Oral Biology
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Lecture - 14
Mucosal and regional immunology

Welcome to the lecture cast on Mucosal and regional immunology. Mucosa represents the membrane that lines the inner surface of the body. Like skin, it forms a barrier between the internal and the external environment.

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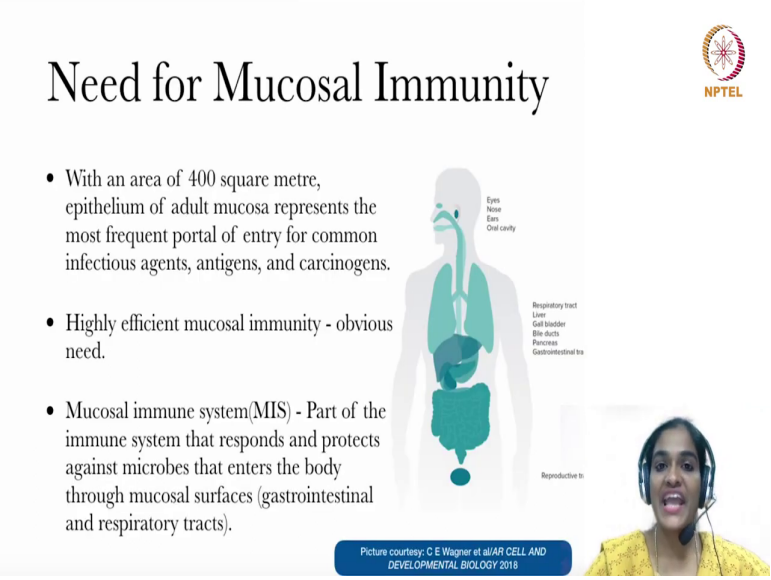

With an area of 400 square metre, the epithelium of adult mucosa represents the most frequent portal of entry for common infectious agents, antigens and carcinogens. Thus highly efficient mucosal immunity is of paramount importance. Mucosal immune system is defined as a part of the immune system that responds and protects against the microbes that enter the body through the mucosal surfaces.

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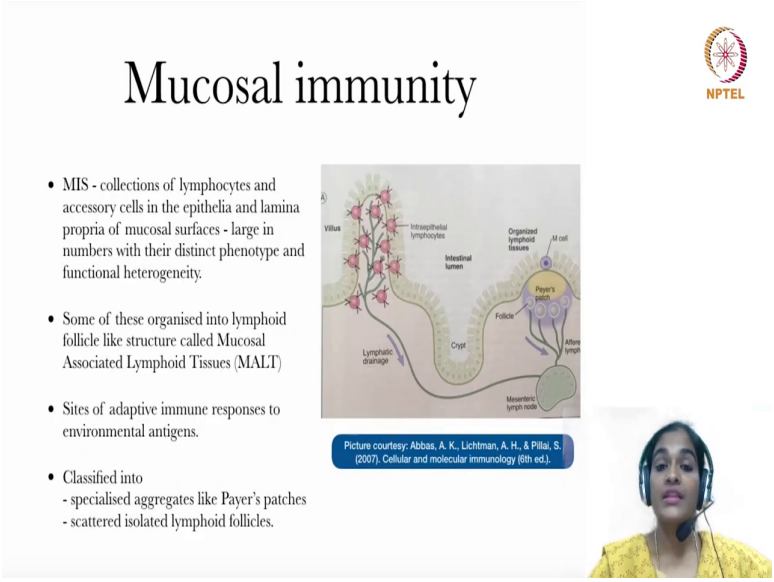

The mucosal immune system is provided with a rich collection of lymphocytes and accessory immune cells likeIgE, IgA and macrophages. These are present in the epithelia and the lamina propria of the mucosal surfaces. You can see in the picture the collection of lymphocytes in the intraepithelial and subepithelial lamina propria. These cells are large in number with the distinct phenotype and functional heterogeneity.

Some of these cells are organised into a lymphoid follicle-like structure called mucosal associated lymphoid tissue. These are the sites of adaptive immune responses to the environmental antigens. The MALT tissues are classified into specialised aggregates (in peyer's patches) or as scattered isolated lymphoid follicles.

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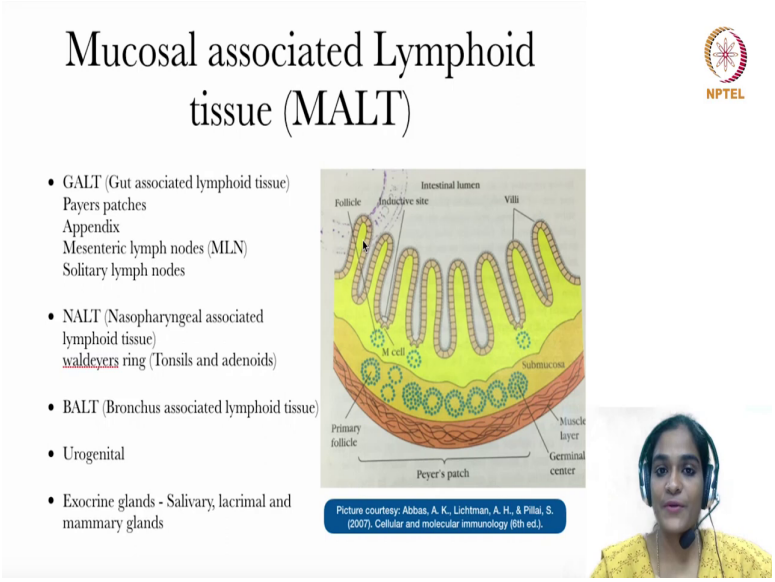

The MALT tissue is distributed all throughout different mucosal surfaces of the body. When they are present in gut they are called as GALT; Gut Associated Lymphoid Tissue. It comprises peyer's patches, appendix, mesenteric lymph nodes and solitary lymph nodes.

Those lymphoid tissue present in the nasopharyngeal area or the NALT tissue, the Waldeyer's ring including the tonsils and the adenoids form the component of the NALT tissue. Other lymphoid tissue associated with mucosa are BALT with the bronchial region, urogenital lymphoid tissue and those lymphoid tissue associated with the exocrine glands like salivary, lacrimal and mammary glands.

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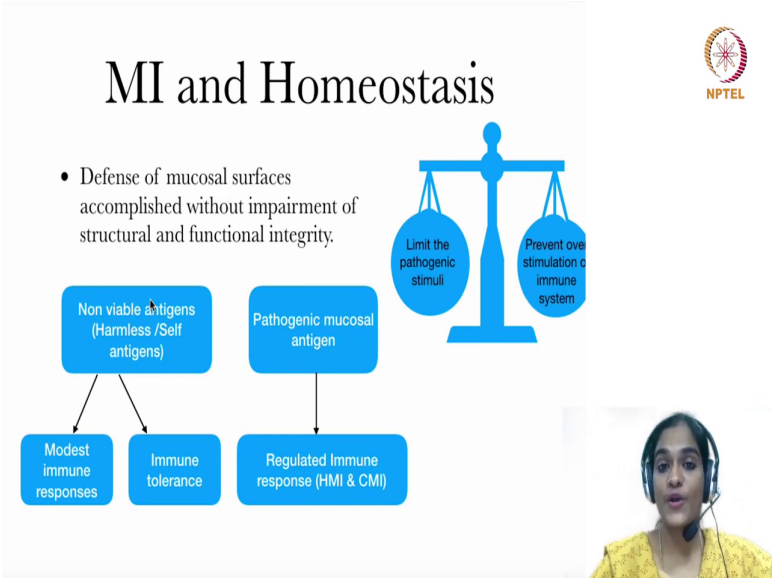

The ultimate aim of mucosal immunity is to bring about the homeostasis that is the defence mechanisms of the mucosal surfaces should be established in such a way that there is no impairment of the structural and the functional integrity of the mucosa. The mucosal responses to the pathological stimuli should be limited to prevent the overstimulation of the immune system so that the integrity of the mucosa is preserved.

Against a nonviable antigen which is the potentially harmless or a self antigen, a modest to no immune response should be elicited. Against a pathogenic mucosal antigen, a regulated immune response is elicited. What do you mean by regulated immune response? The regulated immune response represents the heightening of the immune activity once the antigen is encountered. Following the elimination of the antigen, the immune system is brought back to normal sense.

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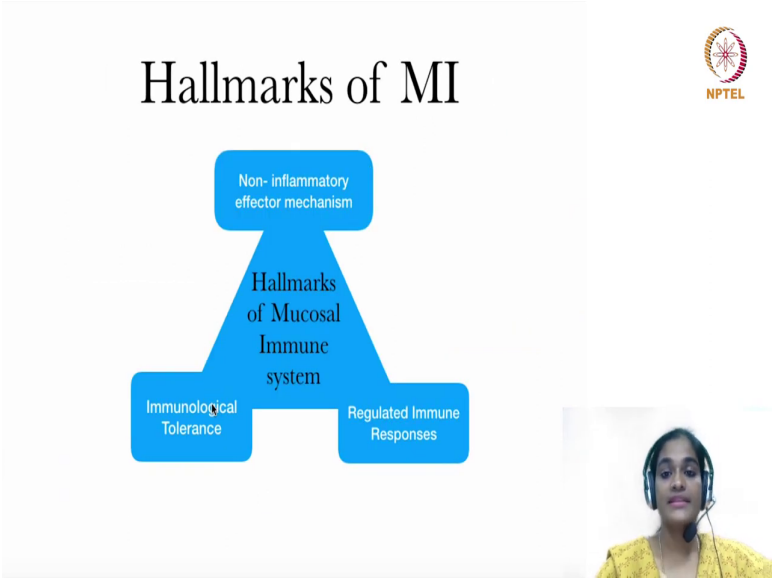

Thus, the hallmarks of mucosal immunity include the non-inflammatory effector mechanism by which the various immune mechanisms are mediated through a non-inflammatory process. There is immune tolerance against a self antigen or a potentially a harmless antigen and regulated immune response towards pathogenic stimuli.

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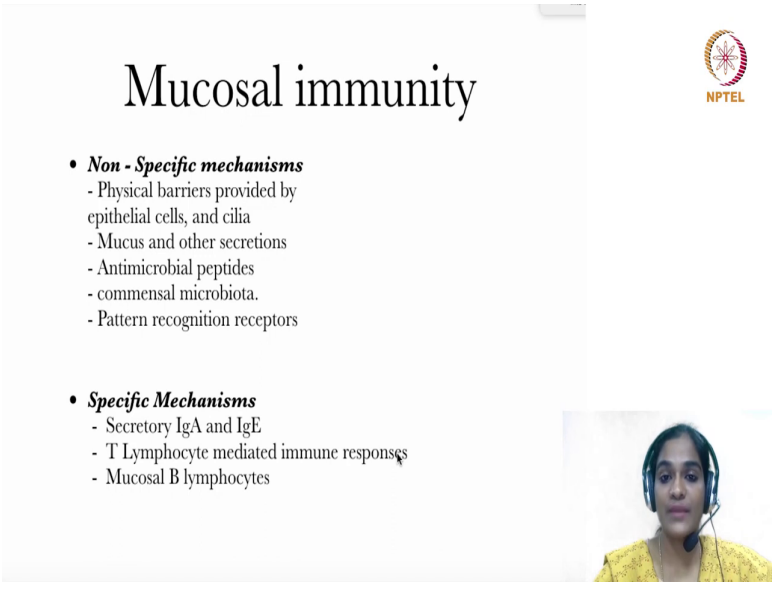

The various mechanisms of the mucosal immune system include non-specific mechanisms and specific mechanisms. Non-specific mechanisms include the physiological barriers as provided by the epithelial cells, cilia, mucus and other secretions those given by the

antimicrobial peptides, commensal bacteria and the pattern recognition receptors. Some of the specific mechanisms include those given by the antibody mediated cell mediated and humoral mediated responses.

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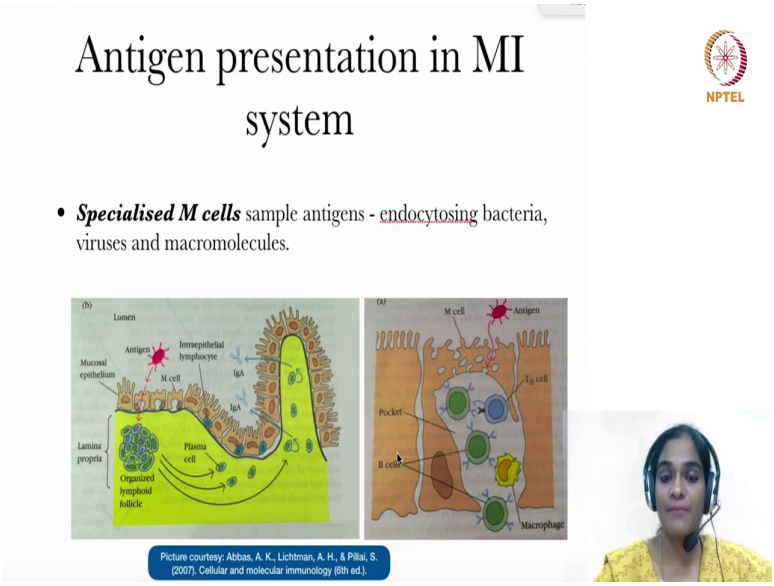

Before going into the details of the immune mechanisms of the mucosal immune system, let us see how an antigen is being presented to the mucosal surface. There are specialised M cells or the multi fold cells which are present on top of the mucosa associated lymphoid follicles. Over the GALT and NALT lies the M cells e, which are the specialised epithelial cells. They do not have the microvilli.

These take the antigen from the lumen to be processed by the lymphoid follicle. In the follicle there are presence of B cells which on encountering antigens get converted into specialised plasma cells. Those plasma cells produce the specific IgA or the immunoglobulin A to respond to the particular antigen. These are secreted through the lamina propria into the lumen, to encounter the specific antigen.

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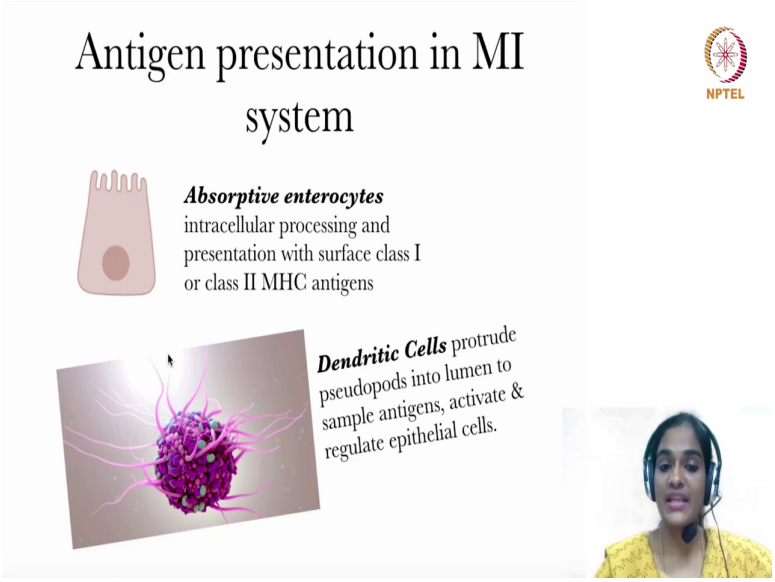

We have the epithelial cells (for example, the enterocytes). These take up the soluble antigen with the help of MHC class 1 and class 2. They process and present them to the underlying T cells or the intraepithelial T cells for the immune tolerance or immune stimulation.

There are dendritic cells which are present in the basal epithelial layer or they can also be seen in the lamina propria which protrude their pseudopods into the lumen to sample the antigen so that they activate and regulate the epithelial cells.

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Coming on to the mechanisms of the mucosal immune system, there are nonspecific barriers- most predominantly the epithelial cells play an important role. They have the intercellular junctions and the keratin formation which prevents the transit of antigens and pathogens into the mucosal surface.

Some of the epithelial cells which are labelled as type 2 epithelial cells - show stratification. they constantly shed their superficial layer. Because of the superficial shedding, there is no colonization of bacteria in the epithelial layer.

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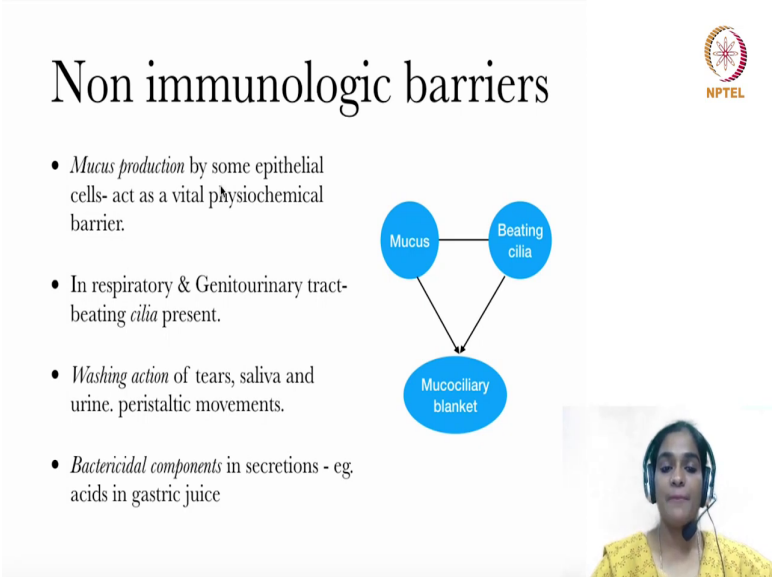

The mucous production by some epithelial cells act as a vital physiochemical barrier. The mucus produced along with the beating cilia form the mucociliary blanket. This mucociliary blanket effectively traps the antigen and expels the same. So, in the various mucosal surfaces, you have secretions like tears, saliva and urine, which causes the washing action.

There are some of the reflexes like peristaltic movement, sneezing, coughing which helps to expel the antigens. There are bactericidal components in some of the secretions. Example: an acid in a gastric juice, lactozyme in tear saliva, lactoperoxidase in mammary secretions and spermine and zinc in sperms. These help to kill the microorganisms encountered by the mucosa.

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The residual microbial flora have an extensive and vital interaction with the mucosa. They produce the microbial antagonism. That is they suppress the growth of the various pathological bacteria and fungi, by competing for the essential nutrients and producing various inhibitory substances. For example , lactic acid produced by the vaginal flora helps to get rid of the pathogenic fungi colonization.

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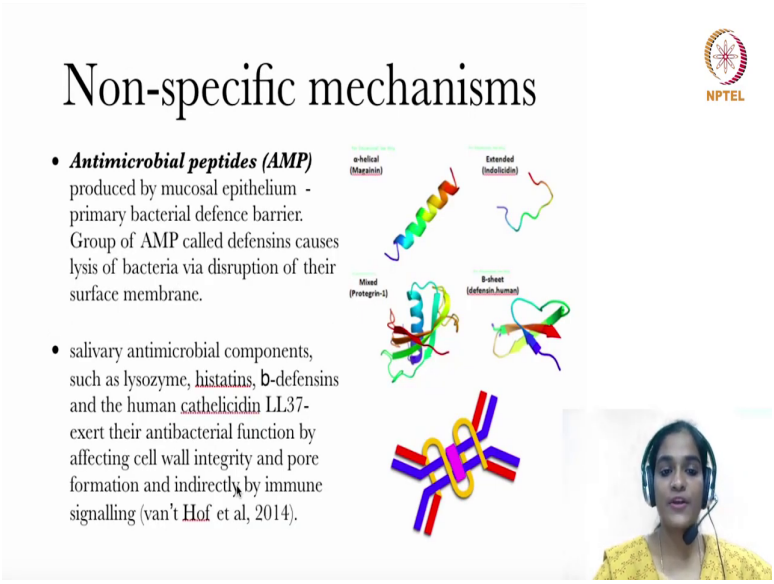

The antimicrobial peptides produced by mucosal epithelium forms a primary bacterial defence barrier. There are groups of antimicrobial peptides called defensins . They get

inserted themselves into the bacterial membrane and cause the disruption of the same. Because of which, there is loss of cellular contents causing the lysis of the bacteria.

Similar mechanism is being shown by salivary antimicrobial compounds like lysozyme, histatin, beta defensin and human cathelicidin, which also affects the cell wall integrity and pore formation. Some of them also trigger the immune mechanisms that cause the elimination of the pathogen.

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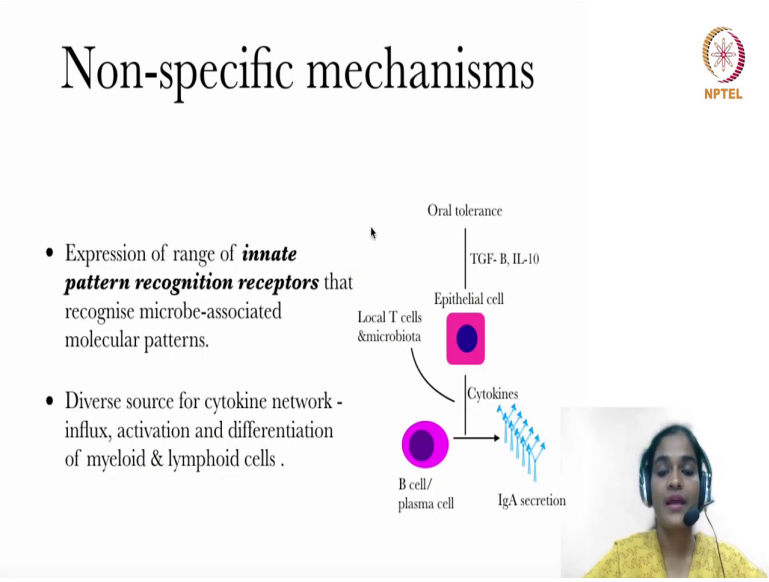

Some of the phagocytes and epithelial cells express the innate pattern recognition receptors. These receptors recognize the microbial associated molecular patterns. These patterns are nothing but lipopolysaccharide in case of a gram negative bacteria or a lipoteichoic acid in case of a gram positive bacteria and a glycolipid in case of the mycobacteria.

when the innate pattern recognition receptors combine with the microbial associated molecular patterns (also called as PAMP), there is an induction of diverse amounts of cytokines which causes influx, activation and differentiation of myeloid and lymphoid cells.

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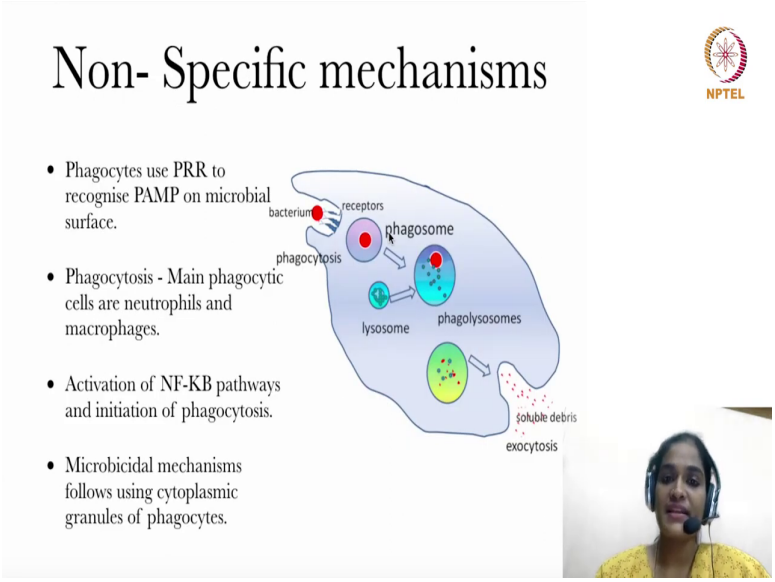

The other mechanism as soon as a PRR encounters the PAMP is that there is initiation of phagocytosis, that is after the PRR combines with the PAMP there is NF-kappa B pathway which gets activated because of which there is stimulation of phagocytosis. Thus, the phagocytes throw their pseudopods to engulf the antigen and form the phagosome.

And as soon as the antigen is internalized inside, these combine with the cytoplasmic granules of the phagocytes causing various microbicidal mechanisms like reactive oxygen and nitrogen mediated pathways. Soon soluble debris is being expelled after the lysis of the microorganism.

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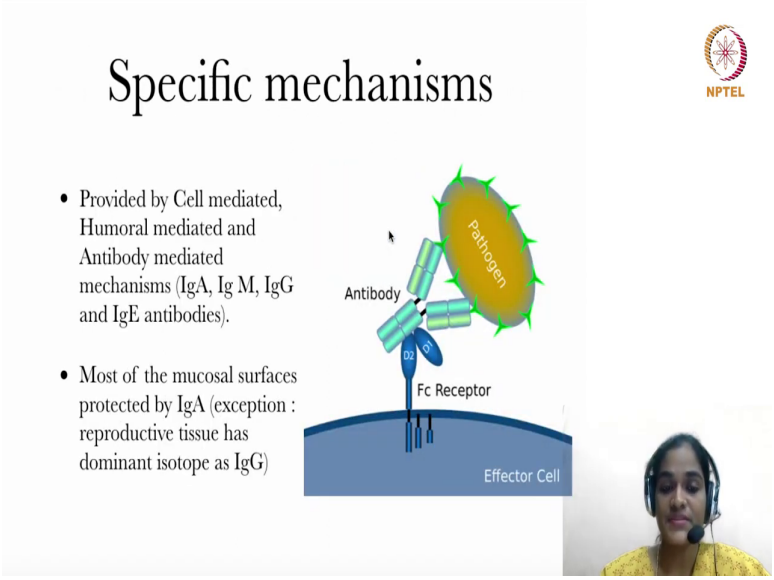

Various specific mechanisms are provided by cell mediated, humoral mediated and antibody mediated responses. The specific mechanisms of the mucosal immune system are mediated by the lymphocytes and antibodies. IgA is the dominant type of antibody, which is seen associated with a mucosal surface. More than the systemic circulation, it is commonly seen associated with the mucosa.

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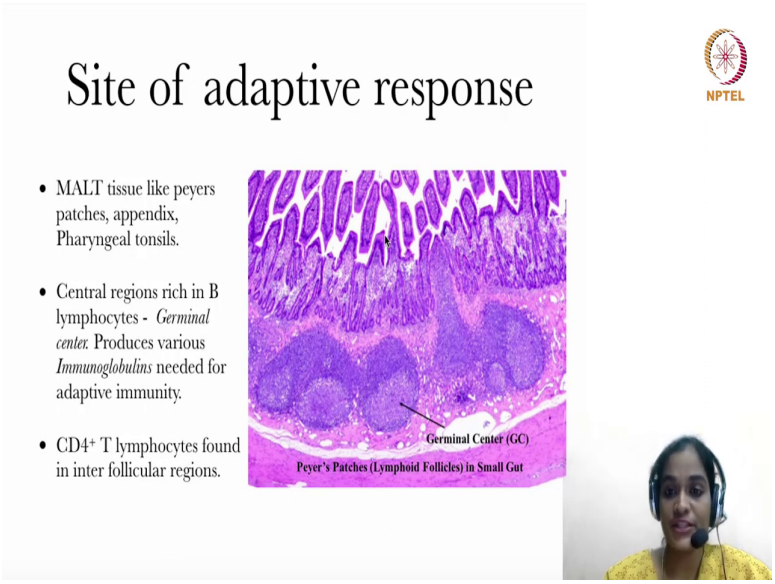

The appropriate site where the adaptive response or a specific response of the mucosal immunity occurs are the MALT or the Mucosal Associated Lymphoid Tissue. These MALT

tissues have follicles . The center of the follicle is B lymphocyte l rich also called a germinal center. These are the sites where the antibodies specific to antigen are being produced. In the interfollicular region, the CD4positive T lymphocytes are seen and these are the sites of cell mediated immune responses.

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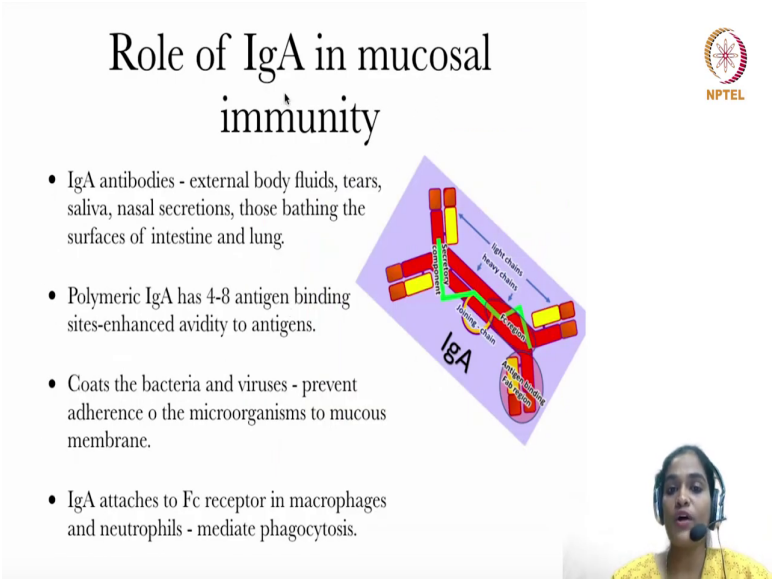

Now, we will see the role of IgA in mucosal immunity. These IgA antibodies are seen bathing in the extracellular body fluids; tears, saliva, nasal secretions and also the intestine and the lung. These are polymeric. They have 4 to 8 antigen binding sites. Thus they have the enhanced avidity or attraction to the antigen. These coat the bacteria and the virus and various other microorganisms. They prevent the adherence of them to the mucosal membrane. These IgA attach to the Fc receptor in the macrophages and the neutrophils - mediating phagocytosis.

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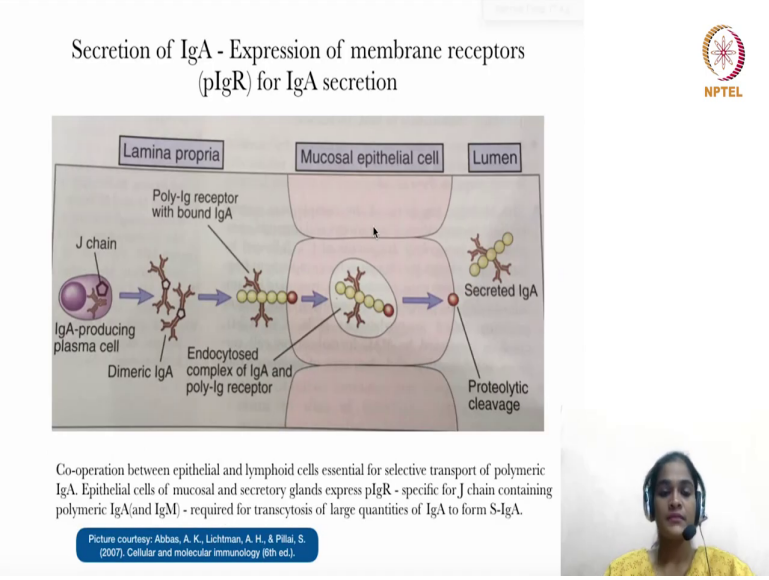

An IgA molecule is a dimer, which has been cross linked with the help of a J chain. These are produced in the lamina propria. They are being transported with the help of a poly IgA receptor on the cell surface of an epithelial cell. These receptor, combined with the IgA is transported through the membrane and finally, after the lysis (proteolytic cleavage) of the transporting molecule, the secreted IgA occurs in the luminal surface.

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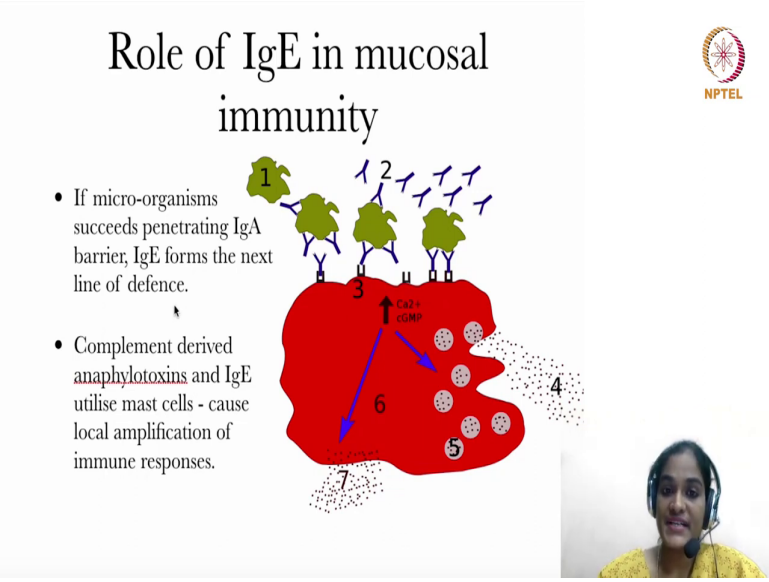

If the micro-organism succeeds in penetrating the IgA barrier, the IgE next comes into play. They are the next line of defence. The complement derived anaphylatoxins and the IgA

utilise the mast cells. They interact with the mast cells to cause the release of pre-secreted mediators of inflammation, which causes the local amplification of immune responses.

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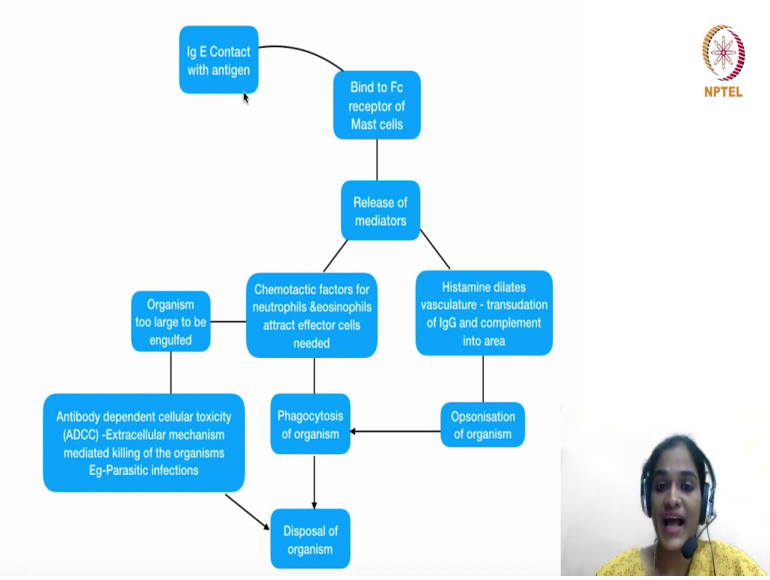
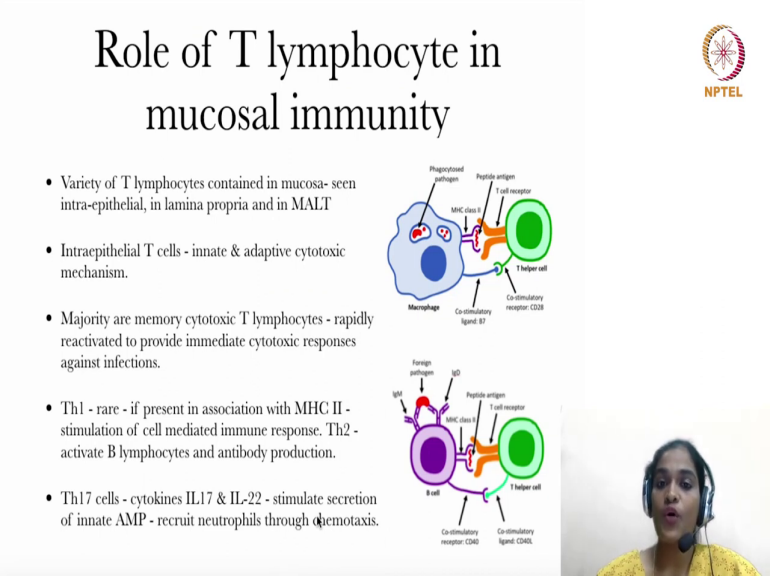


The IgA when it contacts with the antigen it binds to the Fc receptor of the mast cells due to t release the mediators. The histamine released dilate the vasculature causing transudation of IgE and complement into the area. These opsonize the organism causing the phagocytosis.

Some of the chemo factors released from the mast cells attract the neutrophils, eosinophils and other effector cells which causes the phagocytosis. Larger organisms are eliminated by means of an extracellular mechanism called antibody dependent cellular toxicity..(Refer Slide Time: 15:34)



Now, let us see about the role of T lymphocytes in mucosal immunity. The variety of T lymphocytes are contained in the mucosa. They are seen in the intraepithelial, subepithelial lamina propria and also associated with MALT tissue. The intraepithelial T cells are predominantly CD8 positive lymphocytes and also memory T cells.

The CD8 positive T cells or the cytotoxic cells cause the innate and adaptive cytotoxic mechanism. The memory T cells rapidly get reactivated to provide for the immediate cytotoxic responses needed for an infection. The lymphocytes are also present in the lamina propria, which are CD positive T helper cells.

The T helper cells recognize and respond to the antigens in the lymph nodes draining the particular mucosal surface and migrate back to the mucosa to populate the lamina propria. These are predominantly Th2 type of lymphocytes. They activate B cells and antibody production.

Some of them are only Th1 type of cells that are associated with MHC class 2. They stimulate the cell mediated immune response, whereas some of the helper cells are Th17 type. Due to the stimulation of IL17 and IL22 they cause the secretion of innate antimicrobial peptide and also recruit the neutrophils through chemotaxis.

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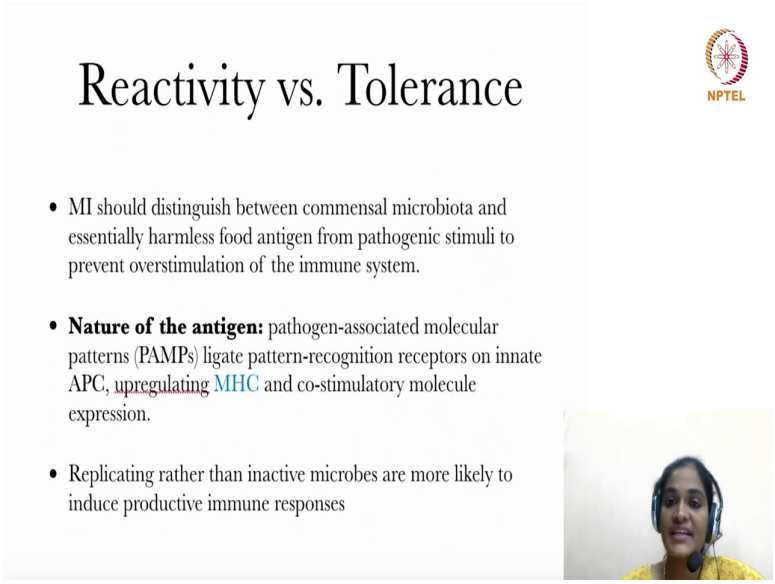

Reactivity versus tolerance; how does a mucosal immune system distinguish between a self and a non-self antigen? They have to differentiate between the commensal microbiota and essentially harmless food antigen from a noxious pathogenic stimuli. How does a mucosal immune system distinguish between a self and a non-self antigen? They do this with the help of major histocompatibility antigen (MHC) and also the co-stimulation.

When a particular cell recognizes the pathogen associated molecular pattern, the MHC molecule co-stimulates; they get upregulated and there is also co-stimulatory molecule expression. Only after seeing the co-stimulation and molecular MHC upregulation there is activation of the immune response. When there is absence of the same, you have immune tolerance. Replicating rather than an inactive microbe is more likely to induce immune response.

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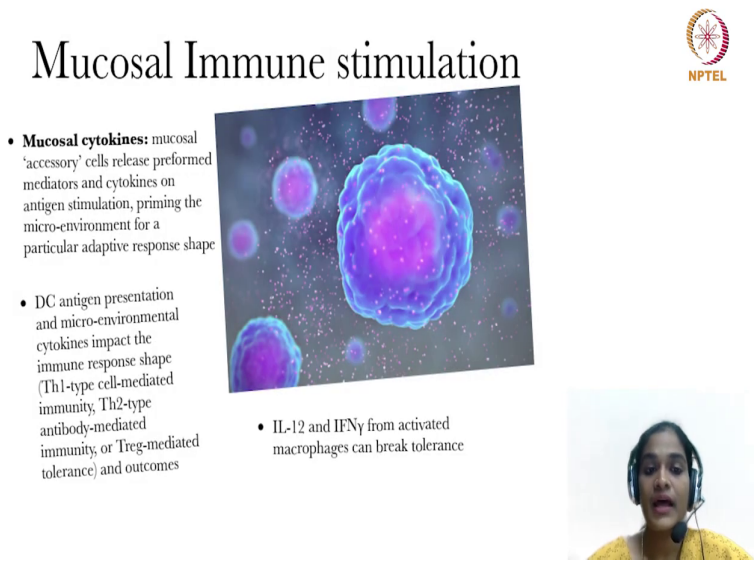

There are various cytokines and mediators which have been produced by accessory immune cells which primes the micro environment for a particular adaptive response. For example, if there is production of interleukin 2, 12, interferon gamma, Th1-type of cell mediated immunity gets activated. If there is interleukin 4, 6, 5 and 10 being produced, Th2-type of cell mediated immune response becomes activated. The interleukin 12 and interferon gamma break the tolerance state and reactivate the immune stimulation or heightened response.

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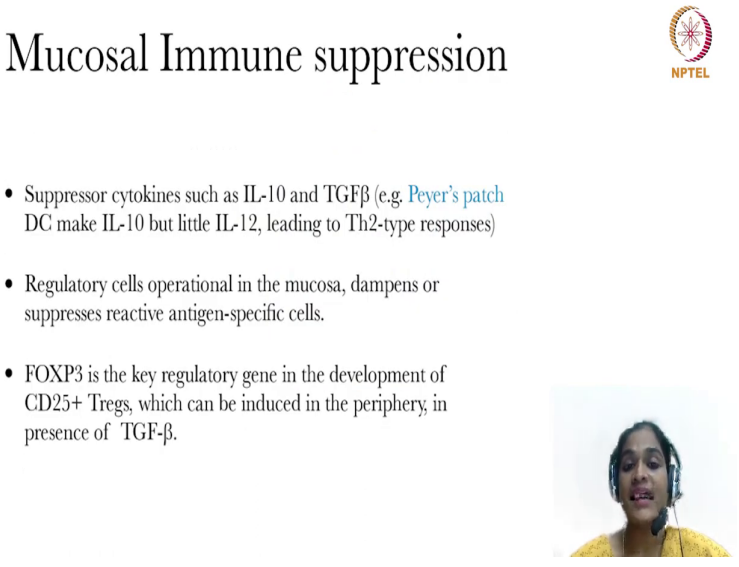

There are certain suppressor cytokines like interleukin 10 and TGF beta which cause the immune suppression or tolerance. The FOXP3 is a gene which converts the naive T cell into a T regulatory cell in presence of TGF beta. These regulatory cells are present in the mucosa. They dampen or suppress the reactive antigen specific cells.

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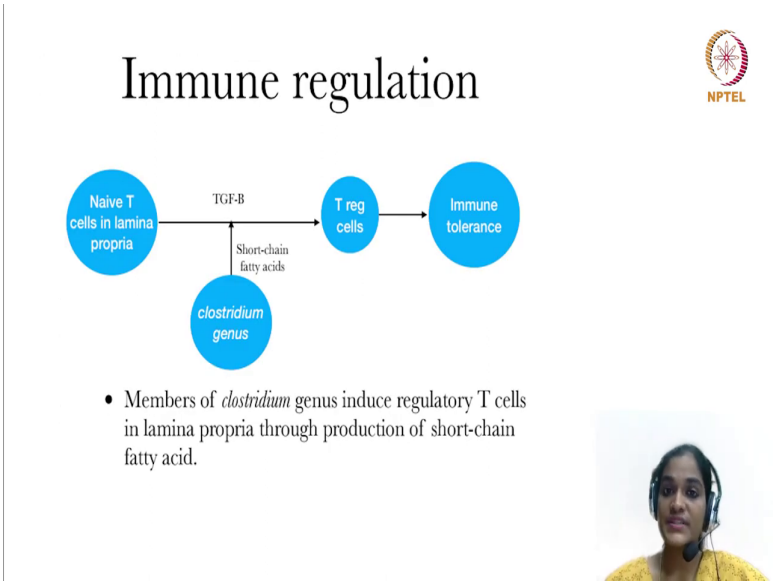

There is a particular contributory role which is shown by the intestinal microflora or mucosal microflora. These organisms, release the short fatty acid, which contributes to the conversion of naive T cell to a T regulatory cell ultimately leading to immune tolerance.

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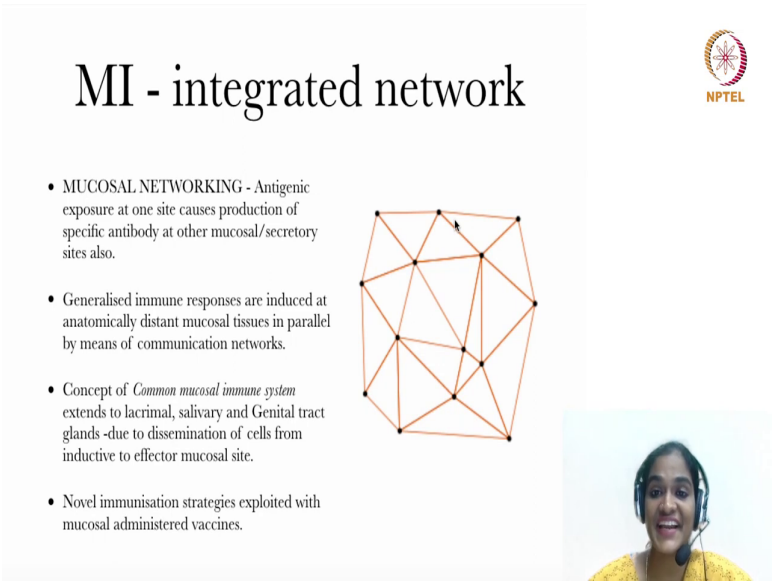

The mucosal immune system acts as an integrated network. When there is an antigenic exposure to one particular site of the mucosa, there is production of specific antibodies at the other mucosal or the secretary sites also. How is it? These generalised immune responses are brought about by means of communication networks.

The concept of a common mucosal immune system also extends to the exocrine glands like the lacrimal, salivary and a genital tract glands also. These are brought about with the help of dissemination of cells from the inducers site to the effector site. This is a particular novel immunisation strategy, which has been much exploited with mucosal administered vaccines.

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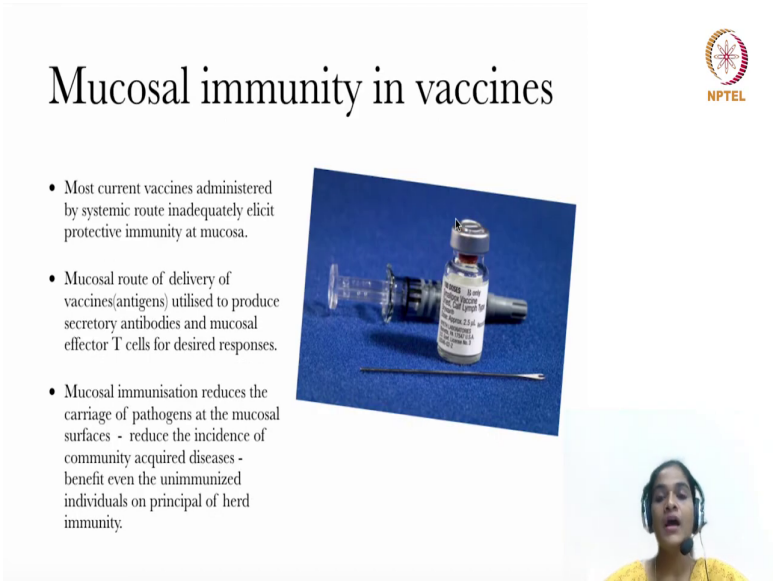

Most of the current vaccines which have been administered by systemic route do not adequately elicit the protective response from the mucosa. The mucosal route of delivery is being utilised to produce a secretory antibody and memory effector T cells for the desired responses. The mucosal immunisation reduces the carriage of pathogens at the mucosal surface. Thus they reduce the incidence of transfer of organisms in a communicable disease. Particular strategy is also being used by the principle of herd immunity.

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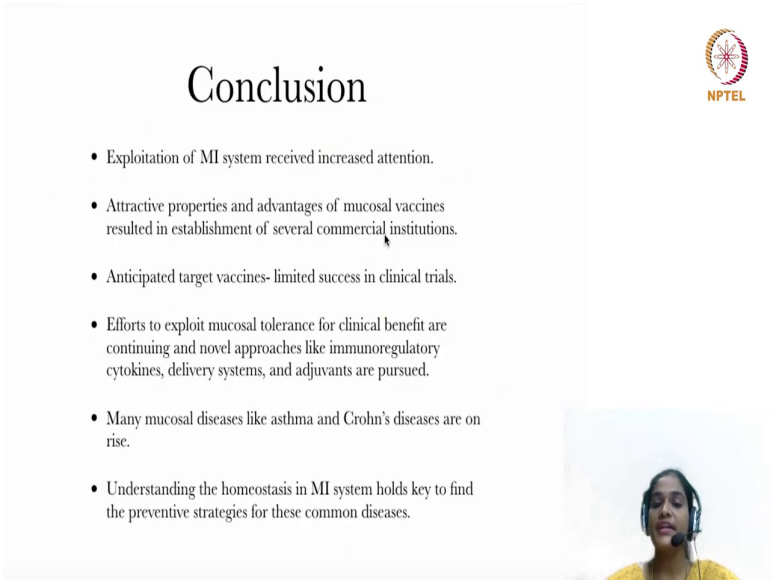

The exploitation of the mucosal immune system has received immense attention in recent years. The attractive properties and advantages of mucosal vaccines has resulted in establishment of several commercial institutions. Although the anticipated targeted vaccines have not achieved success in the clinical trials, various mucosal adjuvants are being tried as vehicles for the transport of mucosal immunity.

Efforts have been made to exploit the mucosal tolerance for clinical benefit. Novel approaches like immune regulatory cytokines, delivery systems and adjuvants are pursued. The many mucosal diseases like asthma and Crohn's disease are on rise. Understanding the homeostasis in the mucosal system holds the key to finding preventive strategies for these common diseases.

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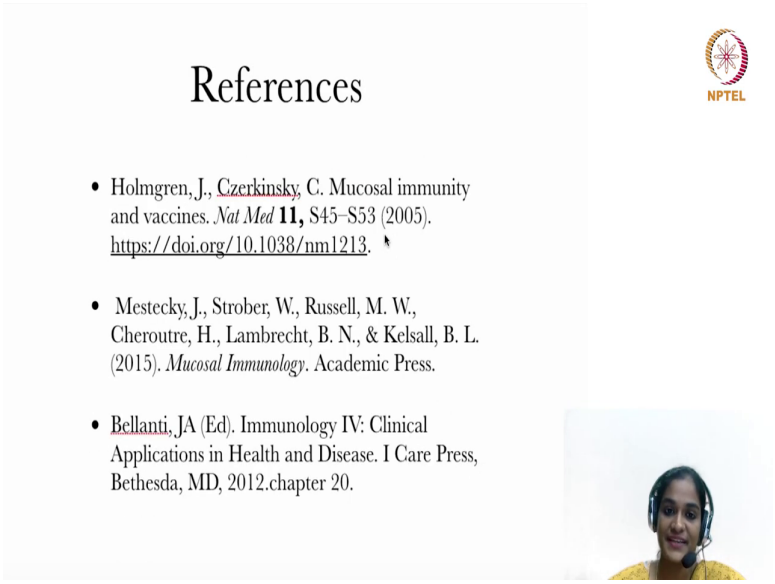

These are the references for further study.

Thank you.