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REVIEW ARTICLE

THE ROLE OF MUCOSAL IMMUNITY: AN UPDATE

F. PREGLIASCO, A. GIANI, L. FONTE and S. SCHIEPPATI

Istituto di Virologia, Università degli Studi di Milano

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Abstract: There is considerable evidence that the mucosa associated lymphoid tissues (MALT) of the body play an active part in triggering off and conducting the immune system's response to both viral and bacterial pathogens. Effectors are capable of intercepting the micro-organisms and rendering them harmless before they penetrate through the mucous membranes, or of expelling and inactivating them after they have penetrated. The system is consequently useful both in the prevention of infection and in the humoral or cellulo-mediated immune response. These operations, whose principal protagonists are Immunoglobulins A and dendritic cells, are made possible by the high degree of functional interconnection which binds the effectors of the system and the anatomical structures located in the mucosae. The data provided in literature consequently infer that appropriate stimulation of mucosal immunity, which takes into account the new acquisitions in the field of immunology, can enable oral vaccination to overcome the obstacles encountered up till now in terms of insufficient protection against diseases.

Under conditions of integrity of the body's anatomical barriers, the only available pathway for access of the micro-organisms is represented by the mucosae.

That is why importance that should be placed on studying mucosal immunity in terms of: knowledge of the cells involved in controlling microbial attacks and in the response of the immune system, knowledge of the relations which bind the effector components to one another, and lastly, the incidental possibility of exploiting this type of immunity after appropriate and targeted stimulation as a weapon of prevention, with the purpose of strengthening the defensive action for which mucosal immunity already naturally exists.

The human body is anatomically organised in such a way that under physiological conditions it possesses a system of protection which compensates for the relative lesser resistance that the mucosae offer to the entry of micro-organisms as compared to intact skin; this lesser resistance is related to the functional characteristics of the mucosae, which must interact with the contents of the lumen that they line.

The presence of lymphoid structures, macroscopically observable in the most easily penetrated anatomical regions, such as Waldeyer's ring in the oropharyngeal region or Peyer's patches at the intestinal level, are examples of the need for defense in the most easily assailable mucosae. All inhaled air must be controlled and rid of any possible pathogens before reaching the pulmonary alveoli, and Waldeyer's ring does this. Peyer's patches have an even more extensive task; they create a barrier against the microorganisms which could easily invade the intestinal wall, because of the high permeability of the mucosae due to its function of absorbing nutrients introduced in food, and also of discriminating between pathogenic and commensal microorganisms (1).

Key words: mucosal immunity, oral vaccines, IgA, dendritic cells

Mailing address:
Dr. Fabrizio Pregliasco
Istituto di Virologia, Università degli Studi di Milano
Via Pascal, 38 - 20133 Milan, Italy
Tel: +390250315135 Fax: +390250315120
E-mail: Fabrizio.Pregliasco@unimi.it

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In addition, there are the observations from studies on the ontogenesis of the immune system which link the thymus gland, the main responsible organ for the development of a sufficient pool of lymphocytes to protect against diseases, with the MALT system (2): the explanation of this apparently derives from the fact that the palatine tonsil and the thymus develop, respectively, from the second and third pharyngeal pouch, which during the initial stages of development are joined (3) (Figure 1).

THE ROLE OF IGA

Several studies conducted for the purposes of explaining the efficiency and functioning of the mucosal immune system observed relationships which link the predisposition to develop a disease, or the presence of the latter, with changes in quantity of the immunity effectors or of the immunoglobulins.

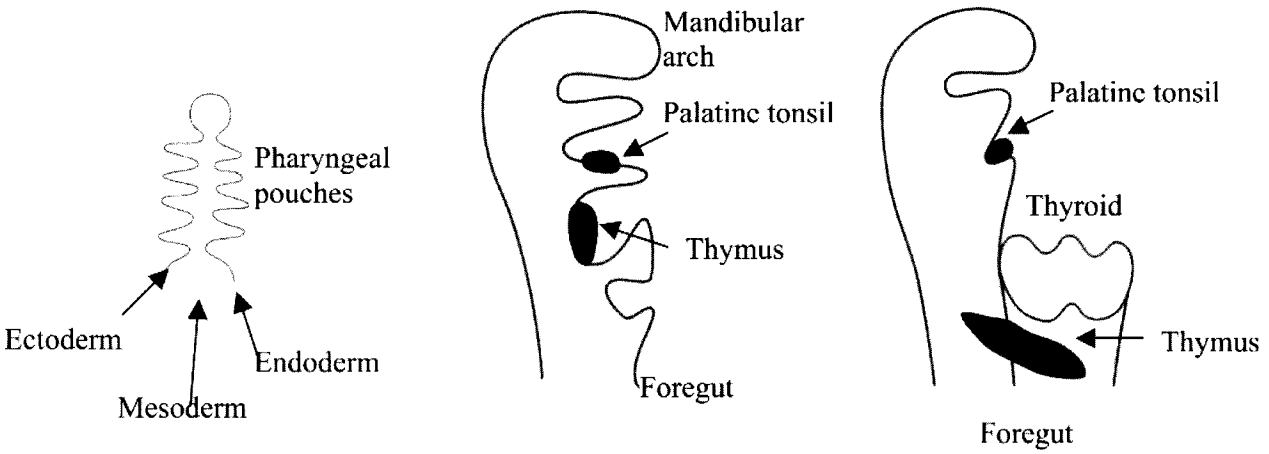
For example in the case of pulmonary diseases, it was observed that the presence of an increase in the rate of specific IgA for a given pathogen may indicate an infection in progress caused by the latter, moreover it provides a reasonably non-invasive method of assistance in diagnosis (4).

It has long been known that the salivary glands can be acknowledged as an integral part of the mucosal immune system (5): in fact, studies conducted in a population of young athletes in good, general state of health (6), and in a population particularly susceptible to respiratory infections, such as Down's syndrome subjects (7), different levels of secretory IgA detectable in the saliva (IgA specific and non-specific for the bacteria which cause the pathologies later observed) correlate in an inversely proportional manner to the number of respiratory infections. In both cases, reduced secretion of IgA in the mucosae proved to favor the higher incidence of respiratory pathologies.

Following these indications, it is possible to ascribe to the low level of IgA secretion the role of a predictive indicator in contracting a large number of infections of the tracheo-bronchial tree during the periods of the year in which these pathologies record a peak incidence. The measurement of the concentration of secretory IgA in the saliva can be considered as a reliable indication of the integrity of the mucosal immune system.(8)

Consequently, from the data shown, it appears evident that the mucosae cannot be thought of as playing a passive part in protecting the body: in fact, through the structures of the immune system , they are able, not only to produce mediators which are active against infections, but also to activate the humoral and cellulo-mediated immune response, involving all the cells of the system, from the macrophages to the T cells, B cells and Natural Killers, through the fundamental action of the dendritic cells (DC)(9). This offers the possibility of controlling

Fig. 1.



Development of the phatyngeal pouches.

both viral and bacterial micro-organisms, (10), which could lead to an infection not only localized at the site of contact but potentially capable of spreading throughout the entire body (11).

MALT SYSTEM

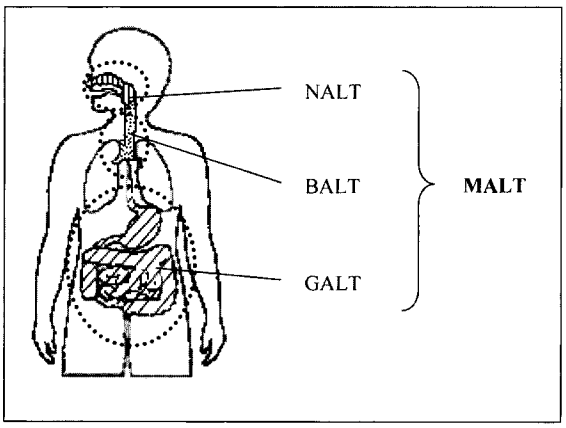
The fundamental role in this mechanism of defense is carried out by the tissues referred to as "mucosae associated lymphoid tissues" (MALT) which are located in the oropharyngeal mucosae (NALT), gastrointestinal mucosae (GALT), and bronchial mucosa (BALT) (Figure 2).

The importance of the system lies in the capacity of the different mucosal sites to interact and exchange information with one another: by stimulating one mucosal region it is possible to obtain a specific immunological response in all the mucosae, even the least accessible (12), though achieving a relatively lower degree of protection in the regions not directly involved by the stimulation. The cells of the immune system present at these levels trigger off the first steps of the start of the response in terms of capture of the micro-organisms, processing, transport and presentation of the antigens (13): whereas during the capture the leading role is carried out by the immunoglobulins, the second phase is taken over by the dendritic cells, which are the best antigen-presenting cells (APC) in our body (14).

THE SECRETORY IGA

Among the immunoglobulins, those involved in mucosal immunity to the greatest extent are the secretory IgA (15,16): their structural code is provided with a domain which, once it has acquired a three-dimensional form, enables them to pass through the epithelia and emerge on the surface, and they are represented in secretions, such as saliva, milk, urine and gastrointestinal fluids (17,18). In addition to binding themselves to the surface of the pathogens, opsonizing them, IgA specifically recognizes the micro-organism which not only eliminate it, but are also capable of facilitating the expulsion of the pathogen from the epithelial cells and from the subepithelial stroma (19). IgA also eliminate any toxins that may have been released by the pathogen itself, using the same excretion pathways as the free IgA. As soon as they are produced, IgA in a certain sense "go on duty" in the region that they have to protect, and consequently through bile and exocrine secretions of various kinds(20). In addition to these characteristics, IgA possess the ability to inactivate certain viruses even at mucosal level (21) thereby preventing them from attacking and subsequently penetrating through the mucosae.

Fig. 2.



Localization of the mucosa associated lymphatic tissues (MALT)

Since the mucosal immune system is a highly complex system and not devoid of mechanisms still to be clearly defined, a thorough investigation of the characteristics and interactions between what are currently considered to be its two most important components, namely DC and IgA, appears to be essential.

The IgAs, as mentioned previously, are found in the secretions of all mucosae even in physiological conditions, and following each immunogenic stimulus or each time a mucosa comes into contact with a new antigen the production of IgAs increases, thereby increasing the protection related to their action (22); in addition, subsequent stimulations improve the production capacity of immunoglobulins in terms of speed, due to the fact that the plasma cells which produce them retain in their memory the specific structure of each pathogenic micro-organism that they have previously been stimulated to respond to; this occurs both for the secretion of highly specific IgAs and for the production of non-specific IgAs, which permit rapid intervention in the event of an as yet unknown attack on the immune system (23) and consequently raising the level of defense on a general scale.

The specific IgAs appear to be able to prevent the entry of the pathogen into the tissues in that they are capable of canceling its capacity to penetrate the mucosae: by means of this mechanism it is possible to eliminate any risk of attack on the mucosal surface

and subsequent bacterial colonization of the organism (24).

For example, it has been observed that high concentrations of specific IgAs secreted into mothers' milk and then subsequently present during breastfeeding on the mucosae of the oropharyngeal tract of the baby can contribute towards reducing the incidence of pathologies such as infection caused by H.Influenzae in subjects who, due to the immaturity of their own immune system, are not entirely capable of independently producing sufficient defenses (25).

A further indication of the efficiency of secretor IgA was brought to light by studies conducted in subjects who, despite prolonged exposure, do not develop infections or, consequently, serious diseases such as HIV: in these cases, particularly high concentrations of specific secretor IgA were observed in the healthy partners of discordant couples (26). In addition to this role of defense and barrier outside the body, the secretor IgAs are the ones which most effectively bind the DCs, permitting the incorporation and subsequent processing of the pathogen (27). This enable us to understand what enormous power that mucosal immunity can have, and the potentials that appropriate stimulation can offer in the prevention of infectious events.

THE USE OF ORAL VACCINE

Although the idea of using oral vaccines was taken into consideration from as early as the end of the nineteenth century, unfortunately the insufficient knowledge of the processes which govern mucosal immunity, and the difficulties involved in antigen presentation by suitable procedures placed great obstacles in the way of the development of oral vaccines (28). The development of new know-how in the field of immunology and of new techniques for antigen presentation and immuno-stimulation, such as by administration of a polybacterial lysate obtained by mechanical lysis (PMBL polyvalent mechanical bacterial lysates) administered by the sublingual route, has today made it possible to develop new and more effective vaccines.

The aim of involving the entire MALT system, in the prevention of diseases, through the application of vaccines on the mucosale surface, will make it possible to achieve diffusion of the protection to all the mucosal regions (29). identical efficacy will not necessarily be obtained in each region and for each route of administration. In fact, it is necessary to bear in mind a number of important indications which came to light while proceeding in the attempt to optimize vaccine stimulation: there are some routes of administration which are more suitable than others (capable of transferring and involving a larger number of sites in the immune response), and the levels of stimulation that can be obtained are highest at the site of administration and in the lymph draining region (30).

The mucosal route, when appropriately used for preventive purposes, permits stimulation which is not restricted to the MALT in its different localization sites, but which is capable of also involving systemic immunity, inducing efficient response.

Parenterally administered vaccines, on the contrary, are not capable of providing coverage which extends to the mucosal surfaces, and very often present a lower degree of acceptability and compliance by the patient than those administered orally (31).

To obtain effective protection, currently, there are several general indications to be taken into consideration (28) without which there is a risk of invalidating the possible good results of preventive action. The antigen presentation must be carried out correctly, and the operation must be performed in the appropriate mucosal regions; the antigens presented must be effectively capable of producing an immune response; it is necessary to choose a therapeutic scheme capable of providing a sufficiently high immune response as well as long-lasting protection.

THE DETRITIC CELLS AS TARGET FOR IMPROVING IMMUNE REPONSE

The cells which intrinsically possess these capabilities of activating the immune system on several fronts are the previously mentioned dendritic cells. These cells, ubiquitous in the mucosae throughout the body, appear to be able to provide an adequate solution to the problem of stimulation. While on the one hand, the DCs are the best antigen-presenting cells and consequently represent the best way of creating memory in the B-cells, which are devoted to the production of immunoglobulins, and of activating the T-cells, on the other, the fact of being widespread throughout the mucosae makes them easily reachable in these sites, especially where the mucosal layer is finer due to the absence of the submucosal tunica as occurs in the sub-lingual region.

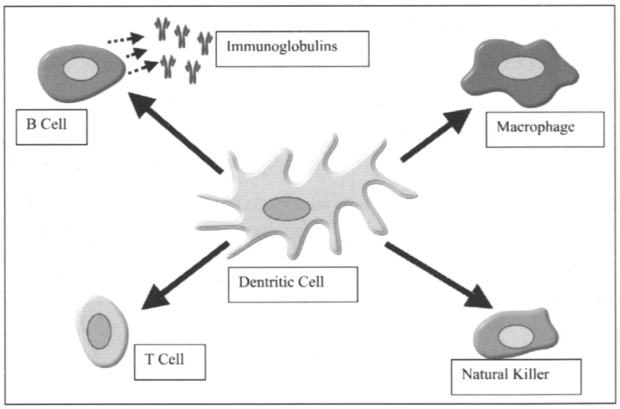
The current indications suggest that by inciting

these cells it may be possible to obviate the difficulties encountered so far in the stimulation of the mucosal immune system; attempts have been made in the past to remedy these difficulties by the administration of adjuvated vaccines ( ). The interactions that take place after the dendritic cells have been put into action are numerous and are capable of interrelating so closely that the actions of the two systems, humoral and cellular-mediated, which are triggered off by them cannot be considered separately from each other.

Upon contact with a vaccine capable of stimulating the dendritic cells, the latter are induced to maturation, that is to say, they acquire the capacity to migrate from their mucosal site, to which they are bound, so as to allow the maturation and activation of different cells, thanks also to the release of sufficient interleukin agents capable of facilitating the activation of the immune system ( ). This dual action, namely migration to the lymph nodes where the immature lymphocytes are located, and the release of interleukins, is as important as it is desirable, especially in those immunologically frail subjects, who are liable to have impaired system activation due to loss of the migratory capacity and increase of interleukins 10, as occurs in elderly subjects with frequent pathological disorders and in subjects under stress, which appears to be fundamental in rendering the action of the inefficient DCs and, in the final analysis, in reducing the body's defences (-36).

The cells affected by activation of the dendritic cells (T-cells, B-cells, macrophages, etc.) (Fig. 3) thereby enabling the systemic humoral immunity reaction and cell-mediated immunity reaction which

Fig. 3.



Cells activated by the dentritic cells.

thanks to the production of IgA capable, as previously mentioned, of crossing the epithelia and entering the mucosal secretions, are able to improve the levels of control of mucosal immunity (22).

The secreted IgA in turn are capable, as all immunoglobulins circulating in the body, of capturing and opsonizing the antigen, amplifying the antigenic signal addressed to the dendritic cells to which they bind through the FC signal present on the surface, thereby ideally closing the circle of a highly interconnected system.

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