

## ORAL IMMUNE RESPONSES

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**Abstract:** The oral mucosa is a part of the mucosal immune system, which cannot be dissociated from systemic immune defences. Over 75% of the immunocytes producing immunoglobulin are located in the digestive tract, primarily in the Peyer plates. An impressive number of “standardized” antigens transit the mouth cavity, some of them by means of the upper airway and others along the digestive tract.

**Cuvinte**

cheie: limfocite,  
imunoglobuline A, M, G,  
D, E, keratinocite,  
MG1, MG2

**Rezumat:** Există un sistem imun al mucoaselor, din care face parte și mucoasa orală. El nu poate fi disociat de apărarea imună sistemică. De remarcat că imunocitele producătoare de Ig în proporție de peste 75% se află la nivelul tubului digestiv, în principal la nivelul plăcilor Peyer. Prin cavitatea bucală tranzitează un număr impresionant de antigene „titrate” la acest nivel, unele luând căile aeriene superioare, altele tractul digestiv.

The existence of a local immunity was first observed by Besredka. Intercellular and molecular interactions that happen at the level of the general immune system were shown to occur locally, as well and exhibit several particular traits.(1)

At the level of the mucosa of the digestive tract (MALT, GALT), the density of the existing Ig-producing cells is:(3)

- IgA - 352,000/mm
- IgM - 51,000/mm
- IgG - 15000/mm<sup>3</sup>

The ratios of the immunocytes associated with major salivary glands in the synthesis of various classes of immunoglobulins are: IgM 6-8%, IgG 4-5%, IgD 2-3%.(4)

The lymphatic cells in the entire exocrine tissue amounts to 80% of the cells that produce immunoglobulins, especially IgA. Estimates are that 10 (10) of this specialized kind of cells exist in each meter of an adult’s gut (Brandtzaeg, Backlien 1976); however, their absolute number is difficult to establish, because the distribution of these cells is unequal in the various secretory tissues. Still, the highest amount of gland-associated IgA precursors is found at the level of the gut (Brandtzaeg, 1986). Including the similar cells found in the bone marrow, spleen and lymph nodes, the number of these cells is over 2.5 x 10.<sup>(10)</sup>

In adult tissues, there exist a variable number of cells which produce the immunity-important secretory IgM. Moreover, 3-5% of the immunocytes in the healthy bowel produce IgG. IgE- and IgD-producing cells are also relatively rare in the gastrointestinal mucosa; 2-10% of the immunocytes produce IgD and are found in the glandular tissue of the upper

respiratory tract, as well as at the level of the salivary glands, lacrimal glands and nasal mucosa

An important role in the humorally-mediated local immune defence is played by the secretory IgA producing cells

(5), at the level of the digestive tract mucosa, the tonsils, and the lymphoid formations of the Waldeyer circle. In the submucosa of the digestive tract, as well as in that of the tracheobronchial branch, one can find lymphocytes, either in clusters or as isolated free cells, originating in the blood circulation and being returned to the blood flow. The role of the latter is to make contact with the macrophages, dendritic cells, in order to receive antigenic information – thus, contributing efficiently to the local and systemic defence of the organism.

The single-layered epithelium of the mucosa represents a permanently-adapting vulnerable barrier, based on physical-chemical defence mechanisms, associated with other factors of local immunity as well. The mucosa is receptive to the aggression of bacteria, parasites, viruses, as well as to food antigens and to those in the environment

The first observations on the fact that the mucosa has its own immune humoral (secretory) system were published in the late twentieth century.(4) In 1965, Tomasi and collaborators described the molecular basics of the activity of the antibodies in exocrine secretions and they characterized IgA<sub>s</sub> as a dimer linked to an epithelial glycoprotein, called the secretory component: SC. Both dimers and polymers result from the synthesis of cells associated with the acini of the salivary ducts.(3)

The synthesis of the immunoglobulinic polymers (A, M) is dependent on the presence of a J polypeptidic chain and on the binding to a glycoprotein, i.e., to the secretory component (SC), deemed as the most important immunoglobulinic receptor (p.IgR).(3) It was conjectured that the J chain and the SC are in a lock-and-key complementary relation. The covalent chemical bonds of the polymers to SC IgA polymers to SC confer increased resistance to the processes of proteolytic decay in the oral fluids.

Quantitatively, the SC represents the most well-defined receptor of the immune system, in charge of the epithelial transport of the major immunohumoral component,

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p.IgA, and of the mucosal titration of immune complexes with p.IgA. The splitting of this receptor, in order to have the SC released into secretions, either free or bounded to immunoglobulinic polymers, is a unique process. Apparently, the excess of SC free in secretions establishes non-covalent bonds with IgM<sub>s</sub>.

The existing protein-sacrificing continuous traffic is motivated by the chemical stabilization of IgA polymers in secretions and it is the best defined (mucous) immune defence system, dependent on a fascinating local cooperation between epithelial cells and circulating B lymphocytes that arrive from various induction places. The molecular biology of the SC is very interesting and complex

In the mouth, immunity works in several stages:(6)

- a. Humoral immunity takes place outside the epithelium, in a liquid (suspension) environment;
  - b. At the epithelial and corium level, defence is evinced by the presence of Langerhans cells and of mastocytes, etc.
  - c. The defence mediated by the mobile cells being carried by blood
- a) There exist two fluid defence mediums: a serous one and a mucous one. As compared to the serous environment, the mucous one features a higher concentration of lactoferrin, lysozyme, peroxidases, as well as IgA<sub>s</sub>, or glycoproteins, in the form of mucins and small peptides (histatins) etc. Salivary glands are rooted in a specialized epithelium which contains cells that secrete antimicrobial substances. The secretion of salivary glands flushes the oral surfaces with up to one litre of saliva per day. The mucosa secretes glycoproteins-carrying mucins, which form a biofilm (pellicle) apt to protect the teeth and the mucosa against the action of various physical and chemical agents. The composition of mucin features two glycoproteins, MG1 and MG2, different in size and content, which play an important role in microbial adhesion. Purified, salivary MG1 forms complexes with amylase, histatins or with various proline-rich proteins. The main function of these two glycoproteins is to erect a barrier against carcinogens, toxins, and hydrolytic enzymes. The soft pellicle that coats the teeth is 1-2 μ thick and contains lipids, various proteins, lysozyme, IgA, reducing the surface tension. In the pellicle (biofilm), the outer layer is formed of MG1, while the inner one is made of MG2.
- b) One needs to mention here tissue resistance as well, such as the epithelial desquamation processes in the presence of leukocytes, Langerhans cells, mast cells and intraepithelial lymphocytes (IEL). The Lymphocytes (IEL) feature receptors (TCR-1) and are recognized as resident leukocytes, involved in homeostasis (3). There also exist a number of non-epithelial cells which produce antimicrobial factors, such as the lingual antimicrobial peptide, whose synthesis is ordered by the "smart cells", such as the lymphocytes and monocytes that release TNF-α and INF α. The keratinization of the epithelium results in the creation of a mechanical barrier. The epithelial keratinocytes function as a barrier, by secreting lipids in the intercellular spaces. The Langerhans cells and the mast cells of the epithelial structures yield important signals for the attraction and activation of specialized cells. On the outside, the hard tissue is active both chemically and physically, because the

same forces that give it strength, makes it reactive as well.

- c) In peripheral blood, approximately 10% of lymphocytes belong to the B series (line); as for the immunoglobulin receptors, 8% of them are IgM and 1.5% are IgG. About 15% of the total serum immunoglobulins are IgA, viz., IgA<sub>1</sub> și IgA<sub>2</sub> (2). The defense promoted by the moving cells from the blood flow is performed by means of PMN, monocytes, T and B lymphocytes, and NK cells.

Future research in this area may result in new insights into the active and passive immunization, as well as in the production of vaccines, immunomodulators

*Abbreviations: MALT – mucosa-associated lymphoid tissue, GALT – gut-associated lymphoid tissue, SC – secretory component, IEL – intraepithelial lymphocytes; TNF – tumoral necrosis factor; INF – interferon*

#### REFERENCES

1. Besredka A. Local Immunization, Williams&Wilkins Eds. Baltimore; 1927.
2. Brandtzaeg P. Two Types of IgA Immunocytes in Man, Nature New Biology. 1973;243:142-143.
3. Cristea V, Crișan M, Mițariu M. Imunologie generală și oro-facială - Ed. a 2-a, rev.-Cluj-Napoca: Editura Medicală Universitară "Iuliu Hațieganu"; 2011.
4. Mițariu M, Cernușcă M. Imunologie oro-facială, Ed. Univ. „Lucian Blaga” Sibiu; 2008.
5. Mestecky J. The Common Mucosal Immune System and Current Strategies for Induction of Immune Response in External Secretions, Journal of Clinical Immunology; 1987 July;7(4):265-76.
6. Mițariu M. Reacții ale mucoasei orale față de principalii factori iritativi – Teză de doctorat; 2009.