 2 cells secrete IL-4 and IL-5 which activate B cells, and IL-10 which suppresses TH1 cells.

Other mechanisms.

- Anti-idiotype mechanism
- Neuroendocrine control: There is increasing evidence that endocrine, nervous and immune systems interact via chemical mediators.