

Oral immune system

Immunity is the sum of all naturally occurring defense mechanisms that protect humans from infectious and other disease. There are two types of resistance mechanisms: non-specific (innate) and specific (acquired). The body's immune system has several components, all of which are active in the oral cavity.

The soft and hard tissues of the oral cavity are under protection by both non-specific and specific immune factors. The function of these protective factors is to:

- 1- Limit the microbial colonization of the oral surfaces.
- 2- Prevent the penetration of noxious substances through the surfaces and ensuing damage to the underlying tissues.

Salivary glands secrete organic molecules that can be categorized into five major groups: amylase, mucins, phospho-proteins, glycoproteins, and immunoglobulins.

Non-specific immune factors

These are factors present in saliva that include lysozyme, the lactoperoxidase system, lactoferrin, high molecular weight glycoproteins and other salivary components that may act as bacterial agglutinins. Unlike antibodies, these non-specific factors lack any aspect of immunological memory and are not subject to specific stimulation. Several of the non-specific immune factors may interact with the specific salivary immune factors which are immunoglobulins, resulting in a mutual amplification of their respective activities.

Lysozyme (LZ): It comes from minor and major salivary glands, gingival crevicular fluid and salivary leukocytes. It is present in newborn babies at level

equal to those of adults and may exert antimicrobial function already before tooth emergence. It has the ability to hydrolyze the specific bonds in exposed bacterial cell walls causing cell lysis and death (muramidase activity). (LZ) has been proposed as a lytic factor for bacteria to which immunoglobulins have bound. (LZ) and other antibacterial systems in saliva exclude susceptible invading pathogens, which are not adapted to oral conditions. This may be the most important action of the salivary antibacterial systems. Lysozyme, as a strongly cationic protein, can activate bacterial autolysins, which can also destroy the cell walls.

Peroxidase system: Peroxidase in saliva is produced in acinar cells of parotid and submandibular glands but not in minor salivary glands. Peroxidase enzymes catalyze the reaction of bacterial metabolic product, hydrogen peroxide (H_2O_2) with salivary thiocyanate (SCN^-) originates from serum to produce hypothiocyanite ($OSCN^-$). This system protects human host protein and cells from hydrogen peroxide toxicity, it is highly toxic to bacterial enzymes required energy production and the bacterial activity is inhibited. The more hypothiocyanite present in saliva, the less can dental plaque produce acids after stimulation with glucose. Peroxidase systems are effective against a variety of microorganisms, such as *mutans streptococci*, *lactobacilli*, yeasts, many anaerobes and also some viruses.

Lactoferrin: It has antibacterial activity. LF is secreted by serous cells of major and minor salivary glands, also polymorphonuclear leukocytes are rich in LF. Ferric iron (Fe^{3+}) is an essential microbial nutrient. Lactoferrin is iron-binding glycoprotein making ferric iron unavailable for microbial use. This phenomenon is known as nutritional immunity. Lactoferrin in its unbound states has direct bactericidal effect on some microorganisms including *mutans streptococci*.

Mucins: They are salivary agglutinins of acinar cell origin and able to agglutinate bacteria. They are of high molecular weight and contain more than 40% carbohydrates. It inhibits the adhesion of bacterial cells to soft tissue surfaces by interacting with adhesins. Mucins also interact with hard tissue surfaces and mediate specific bacterial adhesion to the tooth surface.

Statherin: Although proteases of oral microflora are able to degrade statherin, it seems that concentrations of statherin remain high enough to exert its action as long as saliva remains in the mouth before swallowing. It is present in both submandibular and parotid saliva. The key activity is to prevent precipitation of calcium phosphate in ductal saliva and oral fluid to maintain supersaturation, to prevent the formation of ductal stones and calcium phosphate crystal growth on tooth surfaces. Statherin is also known to promote the adhesion of *Actinomyces viscosus* to tooth surfaces.

Prolin rich protein (PRPs) like statherin are needed to inhibit spontaneous precipitation of calcium phosphate salts in the salivary glands and their secretion. PRPs are readily adsorbed from saliva to hydroxyapatite surfaces and they are present in initially formed acquired enamel pellicle. The multifunctional properties of PRPs, like statherins, are shown by their ability to promote selectively the attachment of bacteria (*A. viscosus* and *Streptococcus gordonii*) to apatitic surfaces. The modulation of bacterial adhesion is mediated by the carboxy-terminal region of the molecule, which is not able to bind to tooth surfaces. They constitute as much as 25–30% of all proteins in saliva, form a complex group with a large number of genetic variants.

Histatins: They have a broad antimicrobial spectrum against bacteria as well as oral yeasts. The histatins are synthesized in the parotid and submandibular glands,

which means that they are practically always present in whole saliva. It modulates the precipitation of behavior of calcium phosphate.

Specific immune factors

These factors include immunoglobulins may be directed at specific bacterial molecules which may be important in the biological activity of the target organisms. The proportion of different Ig classes present in saliva are IgA > IgG > IgM > IgD > IgE.

Immunoglobulin IgA: Salivary IgA is produced by plasma cells located in the major and minor salivary glands. It is the predominant salivary immunoglobulin which under normal condition is the only immunoglobulin secreted in saliva. All exocrine gland secretions are rich in IgA. In individuals with gingivitis or periodontitis, the inflammation in the periodontal tissues will result in the transudation of serum proteins which include IgG, IgA, IgM and complement factors. IgA present in saliva differs from serum IgA with molecular structure. While serum IgA occurs mainly in the monomeric form, IgA in saliva composed of dimeric associated with J chain and secretory component (SC). This complex known as secretory IgA (S-IgA). The ability of secretory IgA to inhibit adherence of bacteria to dental enamel appears to be related to its ability to bind to surface adhesins of bacteria as well as to neutralize their negative surface charge. On the other hand, IgA has been shown to bind to mutans streptococci facilitating bacterial aggregation and removal from the oral cavity. Secretory IgA molecules are multivalent antibodies, and can prevent the adverse effects of bacterial toxins and enzymes. Secretory IgA initiates the inflammatory process. It prevents both bacteria and viruses from adhering to mucous membranes. IgA deficiency is the most common type of immunoglobulin deficiency and is seen in autoimmune diseases such as rheumatoid arthritis and lupus.

Immunoglobulin IgG: It is the predominant immunoglobulin in blood, lymph, peritoneal fluid and cerebrospinal fluid. It accounts for approximately 75% of the total serum immunoglobulins in normal adults and is the most abundant antibody produced during secondary humoral immune response in the blood. IgG is the only class of immunoglobulin that can cross the placenta in humans, and it is responsible for protection of the new born during the first months of life. The direct exposure of the tooth surfaces to gingival fluid, dental plaque may, in addition to salivary immunoglobulins, be exposed to significant amounts of serum immunoglobulins. It is therefore believed that serum IgG has the potential to modulate the oral colonization by plaque-forming bacteria, especially during tooth eruption. A significant proportion of the immunoglobulin molecules, particularly IgG, that become incorporated in dental plaque occur as fragments as a result of proteolytic degradation by enzymes excreted by plaque bacteria. Immunoglobulin G is effective against bacteria, viruses, and fungi.

Effects of IgA and IgG response in relations to protection of tooth surfaces:

- 1- Inhibition of bacterial adherence by:
 - a. Blockage of bacterial adhesins.
 - b. Bacterial agglutination
- 2- Inhibition of bacterial enzymes.
- 3- IgA has anti-inflammatory activity in gingiva, while IgG has the property of induction of inflammation in gingival tissues and opsonization of bacteria thus facilitating bacterial phagocytosis and killing.

Immunization of dental caries: Immunization is a process of exposing the host to an antigen in order to stimulate antibodies. Different types of antigen can be used

as the whole bacterial cells, glucosyltransferase enzyme, cell wall protein and others.

Different routes of immunization have been used to achieve caries immunity in animal studies:

- The classical parenteral route of immunization (subcutaneous) by selected antigen to stimulate serum IgG and to a lesser extent IgM and IgA. Immunoglobulins reach the oral cavity by transduction with crevicular fluid.
- Stimulation of S-IgA antibody response in saliva by repeated injection of salivary gland with antigen vaccine.
- Passive immunization with orally applied antibody.

Protection against dental caries by immunization would be achieved by immune components from serum by IgA antibodies in salivary secretions or by a combined effect of serum and salivary components.

Vaccination

Vaccines are immuno-biological substance designed to produce specific protection against a given disease. It stimulates the production of a protective antibody and other immune mechanisms. Vaccines are prepared from live organisms, inactivated or killed organisms, extracted cellular fractions, toxoids.

Two particular points have to be considered in relation to caries vaccine:

- 1- For developing a vaccine against any infectious disease, the responsible microorganisms must be identified. Lactobacilli were used as the immunogen in 1930s while after the redetection of streptococcus mutans in 1960, this bacterium became the target of all immunization experiment.
- 2- The identification of any antigen preparation that combines maximal immunogenic activity with minimal undesirable side effects.