Immunology summary | week no.7

What did we talk about in lecture 10? Recall briefly.

* B cells are generated in the bone marrow where their early maturation takes place too giving [*Naive B cells*]

* B naive cells go to the follicles (guided by CXCL13 secreted by [*follicular dendritic cells*]) where they sit waiting for raw antigens (otherwise they die 😳)

* Naive B cells express membrane IgM & IgD, and with the help of Igα &Igβ molecules, the binding of the antigens activate these B cells.

* Response is either 1. T **cell-dependent** which produces [*long-lived plasma cells*], the antigen is probably a protein , or 2. **T cell-independent** which produces [*short-lived plasma cells*] &mainly IgM antibodies, the antigen is mainly a polysaccharide or a lipid.

* T cell-dependent response -> Follicular dendritic cells present raw antigens to naive B cells which activates them (**not full activation**) so they start secreting CCR7. On the other side of the world, dendritic cells present processed antigens to helper T cells (on MHC-II) so they start expressing CXCR5 (receptor for CCR7). T cells migrate towards the edge of the follicle and so do B cells until they physically meet in the T cell zone where they react (**B cells full activation**) and the response takes place.

* Haptens are small **not immunogenic molecules** but the bind specifically to antibodies (precise) so we conjugate them to immunogenic molecules (initiate an immune response) in vaccines.

Lecture 11 & 12

***B&T cells interaction**: CD40 chemokines produced by T helper cells bind to CD40R on the surface of the not-fully mature B cells.

1. When B cells present its antigen to T cells, T helper cells get more activated and produce cytokines which in turn further activate the mature B cells.
2. B cells either produce short-lived plasma cells or migrate to the follicles along with T helper cells.
3. In the germinal centre, B cells produce long-lived plasma cells & memory B cells.

Follicular dendritic cells

1. Attract activated B cells to the follicles.

2. Clean dead B cells

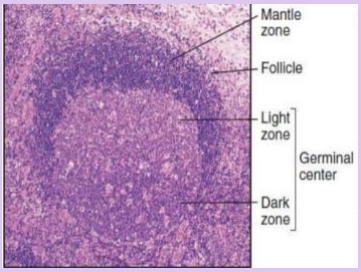
3. Express receptors for complement molecules and Fc receptors for antibodies &display native antigens to naive B cells

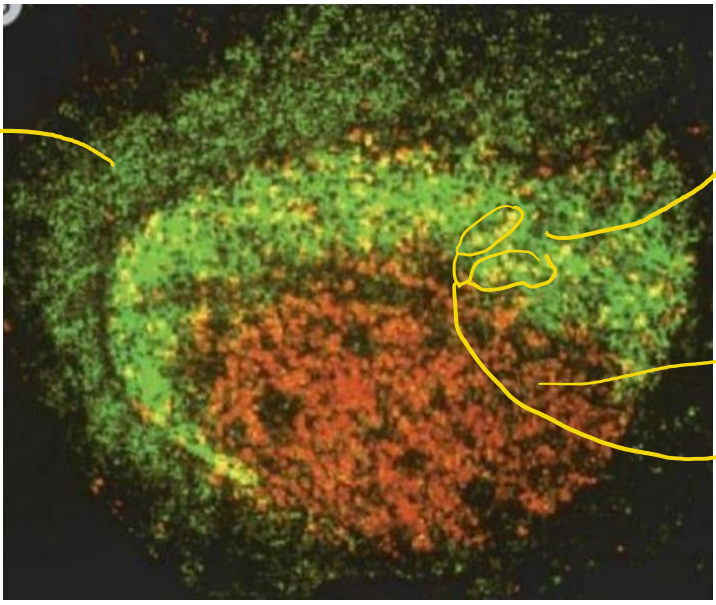
Germinal centres

1. Activated B cells

2. T-helper cells (follicular T-helper cells)

3. Follicular dendritic cells





Anti CD-23 antibodies, found on naive B cells outside the germinal centres

Light zone -> high density of CD-23 on follicular cells.

*Cycling or mitotic B cells

*Yellow -> B cells migrated to the light

Isotype switching: Switching of antibodies isotype in the light zone of the germinal centre. This is activated by cytokines produced by TH -cells. The switching depends on *the microbe that initially activated B cells* &*the anatomical location.*

1.Viruses/Bacteria: long time infection-> IgG

2.Helminths & Allergy rxns -> IgE

E.g. in mucosal surfaces-> IgA in needed

Affinity maturation: Mutations in the B cells DNA when it replicates (in the dark zone) produce antibodies with different affinities to antigens, we only want the ones with high affinity. So, these cells migrate to the light zone where Follicular T-helper cells secrete IL-21 which induces the apoptosis of B cells, the ones bound tightly to antigens presented on FDCs [CR1&CR4] (high affinity) send survival signals and survive.

Humoral immunity:

***Plasma cells** (differ from B cells morphologically, and they don't go under isotype switching (terminally differentiated)) ... produce circulating antibodies.

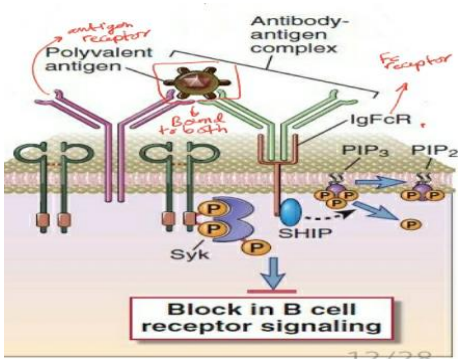
1.**Short lived** (produce ½ of the antibodies)-> after T-independent response, live for 2-3 months and reside in the secondary lymphoid organs & peripheral non-lymphoid tissues.

2.**Long lived** (produce ½ of the antibodies) ->after T-dependent response. Signals from BCRs & IL-21 help in the generation of these cells. They reside in the bone marrow for 20 or 30 years and this is maintained by BAFF.

***B cells differentiation**: **Cell enlargement -> ER prominence -> Switch from membrane antibodies to secreted antibodies.** Bcl-2 [*antiapoptotic*] helps activated B cells to survive.

***Memory B cells:** not terminally differentiated cells, emerge parallel to T memory cells, may remain in the lymphoid organs or circulate the blood. They have better receptors than naive B cells & they initiate the secondary response which is stronger and faster.

Antibody feedback



Antibodies inhibit the production of more antibodies, by binding to an antigen (antigen-antibody complex) then binding to the Fcγ receptors on the B cell surface [*FcγRIIB and the antigen receptor interact w/ the antigen-antibody complex and inhibitory phosphatase block the signals of these receptors*]

Effector mechanisms of humoral immunity

1. Neutralisation of microbes and toxins -> Antibodies *block the primary infection* by binding to microbial antigens that they use to enter the cells, this also *limits the spread* of the microbe. They also *block the binding of toxins to cellular receptors*.
2. Opsonisation and phagocytosis of microbes -> binding of antibodies (IgG (1,3) specially) or complement molecules enhance phagocytosis and active macrophages which leads to:
    - *Phagocyte oxidase production -> H2O2*
    - *Inducible nitric oxide synthase -> NO*
    - *Hydrolytic enzymes & reactive oxygen intermediates -> extracellular large microbes*
3. Antibody-dependent cellular toxicity-> antibody-coated cells react with *FcγRIII* which *activates NK cells to produce INF-γ and discharge their contents* (Perforins&granzymes) to kill the target cells. [Monoclonal antibodies used against tumours, e.g., in many epithelial tumours EGFR is over-expressed and it's targeted by the antibody Cetuximab which blocks its signalling & activate ADCT].
4. Activation of the complement system

Antibody-mediated clearance of helminths.

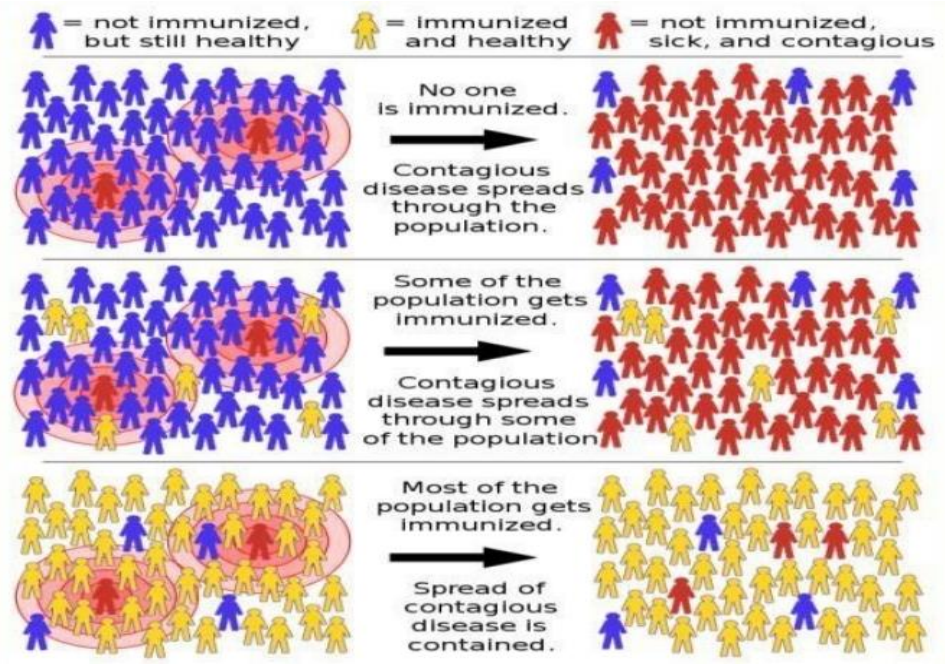
Helminths (*too large to be phagocytised*), so *mast cells, eosinophils and antibodies* mediate the expulsion of them. *IgE, IgG & IgA coat it and bind to eosinophils -> degradation of these cells and release of a major proteins & toxins that form a hole in the parasite's cell wall*. IgE initiate mast cells degranulation (*mast cells cause bronchoconstriction and increase GI mobility to cause the expulsion of the worms*). Some helminths cause *the activation of the alternatively activated macrophages which is involved in immune regulation.*

Vaccination: Giving the patient a ***weakened*** pathogen to initiate a response against it and induce a protective immunity.

Vaccine type	Info/Production	Use/Examples
Live attenuated vaccine	*Alive but weakened *We culture the pathogen multiple times ([chick vitro] culture A then we move the ones that survived to culture B and so on) why? *These become better at infecting the cells they grew in but lost their ability to infect human cells* *Or we culture in different vitro at a temperature lower than that of human bodies so the pathogen won't survive it *They *mimic* the disease *Produced more for viruses (small genetic material)	*We don't normally use it in immunocompromised individuals *Long time immunity after one or 2 doses *E.g., MMR, varicella *The only bacterial is BCG for tuberculosis *Oral polio vaccine is easily obtained, inexpensive and effective. But there's a risk of developing vaccine-related paralytic poliomyelitis.
Inactivated vaccine	*Non-living but still immunogenic *Less effective than live vaccine so we give multiple doses *We can give parts as a vaccine (a protein or a polysaccharide or parts of a virus) How? Purifying antigens or putting a part of the DNA in an expression system	*Safe for immunocompromised individuals *IPV (inactivated polio vaccine but we use the active first) *Whole cell pertussis *Hepatitis A & rabies *Subunits vaccines -> Acellular pertussis vaccines Hepatitis B vaccine -> Recombinant protein vaccine *In malaria there's not enough antibodies since it resides in the RBCs, so we combine a gene of a surface protein of plasmodium falciparum (the pathogen) with HBsAg gene (it'll be more effective)

Toxoid Vaccine	*An inactivated toxin[toxoid] (subunit vaccine) *Do *NOT prevent infection or transmission* (no Herd immunity*)	*Important in bacteria that depends on toxins (clostridium difficile, cyanobacterium diohtheriae, clostridium tetani (tetanus)
Polysaccharide and conjugate vaccine	*We take the polysaccharides out of the bacterial capsule, and make it a vaccine which provides a short-term protection (T-independent response). The solution? *We conjugate it to an adjuvant (protein or something (remember Haptens))*	*E.g., streptococcus pneumonia, hemophilus influenza type b and N. meningitidis *People who have undergone Splectomy are highly susceptible to the infection by the previous bacteria so they should be vaccinated

***Herd immunity->** Protection from an infectious disease when a large population has become immune to it



***Vaccination problems:**

1. some pathogens have antigenic hyper-variability
2. some pathogens have multiple serotypes
3. some pathogens are found intracellularly and can't be detected by antibodies