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Roles of signaling and transcriptional networks in pathological lymphangiogenesis☆

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ABSTRACT

Lymphangiogenesis, the generation of new lymphatic vessels, plays important roles in cancer metastasis. Outstanding progress during the past decade has dramatically increased the novel knowledge and insights of the mechanisms underlying the generation of new lymphatic vessels, the roles of transcription factors and lymphangiogenic growth factors during physiological development and pathological processes such as cancer and inflammation. Furthermore, an understanding of the molecular consequences during tumor lymphangiogenesis has provided chances to develop better diagnostic and therapeutic approaches that aim to limit the progression of cancer. In this article, we will explain the current knowledge of how lymphatic function is altered in various pathological conditions including cancer progression.

Contents

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Footnotes for definition of technical terms

In this review, to avoid misunderstanding technical term definition, we define metastasis as follows. Most tumors that grow in size to some extent recruit both blood and lymphatic vessels. The tumors need these blood vessels or lymphatic vessels to metastasize to distant organs. Hematogenous metastasis is a process in which cancer cells migrate from primary tumors via blood vessels and settle down to distant organs. Lymph node metastasis is a process in which cancer cells migrate from primary tumors to lymph nodes via lymphatic vessels. Please note that cancer cells which pass through lymph nodes further metastasize to distant organs via blood vessels. Metastasis is a migrating process of cancer cells to distant organs. Therefore, when we simply mention "metastasis" in this review, it includes both hematogenous metastasis and lymph node metastasis.
In addition, we define the types of lymphatic vessels as follows. Lymphatic vessel is frequently and widely used as vessels through which lymph fluids flow. When 'lymphatics' is used, it exactly means lymphatic vessels. Lymphatic capillaries are lymphatic microvessels in peripheral tissues which include the smallest lymphatic vessels and initial lymphatics (very tips incorporating lymph fluids). 'Lymphatic vascular' means lymphatic vessel's (possessive) as in lymphatic vascular system.

1. Introduction

The maintenance of fluid homeostasis of vertebrates is regulated by the blood and lymphatic vessels which are distributed throughout the body. In addition to their physiological roles, it is widely known that tumors require microvessel formation in the vicinity in order to incorporate oxygen and nutrition to grow and/or metastasize [1]. Cancer cells migrate to distant tissues via either blood or lymphatic vessels [2]. The lymphatic vessel was reported to be the main metastatic route for oral squamous cell carcinoma [3]. In this review, we will discuss the major findings that have led to the understanding of critical roles for the lymphatic vascular system during cancer metastasis with a specific focus on the transcription factors and signaling cascades involved, and development of novel strategies to therapeutically target the lymphatic vessels in cancer.

2. Lymphatic vessels in physiological conditions

2.1. Lymphatic development

More than 100 years ago, Dr. Sabin postulated that lymphatic vascular system arises by sprouting from blood vessels [4]. This "centrifugal" theory has been confirmed during the last 15 years [5]. During embryogenesis, the lymphatic vessels start to develop after the blood vascular system is established. Around embryonic day (E) 9.0 in mice, shortly after the separation of veins and arteries, a distinct group of BECs of the anterior cardinal vein starts to express LYVE-1, one of the lymphatic endothelial markers. Around E9.75, a population of LYVE-1-positive cells of the cardinal vein starts to express Prox1 transcription factor (Fig. 1) [6,7]. In E10.5 mouse embryos, when the Prox1-positive cells become committed to differentiating into lymphatic ECs, they sprout and bud off the cardinal vein, and then migrate toward the surrounding tissue that expresses vascular endothelial growth factor (VEGF)-C, where they develop primary lymphatic vasculature. The expansion and extension of the lymphatic vessels by sprouting and proliferation lead to the development of the primitive lymphatic sacs (Fig. 1).

The maturation step of the lymphatic vasculature starts approximately at E14.5 and continues until after birth (Fig. 1). During these processes, the primitive lymphatic plexus develops into a hierarchical structure consisting of lymphatic capillaries and collecting lymphatic vessels through the structural remodeling of collecting vessels including the formation of lymphatic valves and the smooth muscle coverage (Fig. 1). The separation of the lymphatic vessels from the blood vessels depends on multiple transcription factors and signaling pathways, whose roles have been reviewed elsewhere in more details [5,8].

2.2. Functions of lymphatic vessels

The lymphatic vasculature is an essential organ of the vertebrate vascular system and plays a number of important roles in homeostasis and disease [5,8]. The mature lymphatic system in mammals consists of the lymphatic vessels and the lymphoid organs including the lymph nodes, tonsils, thymus, Peyer's patches and spleen. The lymphatic vasculature travels over most of the body, with the exception of cartilage, epidermis, cornea, and retina. While it had long been thought that lymphatic vessels are absent in the central nervous system and bone marrow, recent reports have identified lymphatic vasculature in the central nervous system [9,10]. Lymphatic vasculature functions to return interstitial fluid and protein to the blood circulation, to traffic immune cells, and to absorb dietary fatty acids. For example, almost all of body water from peripheral tissues is collected by veins but excessive water that cannot be collected by veins is collected by lymphatic vessels. The reason why lymphatic vessels absorb fat and fatty acid has not been well described yet. However, the need for collecting aqueous solution and hydrophobic fatty emulsion by blood vessels and by lymphatic vessels respectively is a reasonable/possible explanation. Trafficking immune cells to lymph nodes is a critical role of lymphatic vessels since lymphocytes, committed effector cells and macrophages in lymph nodes attack and eliminate pathogens to maintain pathogen-free conditions in the body.

2.3. Structures of lymphatic vessels

The blood and lymphatic vessels are lined by endothelial cells (ECs). The lymphatic vasculature is formed by lymphatic endothelial cells (LECs), which have highly similar properties to blood vascular endothelial cells (BECs). While LECs represent distinct cell populations from BECs, LECs are differentiated from BECs during embryogenesis and are capable of de-differentiate to BECs in the presence of BMP-9 signals [11–13]. The lymphatic vascular network starts with blind-ended lymphatic capillaries in the peripheral tissues (Fig. 2). Lymphatic capillaries consist of a single-cell layer of overlapping LECs which are interconnected by discontinuous button-like junctions without intercellular tight junctions or adherens junctions [14]. Lymphatic capillaries have minimal basement membranes, or are not covered by smooth muscle cells (Fig. 2). They are tethered by anchoring filaments to collagen fibers of the extracellular matrix. Under high interstitial pressure, pulling of