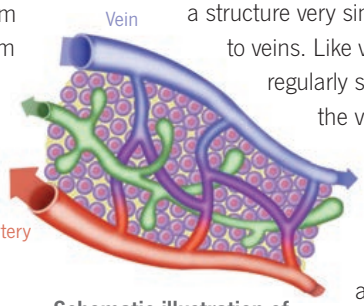
Studying inflammation-induced lymphatic dysfunction to better understand lymphedema

How inflammation contributes to depravation of lymphatic pumping

By Dr. Pierre-Yves von der Weid

The lymphatic system, with its dense network of lymphatic vessels and numerous lymph nodes, is an important player in the maintenance of critical bodily functions. It maintains the fluid content in our tissues and organs to a sustainable level and provides the supporting structure for our immune system to protect the body. In fact, it is through lymphatic vessels that fluid, known as lymph, is drained from tissues back to our blood stream and it is through the same vessels that foreign substances are transported to the lymph nodes, where they are detected and acted upon. It is intriguing to note that through these two functions, the lymphatic system is intimately associated with inflammation, the reaction of our body to infections or wounds characterized by swelling, fiver, redness and pain.

Over the last 15 years, our laboratory has been investigating the basis of the mechanisms driving lymphatic contractile function and lymph drainage and working to improve our understanding of the relationship between the lymphatic system and inflammation, as well as the importance of the lymphatic system in inflammatory diseases.



Schematic illustration of the initial lymphatic vessels.

How is lymph transported through the body?

Fluid that naturally accumulates in every tissue and organ is normally collected by initial lymphatic vessels. Through these finger-like structures, lymph then flows towards collecting lymphatic vessels, which are much larger. These collectors as we call them have muscle cells in their wall, which confer them a structure very similar, but more delicate, to veins. Like veins, they also possess regularly spaced valves. But unlike the veins, lymphatic collectors have the unique ability to contract and relax in a rhythmical fashion to allow the lymph to be actively propelled away in the direction of the valves. This contraction-relaxation cycle we call lymphatic pumping , occurs at frequencies defined by a combination of physical and chemical factors. The major regulator of lymphatic pumping is the volume of lymph to be drained; the more lymph, the faster the pumping. Many chemical mediators have also been shown to modulate this activity. Lymphatic pumping is the main— and in some parts of the body— the only means to move lymph. However, while some molecular elements and mechanisms have been teased out, we still have a very limited understanding of what drives this activity. Our studies revealed the importance of molecules released by neighbouring cells in modulated pumping. We determined their mechanisms of action and implicated the molecules, such as ion channels, that were expressed at the surface of the lymphatic muscle cells in the pumping initiation.

What goes wrong in lymphedema?

Lymphedema is a chronic tissue swelling, which occurs when the ability of the lymphatic vessels to drain lymph is exceeded. Lymphedema can be inherited and more commonly occurs as a complication of lymph node resection and radiation for cancer treatment, affecting more than 5 million people in North America. People afflicted by lymphedema suffer from pain, reduced quality of life, and severe soft tissue infections requiring significant medical care.

Although lymphedema has multiple potential causes, an impairment of lymph drainage is always the precipitating factor. The ensuing lymph stasis and tissue swelling is typically accompanied by inflammation, tissue fibrosis and accumulation of fat which develops over time. Intriguingly, these features are also observed in chronic inflammatory diseases such as ulcerative colitis, Crohn's disease, atherosclerosis or arthritis which, like lymphedema, have no cure.

We do not know much about the status of the lymphatic pumping and lymph drainage in these diseases' inflamed tissues. As a general hypothesis, we proposed several years ago that inflammation, fat deposition

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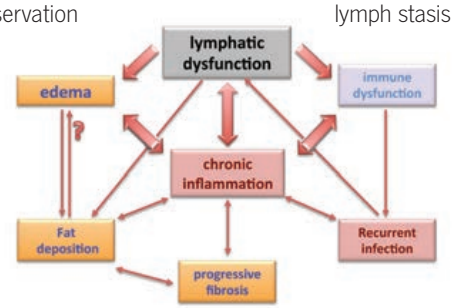
and lymphatic dysfunction/lymph stasis occur as a consequence of each other in a vicious circle manner, each phenomenon exacerbating the others further.

Is lymphatic pumping compromised during inflammation?

When efficiently tuned, lymphatic pumping avoids swelling and, because lymph also transports antigens and immune cells, promotes an adequate immune response. However, whether this holds true during inflammation was not known until it was demonstrated in the last few years that mediators, abundantly produced during inflammation, were able to alter lymphatic pumping. Most of them cause the frequency of the contractions to slow down, which suggests that lymph flow also slows down, potentially triggering swelling.

The decrease in lymphatic pumping in response to inflammatory mediators is an indication that drainage might be compromised during inflammation. To more directly assess the effect of inflammation on lymphatic function, we examined pumping in lymphatic vessels isolated from animal models of intestinal inflammation. Again, we observed that lymphatic pumping was altered and that some chemical mediators, such as nitric oxide and prostaglandins, demonstrated in earlier studies to affect pumping, were indeed responsible for the dysfunction. Further experimental examinations revealed that other molecules, namely cytokines, such as TNF-α and IL-1β—critical in the initial steps of an inflammatory reaction—play an important role in mediating the lymphatic dysfunction. Our findings led to the conclusion that during inflammation molecules present in the environment of the lymphatic vessels, or produced by lymphatic vessel cells, caused an inhibition of lymphatic pumping. Given the role of pumping in lymph drainage, inhibition of this activity may lead to retention of fluid in the tissue and edema/swelling.

These studies are based on animal models of acute inflammation. In this situation, the problem is controlled and inflammation quickly settles. However in the many diseases mentioned above, inflammation is not resolved and becomes chronic. Whether and how the lymphatic system is affected during chronic inflammation has not been looked at. To address these questions, we are currently examining the lymphatic system in a mouse model of Crohn's disease. Our initial findings reveal that lymphatic vessels draining the inflamed gut are larger than usual, just as we had observed during acute inflammation. This observation suggests that, like in acute inflammation, lymphatic drainage is also altered during chronic inflammation.



The lymphatic system is further implicated in inflammatory diseases. In particular, inflammation leads to the growth of new lymphatic vessels in inflamed areas, even in some usually devoid of lymphatics. The importance of this feature called inflammation-induced lymphangiogenesis in the inflammatory process is under debate as well as to whether these new lymphatic vessels promote the resolution of inflammation or help perpetuate it to a chronic state.

Does impaired lymph drainage promote inflammation?

Although a dysfunctional lymphatic system is central to the development of lymphedema, whether this dysfunction is a contributing factor to the other changes, such as inflammation, fibrosis and fat accumulation seen in this condition, is not known. In line with our hypothesis that each of these features might worsen the others in a vicious circle manner, the possibility that impaired lymph drainage causes inflammation definitively exists. Indeed, other researchers refined our initial hypothesis, proposing that in lymphedema, lymph stasis, caused by initial impaired lymph drainage, leads to inflammation, fat accumulation and fibrosis, which further exacerbate the lymphatic dysfunction. This hypothesis has since been successfully tested experimentally. Specifically, the researchers used the mouse-tail model, where the tail of the animal was surgically processed to cause an edema, mimicking lymphedema and demonstrating that lymph stasis results in significant deposition of subcutaneous fat, increased fibrosis in this fat and occurrence of inflammation. These pathologic findings mimic very closely the changes observed in clinical lymphedema and make the mouse-tail model a valid animal model of human lymphedema. These observations are very important, because the research community is in dire need of animal models that recapitulate this condition. This model is now used to help understand the molecular mechanisms that regulate the pathophysiology of lymphedema.

Future perspectives

Research on the lymphatic system has been neglected for many years. New techniques and new molecular markers allow a more thorough identification of lymphatic structures. The landscape is rapidly changing and we are now getting a better appreciation for the important roles and functions this system is playing in human physiology and diseases. This renewed interest is leading many more researchers to enthusiastically investigate the lymphatic system and related diseases such as lymphedema. Progress is being made and our understanding of this system is growing, leading to the reasonable expectation that treatments alleviating the outcome of lymphedema will be developed. LP

A comprehensive set of references can be found at www.lymphedemapathways.ca.

Dianne and Irving Kipnes Lymphedema Imaging Suite.