From Peyer’s Patches to Tonsils
Specific Stimulation with Ribosomal Immunotherapy

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Summary

Ribosomal immunotherapy has been successfully used since the 1960s to boost the immune system and provide protection against microbial infections. We have investigated both whether and how these immunostimulants behave as natural immunogens in the mucosa-associated immune system.

According to current understanding of the physiology of the mucosal immune response, intestinal Peyer’s patches and the related solitary nodules are the primary inductive sites involved in the immune protection of all mucosal surfaces. Sensitised lymphocytes generated at these sites reach the general circulation through lymphatic drainage and relocate in mucosal areas by means of specialised ‘high endothelial venules’. We hypothesised that orally administered ribosomal preparations would yield sensitised B cells specific for bacterial antigens from the parent strains. These cells should then be detectable in the peripheral blood after ribosomal intake, and identifiable as plasma cells in mucosa-associated tissues after completing their terminal differentiation. Ultimately, specific IgA should appear in secretions.

To this end, we studied the immune responses generated in children and adults after ‘Ribomunyl’ administration, according to various consecutive protocols. The initial hypothesis was confirmed by the identification of specific B cells in the peripheral blood, plasma cells in the tonsillar tissue and specific IgA in the saliva. An animal model involving the use of twin sheep enabled detection of the specific cells in mesenteric and cervical lymph nodes. Analysis of these data indicates that ribosomal preparations trigger the production of lymphocytes specific for both ribosomes themselves and whole bacterial antigens. This supports the fact that small antigenic motifs are carried as partly synthesised peptides on the ribosomal particles. Therefore, ribosomes boost an array of B cells that are specific for many antigenic determinants of the bacteria from which they are extracted.

We were also able to show that the stimulation provided was specific, since no response to other bacteria could be detected. Finally, analysis of the kinetics of this stimulation confirmed that oral immunisation generates rapid and transient secretory responses, building increased numbers of memory cells that are readily available to respond to further challenges by either more ribosomal preparations or potential pathogens.
1. Mucosal Immune Response

The physiology of the mucosa-associated immune system has long been overlooked because of its usual silent and efficient functioning. Until recently, it was thought that secretory IgA and a large array of mysterious mucins and enzymes contributed to the efficient repulsion of potential environmental pathogens, allowing the maintenance of homostasia. Progress in the understanding of the functions of the mucosa-associated immune system has begun to disclose a much more sophisticated system, which perpetually implements dynamic and adaptive protection of all mucosae so that current environmental conditions are exquisitely matched.

Although several potential inductive sites have been described, the general consensus is that most external antigenic information is processed in the digestive tract, in the dedicated structures of Peyer’s patches and the solitary nodules. The resulting activation of B- and T-cell clones is followed by the migration of newly generated specific lymphocytes, through efferent lymphatics, to the peripheral blood flow. The presence of adhesion molecules on the surface of these activated cells allows their relocation in secondary lymphoid structures, mainly those of the mucosa-associated lymphoid system. Their relocation is also facilitated by the presence of specialised venules in those areas. Postcapillary venules with particularly well developed endothelial cells, also called high endothelial venules or HEV, express a complementary array of adhesion molecules that very efficiently trap the specific recirculating lymphocytes and allow them to reach the lamina propria of mucosa-associated lymphoid areas.

The fate of activated B cells thus relocated in mucosal areas is the best known: they achieve terminal differentiation into plasma cells and produce secretory immunoglobulins, mostly of the IgA isotype.

According to this schema, orally administered antigens should induce a specific sensitisation in Peyer’s patches, followed by the migration of activated cells through the lymph and peripheral blood and their relocation in mucosal areas. Therefore, successful oral immunisation should ultimately result in the production of specific IgA in secretions. These mechanisms have been demonstrated in a number of animal models and in several studies in humans, and contribute to the constant adaptation of the mucosal immune system to its environment.

2. Ribosomal Immunotherapy

It is known that ribosomes can induce specific immune responses, which efficiently prevent pathological infections upon challenge in immunised animals. Many initial studies were performed in animal models, often after intraperitoneal or intramuscular administration of ribosomal preparations; these studies demonstrated the ability of such preparations to trigger the production of specific humoral immune responses. The antibodies subsequently identified could recognise ribosomes, but, more importantly, also whole bacteria of the parental strain or even of the same species.

This cross-reactivity, potentially conferring cross-protection against other strains, was considered to be a significant property of ribosomal vaccines, and much research was devoted to trying to understand which part of the preparations yielded this interesting property. A role for messenger or transfer ribonucleic acid and for contaminating membrane fragments was considered, then ruled out.

Current hypotheses suggest that the native proteins carried by the ribosomes, which present as many small peptides protruding from a large carrier protein structure, could represent highly effective immunogens. Ribosomes should carry most of the components required for protection against the whole bacteria because they are prepared from growing biomass. Therefore, a large array of both intracellular and extracellular antigens should be present on such ribosomes. This hypothesis finds support both in studies demonstrating that ribosomal immunisation induces the appearance of species- and strain-specific antibodies, and in