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Review

Lymphatic Disease in Cardiology: The Forgettable One

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ABSTRACT

Before molecular medicine era, the lymphatic system was not getting enough attention in medicine world, especially in cardiovascular medicine. Our knowledge about lymphatic system is far left behind compare to vascular system. Many believes lymphatic function is isolated in regulate interstitial fluid hemostasis, fat transport, and immune transport. In deep investigation in lymphatic function shows that alteration in lymphatic vessel could disrupt normal cardiovascular function. Moreover, optimal cardiac lymphatic condition after post-heart tissue injury could enhance tissue regeneration. That is why in modern medicine era preserving optimal lymphatic condition and treat abnormal lymphatic condition might be beneficial in cardiovascular medicine.

Introduction

The lymphatic system is still a mystery box in the modern medicine world. Even it has fundamental relation with other diseases such as cardiovascular, infection, immunology, metabolic, and cancer, many practitioners presume it clinically insignificant [1]. There are several major functions of lymphatic system like immune transport, tissue fluid hemostasis, and absorption of dietary lipid.[2] Together with blood vascular system, the lymphatic vasculatures found in most of the vascularized tissues and complement the blood vessel. However, they both quite different in morphology and function.[3] Beside lack of interest, the lymphatic system is a transparent vessel that make it difficult to observe [1,2].

Discussion

a. Lymphatic Endothelial Cells (LEC)

Lymphatic vessels are unidirectional flow and compose of a single layer of endothelial cell. Ultra-structure morphology of LEC is slightly different compare to the endothelial cell in the blood vessels; more thin, irregular and wider [4]. Unique LEC configuration, overlapping flaps LEC adherence with each other with intercellular junctions in their base and make button-like structure, permits interstitial fluid, macromolecule, and cell enter the lumen more easily [2,4]. The tight junction of the LEC is rich with protein and vascular endothelial cadherin [2]. However lymphatic vessel is very dependent with their extracellular matrix (ECM) to prevent collapse of the vessel and lymphangiogenesis [4]. The lymphatic vessels connect with ECM with anchoring filaments that can

make lymphatic valves in button-like structure to open during high interstitial pressure. The intraluminal lymphatic pressure is rising as fluid move from interstitial into lymphatic vessel and closing the junction to prevent retrograde flow.

In term of lymhangiogenesis, LEC express vascular endothelial growth factors receptor-3 (VEGFR-3) to interact with VEGF family, especially VEGF-C and VEGF-D. Activation of VEGFR-3 induces signaling process for embryogenic lymphatic system, lymphatic regeneration in the adult, and lymphagiogenesis. Besides VEGFR-3, VEGF-C also binds to nonkinase receptor neuropilin-2 (NRP2). Recent animal-lab study shows that NRP2 deficiency correlate with disruption of lymphatic capillaries development [4]. Other vascular growth factor which expressed by LEC is angioprotein-2 (Ang2). Ang2 contributes in lymphangiogenesis and lymphatic maturation [5]. Deficiency of Ang2 in mouse model shows severe lymphedema [4]. Other gene that contributes in lymphaneogenesis and LEC maturation are CCBE1, PTPN14, FOXC2, SOX18 [2].

b. Lymphatic System

Tissue fluid homeostasis

The lymphatic vessels act as unidirectional collector of interstitial fluid, protein, and cells. Those exudates come out from blood vessels because of the osmotic pressure. Special morphology of LEC make it more permeable to macro-molecules but 100-500 more slow in efflux rate from ECM to lymphatic vessels compare with the blood vessels [6]. Lymphatic vessels have integral function with ECM in regulate fluid equilibrium. From previous study shows that as much as 3 L human plasma volume extravasation from arterioles and reabsorb by venules and lymphatic vessel, but mostly lymphatic [2]. Exception in some organ with specialized cell and function like kidney and intestine.

Any disturbance to lymphatic function and mechanical integrity of ECM results pathological fluid accumulation, edema, and/ or fibrosis [6]. Animal model shows that lymphatic defect in neonatal period can make severe embryonic edema and lethality, while if they survive until neonatal period, pulmonary edema is the most concerning condition. In adult, lymphatic system disruption will cause cardinal manifestation lymphedema. The absence of systemic lymphatic system seems to be incompatible with life [2].

Many latest studies argue that lymphatic vessels do not act simply as passive transport but as active transport. The active transport feature provided with valves to prevent back flow and smooth muscle to against net pressure gradient [2,7]. Segment between two valves is called a lymphagion and it is a functional contractile unit in lymphatic system. Perilymph structure, muscle, also contributes in propelling lymphatic content forward. The lymphatic vasculature all across body plays key point in maintain fluid balance which important to regulate cardiac output, especially in pathologic heart condition [8].

Fat absorption

Dietary lipid with long-chain triglycerides is absorbed by multiple steps. Right after rich-fat food reach intestinal lumen, it will be hydrolyzed by enzymatic process become fatty acid and monoglycerides. The hydrolyzed products mixed with bile salts called micelles and enter mucosal enterocytes. After it crosses mucosal enterocytes, they are re-forming triglycerides with help from endoplasmic reticulum enzyme and called chylomicrons and enter lymphatic system. Chylomicrons deliver cholesterol to the liver through blood stream. Lymphatic dysfunction causes

pathologic fat accumulation along blood vessels [3]. Many pathological studies shows that systemic lymphedema not only consist just fluid alone, but also fat accumulation [1]. Disturbance of fat absorption function of lymphatic vessels correlates with atherosclerosis [9].

Immunology system

Lymphatic vessel is like a long pipe route for immune cells to travel across entire body. Together with macro-molecule and other cell, immune travels in lymphatic vessel with lower flow rate and shear stress compare with blood vessel. Lymph node (LN) in lymphatic vessel serve as pit stop for immune cell to temporary stop and proliferate [6]. Cellular studies shows that movement of leukocytes and antigen presenting cell (APC) from tissue to lymphatic vessel controlled by lymphoid homing chemokines, especially CCL21 and CCL19. Those chemokines attract immune cells which express receptor C-C chemokine receptor type 7 (CCR7) and C-C chemokine receptor type 11 (CCRL1) and it enters the lymphatic system with help from LEC's adhesion molecule, intercellular adhesion molecule-1 [2]. Dendritic Cell (DC) also enter the lymphatic system through attachment of phexin-A1/neutropilin-1 receptor complex and semaphoring-3A. Recent study also reveals LN LEC itself also contribute in tolerogenic antigen-presenting cell correlate with autoimmunity through major histocompatibility complex (MHC) class I, class II, and coinhibitory receptor programmed death-ligand 1(PD-L1) [2]. Meanwhile, lack of immunoregulator effects post-cardiac injury in regenerative process [10].

c. Lymphatic Dysfunction and Cardiology

In animal model study shows that alteration of lymphatic function, especially in fat transport and absorption could lead to obesity, metabolic syndrome and eventually end up with cardiovascular disease [3]. Mice with abnormal lymphatic fat transport has abnormal fat accumulation which characterize with chylous ascites (milky fluid consist of cholesterol, phospholipids, triglycerides and apolipoproteins), intra-abdominal/visceral adipose tissue (VAT) and sub-cutaneous adipose tissue (SAT) fat accumulation [3].

Recent study involve 1.106 participant shows that accumulation of SAT and VAT has greatest positive correlation with cardiometabolic risk profile, even more risky beyond generalized adiposity and central adiposity [11-13]. VAT, as an endocrine organ, stimulates hypertrophy of existing adipocyte tissue through maturation cell from pre-adipocyte cell into adipocyte cell and also increase accumulation of macrophage cell. As an active endocrine organ, it is secreting several hormones for nutritional intake (leptin, angiotensin), inflammatory mediator (tumor necrosis factor, interleukin), and hormone-related insulin [14]. Macrophage accumulation also become source of proinflammatory cytokines in body. Persistent low-grade inflammation process from adipocyte and macrophage will induce lymphatic remodeling and impair cardiovascular condition [3].

Previous cellular study elaborates association between chronic inflammation induced by macrophage accumulation, especially in epicardial adipose tissue, with atherosclerosis and coronary diseases [15]. Macrophage with cholesterol ester builds up fatty streak on endothelial blood vessel and over long asymptomatic period, fatty streak become plaque. Progressive chronic inflammatory condition sustained by atherosclerotic lesion and undesirable immune respond against cholesterol crystals and cholesterol-associated apolipoproteins [2,16].

Reverse cholesterol transport (RCT) is cholesterol's movement from peripheral tissue to liver and biliary system for excretion. There are two major steps during RCT process are cholesterol movement inside peripheral cell to circulating high-density lipoprotein (HDL) and Cholesterol esterification within plasma lipoprotein (HDL). In macrophage, cholesterol homeostasis not regulated by cholesterol accumulation inside cell and as consequences cholesterol accumulation become an issue [9]. RCT serve as athero-protective mechanism by movement of the cholesterol, via macrophage and other mechanism, to the liver and then to the intestine for excreted together with fecal excretion. Recent studies show that dysfunction of lymphatic system will alter athero-protective mechanism of RCT [2, 17]. Animal model studies using mice conclude that blocking lymphatic vessel growth prevent cholesterol efflux from blood vessel plaques [2].

The most common complication of prolong arteriosclerosis is myocardial infarct (MI). There are several responses after MI like acute inflammatory reaction followed by promoting granulation tissue, remodeling of post injured cardiac tissue, and lymphangiogenesis in effected area [2]. Lymphatic vessel in cardiac tissue also makes sure proper early immune response after cardiac tissue injury for optimization of heart recovery process [10]. Without proper cardiac healing process, the injured tissue could be replaced by granulation tissue and lead to the heart failure condition. Molecular study shows that post MI patient present with high level of anti-cardiac auto-antibodies and could lead to anti-cardia autoimmunity [18].

Current hypothesis tends to predict increase lymphatic vasculature in heart by lymphangiogenesis could augment cardiac tissue repair and prevent advance heart modeling after injury. During heart diastole, ventricular heart chamber pressure is increasing and drives lymphatic fluid from subendocardial to myocardial vasculature, and vise versa. Unfortunately, during heart failure, the cardiac pressure is in suboptimal condition which leads to myocardial interstitial edema. Even small changes in interstitial pressure could have massive impact on cardia output [19]. Prolong interstitial edema also become one of the contributed factors for tissue fibrosis, recruitment of immune cell and some studies show that augmentation of lymphatic number in affected area could reduce inflammation process in heart [19].

Conclusion

Our understanding about lymphatic is still far behind compare to blood vascular system. It is a challenging process to study about lymphatic association with other system, especially cardiovascular medicine. However, molecular studies help our perspective in learning connection between lymphatic system and cardiovascular disease. Recently, many studies support that lymphatic system contributes in pathologic condition in cardiovascular diseases. Lymphatic system dysfunction could impair normal heart condition and it also could precipitate pathologic heart condition. Based on current studies, many suggest preserving normal lymphatic function and treat abnormal lymphatic function could be beneficial in cardiovascular medicine.

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