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REVIEW ARTICLE

LYMPHOCYTES IN THE INTESTINE: ROLE AND DISTRIBUTION

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The human immune system is well adapted to cope with the wide variety of foreign antigens encountered throughout life. To date our understanding of immune mechanisms and of their failures, is far from complete. With the development of new techniques, knowledge is emerging which, while increasing our understanding, is also revealing the complexity of the immune system. This review will attempt to describe current knowledge regarding the cellular immune component of the intestine with a brief introduction to the general cellular immune system. Readers interested in an overall review of gut-associated lymphoid tissue may refer to the review by Kagnoff (1).

I. General characteristics of the cellular immune system (Table 1)

Lymphocytes comprise the main cells of the immune system and arise from stem cells in the bone marrow. There are two distinct types of lymphocytes: T-lymphocytes and B-lymphocytes, and characteristics of the lymphocytes are summarised in Table I. Bone marrow stem cells which will differentiate into T-lymphocytes, enter the thymus. Under the influence of the thymic micro-environment, these stem cells mature into immunologically competent T-lymphocytes which then enter the circulation and the peripheral lymphoid organs. B-lymphocytes on the other hand, develop in the liver of the foetus and the bone marrow. Like mature T-lymphocytes, mature B-lymphocytes leave the bone marrow and enter the circulation to populate peripheral lymphoid organs. Thus, the bone marrow, foetal liver, and thymus are central or primary lymphoid organs; peripheral or secondary lymphoid organs include lymph nodes, the spleen and mucosa-associated lymphoid tissue (i.e. gut-associated and bronchus-associated lymphoid tissue).

The development of mature T- and B-lymphocytes occurs in discrete steps not all

TABLE I – CHARACTERISTICS OF T AND B LYMPHOCYTES

	T lymphocytes	B lymphocytes
1. Development	Thymus	Bone marrow
2. Cell surface antigens (phenotype)	e.g. CD3	e.g. CD20
3. Antigen receptor	T cell receptor (TCR)	Surface Immunoglobulin
4. Functions	i) Regulatory T helpers (CD4) provide help to other cells.	Secrete Ig molecules which destroy antigen by opsonisation, antibody dependent cytotoxicity, etc.
	T suppressors (CD8) suppress the immune responses.	
	T contrasuppressors (CD8) provide help by suppressing immune suppressors.	
	ii) Effector T cytotoxic lymphocytes (CD8, CD4) cytolyse target cells.	

of which are clearly understood. Mature cells are recognised by the expression of cell-specific surface antigens. Thus mature T-lymphocytes bear the cell surface antigens CD3 and the T cell receptor (TCR), both of which are used in conjunction by T cells to recognise foreign antigens. The TCR is a heterodimeric molecule and in most mature T cells it consists of α- and β-chains. The expression of αβ TCR involves gene rearrangement processes which occur in the thymus. However, instead of the αβ heterodimer, T-lymphocytes may also express the τ/δ heterodimer mainly in the epidermis, thymus and spleen. The function of the τ/δ receptors is not clearly defined (for review see ref. 2).

Mature B-lymphocytes express many cell surface antigens, such as CD20 and antigen receptors which are actually membrane-bound immunoglobulin (Ig) molecules called surface Ig. When B-lymphocytes differentiate into plasma cells they secrete Ig of the same specificity as that of the surface Ig, although its isotype may not be the same, if a switch from its initial isotype to a new one has already been induced, for example from IgM to IgG.

The interaction between lymphocytes and antigens leads to cellular activation and proliferation, and finally, the generation of protective mechanisms. As mentioned earlier, cell surface antigens or receptors are needed for interaction with antigen. T-lymphocytes do not interact with soluble antigens but only with antigenic peptides presented on the surface of antigen presenting cells, such as macrophages and dendritic reticular cells. The interaction is complex and involves many cell surface antigens including CD3 and the T-cell receptor on T-lymphocytes, and foreign antigen in association with major histocompatibility complex (MHC) antigens on antigen presenting cells. On the basis of their interaction with MHC antigens T-lymphocytes can be divided into two main groups.

1. CD4 positive T-lymphocytes, which interact with antigen in association with major histocompatibility complex II (MHCII) antigens. Most of these T-lymphocytes are helper cells which provide help to other T-lymphocytes, B-lymphocytes, monocytes, etc, mainly by the release of soluble mediators or lymphokines, such as interleukins and interferons. T-lymphocytes bearing the CD4 marker can also be cytotoxic in some instances and can destroy cells bearing foreign MHCII antigens.
2. CD8 positive T-lymphocytes, which interact with antigen in association with MHC1 antigens. These are cytotoxic/suppressor cells having both effector and mediator functions. CD8 positive cytotoxic T-lymphocytes destroy intracellular pathogens by releasing chemicals that induce pore-formation on target cells such as those containing pathogens, which are thus lysed. CD8 positive suppressor T-lymphocytes can suppress the development of immunity, also by the release of inhibitory factors which are not yet well described.

Unlike T-lymphocytes, B-lymphocytes interact with soluble antigens with the help of surface immunoglobulins which specifically recognise antigens. B-lymphocytes are then activated and proliferate to give rise to clones of daughter B-lymphocytes which either generate memory B-lymphocytes or differentiate into Ig secreting plasma cells or both.

Although lymphocytes are central to the generation of an immune response, other cells are also essential. Antigen presenting cells are necessary to present antigenic peptides to T-lymphocytes. These cells can take up antigen, process it internally and express the processed antigen in association with MHC antigens; the complex is then recognised by T-lymphocytes. Cells capable of presenting antigen include macrophages, dendritic reticular cells, B-lymphocytes and also possibly MHCII positive intestinal epithelial cells (enterocytes). In addition to antigen presenting cells, natural killer (NK) cells and killer (K) cells provide important non-specific immune defence mechanisms. Both NK and K cells are cytotoxic cells.

II. The cellular immune system of the intestine

The induction of an immune response irrespective of location, relies on the effective uptake of antigen by the antigen presenting cells and its presentation to the lymphocytes via cellular interactions and generation of mediator and effector functions by lymphocytes. In the intestine the surface epithelium, Peyer's patches, the lamina propria and the mesenteric lymph nodes are all sites of immune activation. This section will describe the cellular immune component of each ana-

tomical site and then draw the information together to form a picture of intestinal immune functions.

Components of the surface epithelium of the intestine

The intestinal epithelium is the first barrier to antigens in the lumen of the gastrointestinal tract. Overlying Peyer's patches there is a specialised layer of cells called the follicle associated epithelium which contains specialised cells termed M cells. M cells were first described in humans by Owen and Jones in 1974 (3) and are the main cells involved in antigen transport across the surface epithelium of the intestine. M cells differ from adjacent columnar epithelial cells: they are (M cells) flat and have microfolds on their luminal surface, while the antiluminal surface is indented by underlying lymphocytes and macrophages allowing close contract between them. Structurally and functionally M cells are antigen transporting but not antigen presenting cells (for reviews see references 4,5). Not only do M cells transport antigens to lymphoid follicles, immunocompetent lymphocytes can traverse through gaps in the apical cytoplasm of M cells into the lumen where they may play an important protective role (6). Whether M cells function as antigen presenting cells is not known, although this appears to be unlikely as they do not express MHC II antigens, the possession of which is a prerequisite for antigen presenting cells, and they are not capable of efficiently processing ingested molecules (5).

Because of the tremendous antigenic load in the intestinal lumen and the limited number of M cells, the question of an alternative means of antigen entry has been raised. In particular, attention has been focused on intestinal surface epithelial cells (enterocytes) as these cells are situated between luminal antigens and mucosal lymphoid cells, they express MHC II antigens (7), and they possess enzymes that can break down proteins. MHC II molecules are constitutively expressed on fully differentiated enterocytes and this expression can be altered by changes in immunity (for a review see reference 8). The induction of MHC II antigens on epithelial surfaces appears to be dependent on interferon τ (IFNτ) secreted by intraepithelial lymphocytes (9,10). Mayer and Shlien (10) have shown that MHC II-positive enterocytes can function as antigen presenting cells: they can take up, process and present antigen to antigen specific T-lymphocytes, possibly of the cytotoxic/ suppressor phenotypes.

In addition to functioning as antigen presenting cells, it has been hypothesized that MHCII bearing enterocytes induce differentiation of intraepithelial lymphocytes, which in turn secrete IFNτ. An immunological link is thus established, as IFNτ induces MHCII expression on enterocytes (9) (Fig. 1).

The surface epithelium of the intestine contains up to 20% non-epithelial cells, mainly lymphocytes present over the basement membrane and between epithelial cells. These intraepithelial lymphocytes are a heterogeneous population of cells; most are medium sized lymphocytes rarely dividing *in situ* (11) and containing membrane-bound granules (for a review see reference 12).

Intraepithelial lymphocytes are mainly T lymphocytes of the cytotoxic/suppressor phenotype (7,13), expressing MHCI antigens (14). Recently, with the help of monoclonal antibodies, new antigens specific for intraepithelial lymphocytes have been identified (15). The restriction to these antigens on intraepithelial lymphocytes suggests one of two possibilities: these cells do not migrate and are restricted to the epithelium or these cells are in a specific stage of differentiation which occurs only in the epithelium (15). Further characterisation of these antigens is required to evaluate such assumptions.

Considerable interest has been generated in T lymphocytes which are present within intraepithelial lymphocytes as they bear the T cell receptor $\tau\delta$ (16,17). These cells appear to be different from $\tau\delta$ receptor positive T-lymphocytes present in other sites, suggesting that intraepithelial lymphocytes represent a distinct T-lymphocyte lineage (18).

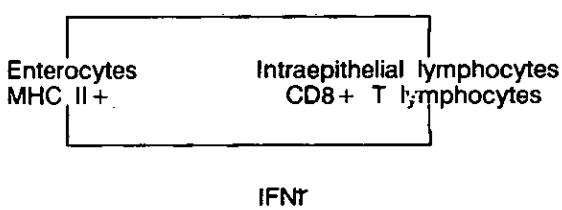

Fig. 1 – Interrelationship between MHC II+ enterocytes and intraepithelial lymphocytes.

The functional role of intraepithelial lymphocytes remains unclear. Experiments show that these cells in large numbers can suppress Ig secretion by B-lymphocytes (13). Lefrancois and Goodman (18) have shown the role of these cells in immunity against intestinal pathogens. They have shown that freshly isolated τ/δ positive intraepithelial lymphocytes from normal mice exhibit spontaneous cytolytic activity unlike similar cells from nude mice, which genetically do not possess a thymus and are raised in germ free conditions. However, when the nude mice are exposed to an environment similar to normal mice, their τ/δ positive intraepithelial lymphocytes also exhibit spontaneous cytolytic activity. In addition to suppressor and cytolytic functions, intraepithelial lymphocytes secrete τ interferon, as mentioned earlier, which can induce MHC II expression on enterocytes (9). Moreover, the distinct phenotype of intraepithelial lymphocytes suggests that they may possess the special property of homing to the intestinal epithelium (17).

Thus, the surface epithelium of the intestine not only constitutes a part of the epithelial barrier to antigens but can also transport and present antigens to underlying lymphocytes. In addition, mediator and effector functions of cell mediated immunity may well be exerted at this level.

Peyer's patches

A Peyer's patch is a non-capsulated collection of 10 to 60 lymphoid follicles and is present on the luminal surface of the small intestine. Like a lymph node, it is organised into follicular or B-lymphocyte areas and parafollicular or T-lymphocyte areas. One or two germinal centres are present only in secondary lymphoid follicles. It contains T-lymphocytes, B-lymphocytes, dendritic cells and macrophages, and is a crucial site of cellular interactions with antigens.

The majority (55%) of the lymphocytes in Peyer's patches are B-lymphocytes (21) and are both small, resting B-lymphocytes and large, activated B-lymphocytes (22). The activated B-lymphocytes are present in the germinal centres and have IgA (sIgA) on their surfaces (23). B-lymphocytes actively divide in germinal centres and generate both plasma cells and memory B-lymphocytes (24).

T-lymphocytes present in Peyer's patches are mainly of the helper phenotype, although some cytotoxic/suppressor cells are also present (20). These helper T-lymphocytes assist B-lymphocytes to secrete Ig; and the main Ig isotype in mucosal secretions is IgA. It is not clear whether IgA secretion is induced by B-lymphocytes precommitted to IgA which localise in Peyer's patches (25) or whether there are regulatory elements that preferentially switch B-lymphocytes to IgA secretion. The role of T-lymphocytes in regulating IgA responses in the intestine has been extensively, although not conclusively, studied. Single T-lymphocyte clones are known to provide help to B-lymphocytes to produce several Ig isotypes (26) and also, on the other hand, to provide help of a particular isotype (27). Thus helper T-lymphocytes in Peyer's patches may induce B-lymphocyte differentiation to begin IgA secretion in 2 ways: isotype specific T-helper lymphocytes may selectively act on surface IgA positive B-lymphocytes (27), or switch T-lymphocytes (Tsw) may act on B-lymphocytes of any isotype and cause a preferential switch to surface IgA (28). In addition to T-lymphocytes themselves, lymphokines including interleukins 5 and 6 (IL5 and IL6), secreted by T-lymphocytes provide B-lymphocytes with help (22,29).

In addition to T-helper lymphocytes, Peyer's patches contain T-cytotoxic/suppressor lymphocytes (30). These suppressor T-lymphocytes may have a role in the development of systemic unresponsiveness to orally given antigens as a result of their migration to other lymphoid organs. This phenomenon is usually known as oral tolerance (31,32). These T-lymphocytes can also suppress local IgA responses after oral protein antigens (20).

The presence of contrasuppressor T-lymphocytes (Tcs) has also been suggested in Peyer's patches. Contrasuppression (33) is mediated by soluble factors released by a unique T-lymphocyte subset which inhibit T-lymphocyte-induced suppression and thereby provide B-lymphocyte help. Contrasuppressor T-lymphocytes have not yet been characterised. Schoenbeck *et al.* (34) suggest that IL5 secreted by Peyer's patches T-lymphocytes mediate contrasuppression by enhancing local IgA secretion while suppressing systemic responses (35).

Besides lymphocytes, Peyer's patches also contain dendritic cells and macrophages (36).

Dendritic cells are MHC II positive stellate cells which can present antigen to T-lymphocytes. Antigen presentation by dentritic cells can be enhanced by macrophages when the latter are present in small numbers (19). It is unclear whether macrophages in Peyer's patches are capable of presenting antigens.

Peyer's patches are, therefore, sites of intense cellular interactions. Following antigen presentation by dentritic cells, T-lymphocytes help B-lymphocytes already committed to secrete IgA and induce isotype switching in surface IgA negative B-lymphocytes. Activated T-lymphocytes secrete interleukin 4 and interleukin 5 which act specifically on sIgA positive B-lymphocytes. Other regulatory T-lymphocytes such as suppressor and contra-suppressor cells may also be effective both locally and at distant sites.

Lamina propria

The lamina propria contains lymphocytes, macrophages, eosinophils, basophils and mast cells. Both T- and B-lymphocytes are present (21). Plasma cells are abundant, 80%-90% of which secrete dimeric secretory IgA and the rest secrete IgM (11). The remaining B-lymphocytes in the lamina propria are resting cells, most being sIgM positive although a few sIgA positive cells are also present.

Around 30% of the lymphocytes are T-lymphocytes (21) containing cytoplasmic granules. Most T-lymphocytes in the lamina propria are helper cells (37) and are more activated than T-lymphocytes present at other sites as they show spontaneous proliferation, contain IL2 receptor (IL2R) mRNA, express IL2R and MCHII antigens and show a higher proliferative response to IL2 (38,39). Cytotoxic and contrasuppressor T-lymphocytes are also present in the lamina propria (20,40,41).

The lamina propria is, therefore, rich in plasma cells which secrete mucosal antibodies. It also contains some cytotoxic T-lymphocytes effective against intestinal pathogens. Regulatory T-lymphocytes, helpers and contrasuppressors, presumably monitor immunoglobulin secretion of B-lymphocytes and induce cytotoxic activity of T-lymphocytes.

Table II summarises the distribution and functions of lymphocytes in the intestine.

III. Lymphocyte migration and homing

The migration of lymphocytes within the gut-associated lymphoid tissue has been studied by tracing radiolabelled Peyer's patches lymphocytes (42). Lymphocytes enter Peyer's patches from the circulation via post-capillary high endothelial venules and leave via the lymphatics. Following antigenic stimulation in Peyer's patches, lymphocytes (both T and B) enter mesenteric lymph nodes and spleen for further processing and eventually enter the thoracic duct and hence the peripheral cirulation. However, gut lymphocytes home back to the gut where they reside in the lamina propria and the epithelium (43). The mechanism of such selective migration or homing is not understood. Homing does not appear to be determined by antigens which merely cause accumulation and expansion of responding cells to the site of antigenic stimulation. Neither does the processing of antigens in spleen and mesenteric lymph nodes appear to be necessary for homing (12). However, on the basis of the finding that lymphocytes of Peyer's patches adhere better to the high endothelial venules (HEV) of Peyer's patches than those in other sites, and that B-lymphocytes preferentially home to Peyer's patches, Stevens *et al.* (44) have suggested that lymphocytes express surface receptors which recognise organ-specific endothellal cell determinants. In addition to receptors for HEV-specific determinants, lymphocytes may also acquire other specific markers after activation in Peyer's patches which determine their migratory pattern and in this context vasoactive intestinal peptides (VIP) present on T-lymphocytes may play a significant role (45).

In addition to homing back to the gut, gut lymphocytes migrate to extraintestinal secretory sites, such as the mammary glands, salivary glands, bronchial tissue and the female genital tract (fig. 2). Plasma cells in mammary glands have been found to secrete Ig (mainly secretory IgA) against gut bacteria, such as *Escherichia coli, Vibrio cholerae* and against some food antigens. Thus, the migration of primed gut lymphocytes to the mammary glands and their presence in breast-milk has particular significance in providing passive immunity to breast-fed infants (46).

TABLE II – DISTRIBUTION AND FUNCTIONS OF LYMPHOCYTES IN THE INTESTINE

Anatomical Site	Cell component	Functions
Surface epithelium	M cells	Antigen transport
	Enterocytes MHC II+	Antigen presentation; stimulation of suppressor T lymphocytes
	Intraepithelial lymphocytes	Secretion of T interferon. Cytolytic against intestinal pathogens.
Peyer's patches	B lymphocytes (mainly sIgA+)	Generation of memory B lymphocytes and plasma cells.
		Precommitted B lymphocytes destined for the lamina propria after traffic through mesenteric lymph nodes and spleen.
	T – lymphocytes	
	Mainly helper (CD4+)	Provide B lymphocyte help in some cases by inducing isotype switch. Secrete IL4, IL5.
	Some cytotoxic/ suppressor (CD8+)	Suppress both local and systemic B lymphocyte responses. Contrasuppression
Lamina propria	Plasma cells (80 – 90% IgA secreting).	IgA secretion in intestinal lumen
	B lymphocytes (mainly sIgM+)	IgM secretion in intestinal lumen
	T lymphocytes (CD8+)	
	Helper (CD4+)	Provide B lymphocyte help
	Cytotoxic/suppressor	Cytotoxic to intestinal pathogens. Contrasuppression

IV. Summary

Once a pathogen penetrates the surface epithelum, the process of immune activation begins. The pathogen is transported across the intestinal epithelium by M cells and presented to the underlying lymphocytes in Peyer's patches by MHCII positive enterocytes. At the same time, intraepithelial lymphocytes are activated and secrete interferon τ which increases the ability of enterocytes to present antigen. Simultaneously, intraepithelial lymphocytes may also cytolyse pathogens. In Peyer's patches, T – lymphocytes in parafollicular areas interact with antigen presenting cells and antigenic peptides to become activated. B – lymphocytes in follicular areas are also initially activated by the interaction of antigen and their surface Ig. B – lymphocyte activation is enhanced by helper T – lymphocytes so that B – lymphocytes begin to proliferate in germinal centres. Most B – lymphocytes at this stage are surface IgA positive whether induced by T – switch cells or by isotype specific T – lymphocytes. At the same time activated T – suppressor cells and contrasuppressors regulate the immune response to maintain it at an optim level. All these lymphocytes then leave Peyer's patches via blood vessels to mesenteric lymph nodes and the

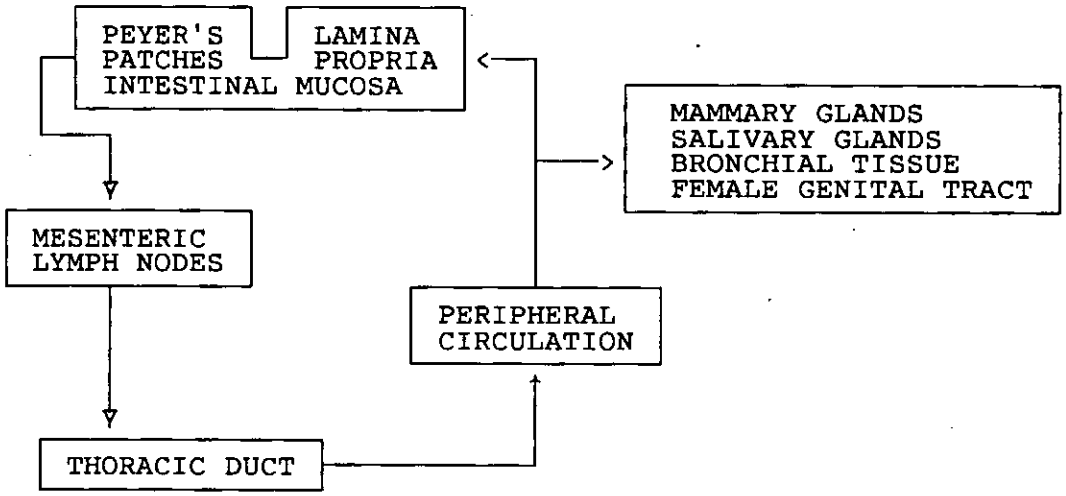

Fig. 2 – Schematic representation of lymphocyte traffic to extraintestinal sites.

spleen where further cellular activation occurs. Thereafter, activated lymphocytes return to the intestine either directly or via the peripheral circulation. Those that reach the intestine directly, differentiate into effector cells and enter the lamina propria. In the lamina propria, plasma cells and cytotoxic T-lymphocytes destroy pathogens by secreting specific Ig and by cytotoxicity respectively. Activated helper T-lymphocytes in the lamina propria probably help in local responses by acting on the few resting B-lymphocytes present there. T-suppressor lymphocytes enter the epithelium to become intraepithelial lymphocytes and regulate responses by suppressor and contrasuppressor activities. Intraepithelial lymphocytes are also cytotoxic for luminal pathogens.

Activated lymphocytes which do not return to the intestine directly enter the thoracic duct and thereby the general circulation. In this way a local gut response is converted into a systemic one and memory lymphocytes are disseminated throughout the body. In addition, suppressor and contrasuppressor T-lymphocytes also become available for peripheral effects. Large number of these lymphocytes remain in circulation, while others return to the intestine to provide local protection. A schematic representation of the traffic of lymphocytes is shown in Fig. 3.

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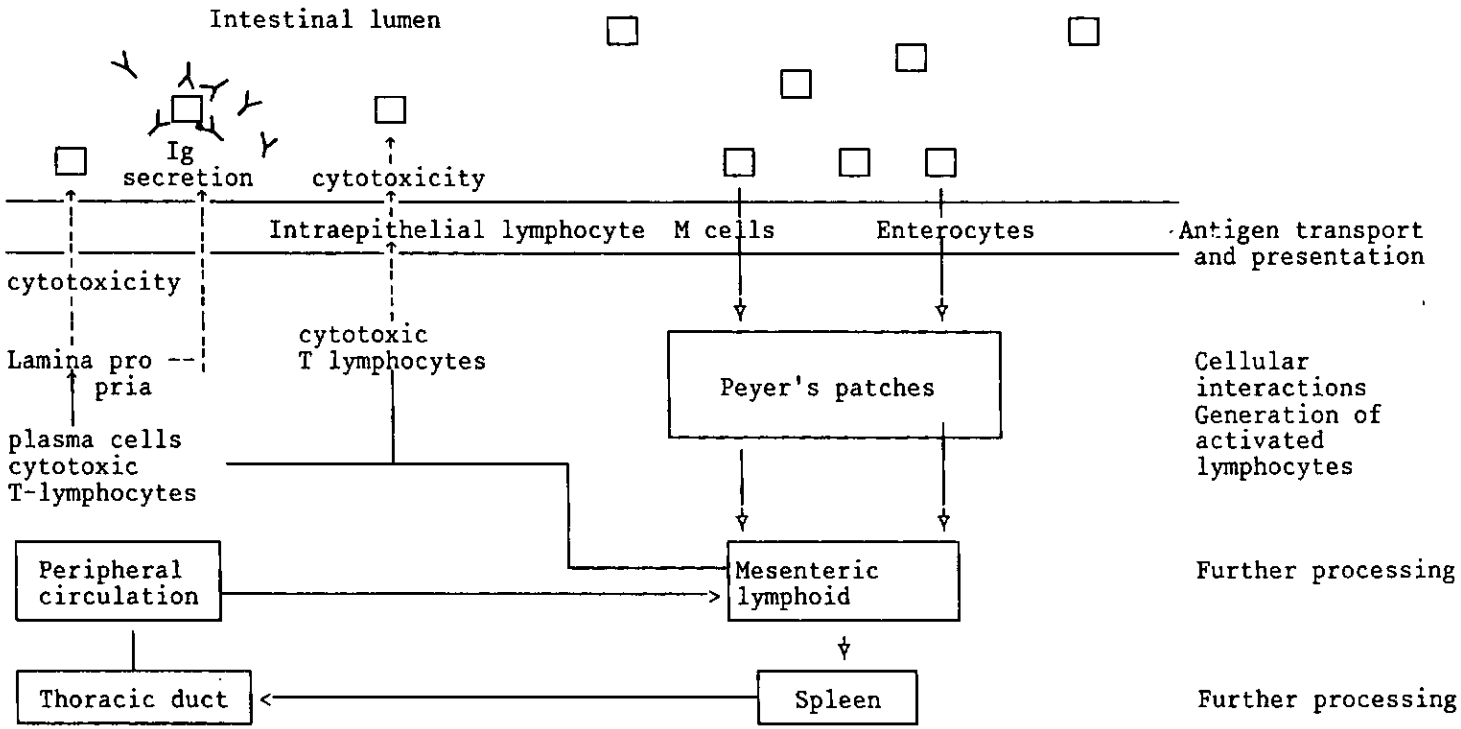

□ = Antigen; Y = Ig

dotted line = functional role.
solid line = anatomical site of processing.

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