

How the Lymphatic System works

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Until the past few years, the lymphatic circulation outside of the lymph nodes was considered a rather uninteresting and unimportant subject. This system, particularly in its most peripheral parts, was inaccessible, fragile and often invisible; therefore conjecture was often substituted for direct observation and experiment. New techniques for visualization and sampling have completely altered the picture. A whole new world of lymphology has been opened - with various subspecialities already developing. This brief account describes the main morphological features peculiar to the lymphatic system. These determine its permeabilities and, hence, much of its functioning. Since extensive reviews have already been published (3, 4, 5, 7, 13, 18, 19, 20), this article is intended more for the non-specialists.

It is generally agreed that the main functions of the lymphatic system are to pick up large molecules, particles and excess fluid, and to transport them from the periphery to the central lymphatics and the venous system. Accordingly, the lymph vessels have particular specializations in different areas in order to perform these two distinct functions: uptake and transport. Uptake occurs in small peripheral vessels, sometimes called "capillary", or "terminal", lymphatics (Since the expression "terminal" is a misnomer as regards the direction of flow of lymph, "capillary" sometimes leads to confusion, and "small" is not very explicit, the term "initial" lymphatics is preferable - 7).

Transport occurs in all lymph vessels, including the initial lymphatics, but it is the large ones which are specialized for this. The differences in function of each class of vessel are based on the differences in their structures.

Structure

The structures of the lymph vessels are very similar to those of the blood capillaries, venules and veins. Endothelium, connective tissue and muscular elements are present in their walls, in varying amounts depending on the sizes of the vessels. In fact, apart from thinner walls relative to their diameters, the collecting and great lymphatics are almost identical to their venous equivalents.

The initial lymphatics exhibit certain differences from the blood capillaries and post-capillary venules. The lymphatic endothelial intercellular junctions are much less firmly closed and frequently lack the distinct adhesion devices. These are common in blood capillaries and completely encircle the cells in some regions (1, 12, 17). Indeed, the intercellular junctions of initial lymphatics are often widely open in regions of the body where there is much motion, where mild injury has occurred, or where the intralymphatic pressure is elevated. These gaps may measure several micra and allow large molecules, particles, and cells to enter the vessels very readily. (Open junctions like these are seen in blood vessels only after injury-12).

The basement membranes of initial lymphatics are poorly developed compared with those of blood capillaries. At times they are not visible at all – especially in regions of the body where there is much movement. There are, however, many fine fibrils attached to the external surface of the endothelial cells, often at specialized regions. These pass into the surrounding connective tissues, and tie the vessels to the tissues (11). They are very important in oedema, since they pull the vessels open against the raised tissue pressures, thus preventing collapse and helping to open the junctions (6, 16). They also assist in opening the junctions during movements of the tissues caused by muscular contractions, etc. Two final features of the endothelium deserve mention. There are many small ($\sim 60\text{m}\mu$) vesicles, which transport material across the cell – probably under the influence of Brownian motion. Secondly, unlike some blood capillaries, no fenestrae have been described in lymphatics. The collecting lymph vessels have fewer and fewer open junctions, until the largest ones and the great lymphatics have none at all. These closed junctions more and more frequently have specialised adhesion devices. Their basement membranes become more prominent. (These give way to an elastic lamina in the largest vessels).

Permeability

The permeabilities of the vessels depend on their structures. The initial lymphatics in quiescent, uninjured regions have permeabilities very similar to those of blood capillaries and small venules. Thus small molecules are able to pass readily through their closed junctions – even if these do possess the adhesion devices (2, 8). It seems that the limit for this passage is reached at some 2–5,000 molecular weight; junctions which are fairly tightly closed, but lack one of the types of adhesion zones (*zonulae occludentes*), allow molecules of up to $\sim 40,000$ to pass (10). As with the blood capillaries, there is a slow passage of larger molecules (plasma proteins, etc.) through the walls of the vessels via the many small vesicles (3, 5, 9, 14). Some of them also remain in the endothelial cells when several of the small vesicles coalesce to form a large one, whose contents adhere. Phagocytosis is also seen. The structures of the collecting lymphatics mean that these have similar permeabilities to those of the initial lymphatics in quiescent regions.

The open junctions of initial lymphatics in active, or injured, regions account for their greatly increased permeabilities to large molecules, particles and cells. Some large molecules still pass via the small vesicles, but their numbers are far fewer than those which pass through the open junctions. It should be emphasized that junctions are usually open in regions where there is a greater than normal pressure difference between the tissues and the lumens of the lymphatics. Some large molecules are moved predominantly by the bulk flow of fluid, and only diffuse slowly (15). This pressure difference with its consequent flow of fluid is the main moving force for the large molecules, etc.

The reasons the junction open are many. They include the poor support given to the cells by the poor basement membrane and few adhesion devices. The flow of

fluid due to the increased pressure differences tends to push the cells apart; any large particles and cells will act as dilators. Finally, the fibrils attached to the cells make them move when the tissues move – especially if the tissues are swollen by oedema, when the cells tend to be dragged apart.

Functioning

It is easy to understand how material enters the initial lymphatics, especially since the factors tending to open the junctions are most pronounced just when there is much fluid or many large molecules needing to be picked up. (The accumulation of large molecules may well cause subclinical oedema, e. g. in active endocrine glands, leading to increased lymphatic uptake.) It is the retention of the contained material which is particularly interesting.

Compression of the tissues, by muscular contractions, respiratory movements, the pulse, etc., causes relaxation of the fibrils attached to the endothelium of the initial lymphatics. This allows the lymphatics to be pushed inwards by the raised tissue pressures, but at the same time it allows the endothelial cells to overlap each other more and their flaps to be pushed together against the resistance of the lymph. Thus, the previously open junctions will tend to be closed and allow only the small molecules to escape. Hence the lymph will be pushed onwards towards the collecting vessels, with minimal leakage back to the tissues. When the external pressures are released, the tissues will re-expand, dragging the lymphatics with them, and re-opening the junctions.

The closed junctions of the collecting vessels allow only the small molecules to pass outwards through the walls. Hence the large molecules of the lymph are retained, and are concentrated as some of the small ones are pushed through the junctions by the hydrostatic pressure – especially when it is raised by the contractions of the muscles in the vessel walls. There is, however, some loss of the large molecules when they pass through the cells via the small vesicles, or remain in them in large ones. This retention is often seen in the lymph nodes.

The above considerations show why large, preferably rather adherent, radio-active molecules should be used for intra-lymphatic therapy – to promote retention by the lymph nodes when treating secondary deposits of neoplasms. They also show why the molecules of intra-lymphatically injected contrast material for lymphography must not be too small – not less than $\sim 2,000$. Again, for indirect lymphography, the molecules must not be too big if they are to be efficiently carried into the lymphatics by the flow of fluid – not much larger than $\sim 10,000$. In addition one can see why the intermittent pressure of massage, or muscular activity, is so necessary to ensure good lymphatic uptake from the connective tissue.

It is apparent that the lymphatic system is both open and closed; thus both sides in that ancient argument were correct. In fact, the whole of the process of lymphatic permeability may be expressed in the form of an aphorism:

Material enters the lymphatic system because of the open junctions: it remains in the system because of the closed ones.

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Studies of the Physiology of Lymphatic Vessel by Microcirculation Methods*

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The study of the lymphatic system is difficult because of the tenuity of its vessels and of the transparency of lymph. MASCAGNI (6) and CRUIKSHANK (2) described the lymphatic collectors within the 18th century, although the knowledge of most peripheral lymphatics remained indefinite. Lymphography, developed by KINMONTH (4), initiated a renewed interest in the lymphatic system. Unfortunately, even though the lymph collectors and lymph nodes are thus shown, the peripheral channels are not demonstrated. In addition, the visceral lymphatics remain inaccessible with this technique.

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