LYMPHOID ORGANS 15. pdf

1: Chapter The Lymphatic System and Lymphoid Organs and Tissues

IL is a cytokine critical for development and maintenance of T lymphoid cells. However, the identity and distribution of ILexpressing cells in lymphoid organs are not well understood.

A lymph node showing afferent and efferent lymphatic vessels A lymph node is an organized collection of lymphoid tissue, through which the lymph passes on its way back to the blood. Lymph nodes are located at intervals along the lymphatic system. Several afferent lymph vessels bring in lymph, which percolates through the substance of the lymph node, and is then drained out by an efferent lymph vessel. There are between five and six hundred lymph nodes in the human body, many of which are grouped in clusters in different regions as in the underarm and abdominal areas. Lymph node clusters are commonly found at the base of limbs groin, armpits and in the neck, where lymph is collected from regions of the body likely to sustain pathogen contamination from injuries. The substance of a lymph node consists of lymphoid follicles in an outer portion called the cortex. The inner portion of the node is called the medulla , which is surrounded by the cortex on all sides except for a portion known as the hilum. The hilum presents as a depression on the surface of the lymph node, causing the otherwise spherical lymph node to be bean-shaped or ovoid. The efferent lymph vessel directly emerges from the lymph node at the hilum. The arteries and veins supplying the lymph node with blood enter and exit through the hilum. The region of the lymph node called the paracortex immediately surrounds the medulla. Unlike the cortex, which has mostly immature T cells, or thymocytes , the paracortex has a mixture of immature and mature T cells. Lymphocytes enter the lymph nodes through specialised high endothelial venules found in the paracortex. A lymph follicle is a dense collection of lymphocytes, the number, size and configuration of which change in accordance with the functional state of the lymph node. For example, the follicles expand significantly when encountering a foreign antigen. The selection of B cells , or B lymphocytes, occurs in the germinal centre of the lymph nodes. Lymph nodes are particularly numerous in the mediastinum in the chest, neck, pelvis, axilla , inguinal region , and in association with the blood vessels of the intestines. It consists of connective tissue formed of reticular fibers , with various types of leukocytes , white blood cells , mostly lymphocytes enmeshed in it, through which the lymph passes. Lymphoid tissue can either be structurally well organized as lymph nodes or may consist of loosely organized lymphoid follicles known as the mucosa-associated lymphoid tissue. The central nervous system also has lymphatic vessels, as discovered by the University of Virginia Researchers. The search for T-cell gateways into and out of the meninges uncovered functional meningeal lymphatic vessels lining the dural sinuses , anatomically integrated into the membrane surrounding the brain. Lymphatic vessel Lymph capillaries in the tissue spaces The lymphatic vessels , also called lymph vessels, conduct lymph between different parts of the body. They include the tubular vessels of the lymph capillaries , and the larger collecting vesselsâ€”the right lymphatic duct and the thoracic duct the left lymphatic duct. The lymph capillaries are mainly responsible for the absorption of interstitial fluid from the tissues, while lymph vessels propel the absorbed fluid forward into the larger collecting ducts, where it ultimately returns to the bloodstream via one of the subclavian veins. These vessels are also called the lymphatic channels or simply lymphatics. Its network of capillaries and collecting lymphatic vessels work to efficiently drain and transport extravasated fluid, along with proteins and antigens, back to the circulatory system. Numerous intraluminal valves in the vessels ensure a unidirectional flow of lymph without reflux. The collecting lymphatics, however, act to propel the lymph by the combined actions of the intraluminal valves and lymphatic muscle cells. The first lymph sacs to appear are the paired jugular lymph sacs at the junction of the internal jugular and subclavian veins. Each jugular lymph sac retains at least one connection with its jugular vein, the left one developing into the superior portion of the thoracic duct. The next lymph sac to appear is the unpaired retroperitoneal lymph sac at the root of the mesentery of the intestine. It develops from the primitive vena cava and mesonephric veins. Capillary plexuses and lymphatic vessels spread from the retroperitoneal lymph sac to the abdominal viscera and diaphragm. The sac establishes connections with the cisterna chyli but loses its connections with neighbouring veins. The last of the lymph sacs, the paired posterior lymph sacs, develop from the iliac veins. The posterior lymph sacs produce capillary

plexuses and lymphatic vessels of the abdominal wall, pelvic region, and lower limbs. The posterior lymph sacs join the cisterna chyli and lose their connections with adjacent veins. With the exception of the anterior part of the sac from which the cisterna chyli develops, all lymph sacs become invaded by mesenchymal cells and are converted into groups of lymph nodes. The spleen develops from mesenchymal cells between layers of the dorsal mesentery of the stomach. The lymphatic system has multiple interrelated functions: Fat absorption[edit] Nutrients in food are absorbed via intestinal vili greatly enlargened in the picture to blood and lymph. Long-chain fatty acids and other lipids with similar fat solubility like some medicines are absorbed to the lymph and move in it enveloped inside chylomicrons. Lymph vessels called lacteals are at the beginning of the gastrointestinal tract , predominantly in the small intestine. While most other nutrients absorbed by the small intestine are passed on to the portal venous system to drain via the portal vein into the liver for processing, fats lipids are passed on to the lymphatic system to be transported to the blood circulation via the thoracic duct. There are exceptions, for example medium-chain triglycerides are fatty acid esters of glycerol that passively diffuse from the GI tract to the portal system. The enriched lymph originating in the lymphatics of the small intestine is called chyle. The nutrients that are released into the circulatory system are processed by the liver , having passed through the systemic circulation. Cells in the lymphatic system react to antigens presented or found by the cells directly or by other dendritic cells. When an antigen is recognized, an immunological cascade begins involving the activation and recruitment of more and more cells, the production of antibodies and cytokines and the recruitment of other immunological cells such as macrophages. Lymphatic disease The study of lymphatic drainage of various organs is important in the diagnosis, prognosis, and treatment of cancer. The lymphatic system, because of its closeness to many tissues of the body, is responsible for carrying cancerous cells between the various parts of the body in a process called metastasis. The intervening lymph nodes can trap the cancer cells. If they are not successful in destroying the cancer cells the nodes may become sites of secondary tumours. Enlarged lymph nodes[edit] Main article: Lymphadenopathy Lymphadenopathy refers to one or more enlarged lymph nodes. Small groups or individually enlarged lymph nodes are generally reactive in response to infection or inflammation. This is called local lymphadenopathy. When many lymph nodes in different areas of the body are involved, this is called generalised lymphadenopathy. Generalised lymphadenopathy may be caused by infections such as infectious mononucleosis , tuberculosis and HIV , connective tissue diseases such as SLE and rheumatoid arthritis , and cancers , including both cancers of tissue within lymph nodes, discussed below, and metastasis of cancerous cells from other parts of the body, that have arrived via the lymphatic system. Lymphedema Lymphedema is the swelling caused by the accumulation of lymph, which may occur if the lymphatic system is damaged or has malformations. It usually affects limbs, though the face, neck and abdomen may also be affected. In an extreme state, called elephantiasis , the edema progresses to the extent that the skin becomes thick with an appearance similar to the skin on elephant limbs. Lymphangiomatosis is a disease involving multiple cysts or lesions formed from lymphatic vessels. Treatment is by manual lymphatic drainage. There is no evidence to suggest that the effects of manual lymphatic drainage are permanent.

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2: Bioengineering of Artificial Antigen Presenting Cells and Lymphoid Organs

The components of the lymphatic system are BLANK, BLANK vessels, lymphoid BLANK and BLANK, and BLANK bone marrow. lymph, lymphatic, tissues, organs, red The two functional types of lymphoid organs/tissues are BLANK lymphoid and BLANK lymphoid.

News The lymphatic system is part of the immune system. It also maintains fluid balance and plays a role in absorbing fats and fat-soluble nutrients. The lymphatic or lymph system involves an extensive network of vessels that passes through almost all our tissues to allow for the movement of a fluid called lymph. Lymph circulates through the body in a similar way to blood. There are about lymph nodes in the body. These nodes swell in response to infection, due to a build-up of lymph fluid, bacteria, or other organisms and immune system cells. A person with a throat infection, for example, may feel that their "glands" are swollen. Swollen glands can be felt especially under the jaw, in the armpits, or in the groin area. These are, in fact, not glands but lymph nodes. They should see a doctor if swelling does not go away, if nodes are hard or rubbery and difficult to move, if there is a fever , unexplained weight-loss, or difficulty breathing or swallowing. Fast facts about the lymphatic system The lymphatic system plays a key role in the immune system, fluid balance, and absorption of fats and fat-soluble nutrients. As lymph vessels drain fluid from body tissues, this enables foreign material to be delivered to the lymph nodes for assessment by immune system cells. The lymph nodes swell in response to infection, due to a build-up of lymph fluid, bacteria, or other organisms and immune system cells. Lymph nodes can also become infected, in a condition known as lymphadenitis. If lymph nodes remain swollen, if they are hard and rubbery, and if there are other symptoms, you should see a doctor. Definition Lymph nodes, or "glands" may swell as the body responds to a threat. The lymphatic system has three main functions: It maintains the balance of fluid between the blood and tissues, known as fluid homeostasis. It facilitates absorption of fats and fat-soluble nutrients in the digestive system. The system has special small vessels called lacteals. These enable it to absorb fats and fat-soluble nutrients from the gut. They work with the blood capillaries in the folded surface membrane of the small intestine. The blood capillaries absorb other nutrients directly into the bloodstream. Anatomy The lymphatic system consists of lymph vessels, ducts, nodes, and other tissues. Around 2 liters of fluid leak from the cardiovascular system into body tissues every day. The lymphatic system is a network of vessels that collect these fluids, or lymph. Lymph is a clear fluid that is derived from blood plasma. They work in a similar way to the blood vessels. The lymph vessels work with the veins to return fluid from the tissues. Unlike blood, the lymphatic fluid is not pumped but squeezed through the vessels when we use our muscles. The properties of the lymph vessel walls and the valves help control the movement of lymph. However, like veins, lymphatic vessels have valves inside them to stop fluid from flowing back in the wrong direction. Lymph is drained progressively towards larger vessels until it reaches the two main channels, the lymphatic ducts in our trunk. From there, the filtered lymph fluid returns to the blood in the veins. The vessels branch through junctions called lymph nodes. These are often referred to as glands, but they are not true glands as they do not form part of the endocrine system. In the lymph nodes, immune cells assess for foreign material, such as bacteria, viruses, or fungus. Lymph nodes are not the only lymphatic tissues in the body. The tonsils, spleen, and thymus gland are also lymphatic tissues. What do the tonsils do? In the back of the mouth, there are tonsils. These produce lymphocytes, a type of white blood cell, and antibodies. They have a strategic position, hanging down from a ring forming the junction between the mouth and pharynx. This enables them to protect against inhaled and swallowed foreign bodies. The tonsils are the tissues affected by tonsillitis. What is the spleen? The spleen is not connected to the lymphatic system in the same way as lymph nodes, but it is lymphoid tissue. This means it plays a role in the production of white blood cells that form part of the immune system. Its other major role is to filter the blood to remove microbes and old and damaged red blood cells and platelets. The thymus gland The thymus gland is a lymphatic organ and an endocrine gland that is found just behind the sternum. It secretes hormones and is crucial in the production, maturation, and differentiation of immune T cells. It is active in developing the immune system from before birth and through childhood. The bone marrow Bone marrow is not lymphatic

tissue, but it can be considered part of the lymphatic system because it is here that the B cell lymphocytes of the immune system mature. Liver of a fetus During gestation, the liver of a fetus is regarded as part of the lymphatic system as it plays a role in lymphocyte development. Below is a 3-D model of the lymphatic system, which is fully interactive. Explore the model using your mouse pad or touchscreen to understand more about the lymphatic system. Function The lymph system has three main functions. Fluid balance The lymphatic system helps maintain fluid balance. It returns excess fluid and proteins from the tissues that cannot be returned through the blood vessels. The fluid is found in tissue spaces and cavities, in the tiny spaces surrounding cells, known as the interstitial spaces. These are reached by the smallest blood and lymph capillaries. Around 90 percent of the plasma that reaches tissues from the arterial blood capillaries is returned by the venous capillaries and back along veins. The remaining 10 percent is drained back by the lymphatics. Each day, around liters is returned. This fluid includes proteins that are too large to be transported via the blood vessels. Loss of the lymphatic system would be fatal within a day. Without the lymphatic system draining excess fluid, our tissues would swell, blood volume would be lost and pressure would increase. Absorption Most of the fats absorbed from the gastrointestinal tract are taken up in a part of the gut membrane in the small intestine that is specially adapted by the lymphatic system. The lymphatic system has tiny lacteals in this part of the intestine that form part of the villi. These finger-like protruding structures are produced by the tiny folds in the absorptive surface of the gut. Lacteals absorb fats and fat-soluble vitamins to form a milky white fluid called chyle. This fluid contains lymph and emulsified fats, or free fatty acids. It delivers nutrients indirectly when it reaches the venous blood circulation. Blood capillaries take up other nutrients directly. The immune system The lymphatic system produces white blood cells, or lymphocytes that are crucial in fending off infections. The third function is to defend the body against unwanted organisms. Without it, we would die very soon from an infection. Our bodies are constantly exposed to potentially hazardous micro-organisms, such as infections. In this case, the lymphatic system enables our immune system to respond appropriately. If the immune system is not able to fight off these micro-organisms, or pathogens, they can be harmful and even fatal. A number of different immune cells and special molecules work together to fight off the unwanted pathogens. How does the lymphatic system fight infection? The lymphatic system produces white blood cells, known as lymphocytes. There are two types of lymphocyte, T cells and B cells. They both travel through the lymphatic system. As they reach the lymph nodes, they are filtered and become activated by contact with viruses, bacteria, foreign particles, and so on in the lymph fluid. From this stage, the pathogens, or invaders, are known as antigens. As the lymphocytes become activated, they form antibodies and start to defend the body. They can also produce antibodies from memory if they have already encountered the specific pathogen in the past. Collections of lymph nodes are concentrated in the neck, armpits, and groin. We become aware of these on one or both sides of the neck when we develop so-called "swollen glands" in response to an illness. It is in the lymph nodes that the lymphocytes first encounter the pathogens, communicate with each other, and set off their defensive response. Activated lymphocytes then pass further up the lymphatic system so that they can reach the bloodstream. Now, they are equipped to spread the immune response throughout the body, through the blood circulation. The lymphatic system and the action of lymphocytes, of which the body has trillions, form part of what immunologists call the "adaptive immune response. Diseases The lymphatic system can stop working properly if nodes, ducts, vessels, or lymph tissues become blocked, infected, inflamed, or cancerous. Lymphoma Cancer that starts in the lymphatic system is known as lymphoma. It is the most serious lymphatic disease. Hodgkin lymphoma affects a specific type of white blood cell known as Reed-Sternberg cells.

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3: Lymphatic system: Definition, anatomy, function, and diseases

Secondary or peripheral lymphoid organs, which include lymph nodes and the spleen, maintain mature naive lymphocytes and initiate an adaptive immune response. The peripheral lymphoid organs are the sites of lymphocyte activation by antigens. Activation leads to clonal expansion and affinity maturation.

Find articles by Ruddle, N. First published March 3, - Version history Abstract Tertiary lymphoid organs TLOs are accumulations of lymphoid cells in chronic inflammation that resemble LNs in their cellular content and organization, high endothelial venules, and lymphatic vessels LVs. Although acute inflammation can result in defective LVs, TLO LVs appear to function normally in that they drain fluid and transport cells that respond to chemokines and sphingosinephosphate S1P gradients. Molecular regulation of TLO LVs differs from lymphangiogenesis in ontogeny with a dependence on cytokines and hematopoietic cells. Ongoing work to elucidate the function and molecular regulation of LVs in TLOs is providing insight into therapies for conditions as diverse as lymphedema, autoimmunity, and cancer. The initial thin-walled vessels, called capillaries, progress to collecting vessels and then to larger vessels such as the thoracic duct. Although other cell types can express some of these markers, none except LVs express the entire range. Fluid is transported through the LVs by means of extrinsic contraction of tissue forces and intrinsic pumping through lymphatic muscle 3. Lymphatic valves prevent backflow and have higher expression of PROX1 than do the cells in the walls of the vessels. LVs have many functions in homeostasis. They maintain fluid balance, preventing edema by providing drainage of interstitial fluid, provide lipid transport, and serve in an immune capacity by carrying antigen and cells throughout the immune system and regulating this transport through production of chemokines and sphingosinephosphate S1P 4. LVs are also found at sites of chronic inflammation, referred to as ectopic or tertiary lymphoid organs TLOs. Cells are directed to their various locations through the activity of chemokines produced by several different types of stromal cells â€” fibroblast reticular cells, marginal reticular cells, and endothelial cells 5. Naive cells enter LNs through specialized blood vessels, called high endothelial venules HEVs , and leave after interaction with antigen, which enters into LNs via LVs. Conduits are very fine microvessels consisting of ECM scaffolding produced by fibroblast reticular cells. They transport low-molecular-weight antigens from the cortex to the paracortex and into the parenchyma of LNs, where they can contact the HEVs 6. The organization of LNs and their vascular features are presented in Figure 1. The signals that organize LNs in ontogeny are tightly regulated, which results in the development of individual LNs on a precise temporal and anatomical schedule 7. The role of stromal cells in SLO development and maintenance is becoming better understood 10 as is the response of these cells to neuronal signals, including retinoic acid DCs accumulate in the subcapsular sinus and transmigrate through the floor of that sinus into the T cell zone, while T cells access the parenchyma of the LN through the peripheral medullary sinuses Efferent LVs drain activated cells from the LN, which then travel through afferent vessels to the next LN in the series, into the thoracic duct, and into the bloodstream via the subclavian veins. Markers that distinguish efferent from afferent vessels are not yet known. S1P is found in high concentrations in the blood and lymph, where lymphocytes express low levels of the receptor, S1PR1. The receptor is re-expressed at higher levels in the LN, where S1P levels are low. Conditional inducible knockouts regulated by PROX1 will provide insight into this question. TLOs TLOs, also referred to as ectopic lymphoid tissues, are accumulations of cells in chronic inflammation reviewed in ref. SLOs arise during development at key locations in the body under the control of a precise developmental program, but chronic immune activity in the adult can give rise to similarly organized accumulations of lymphoid cells in almost any non-lymphoid tissue through a process that is not preprogrammed but rather the result of induction by factors in the environment that could elicit the same signals that contribute to LN development reviewed in refs. It has been suggested that TLOs differ from SLOs by the absence of a capsule; however, TLOs in a variety of chronic kidney diseases are in contact with a fibrous capsule As noted above, the latter arise at predefined locations as a result of stromal and endothelial organizers. Even though most of these elements are also present in TLOs 5 , the order in which they populate the TLO may differ from the precise temporal aspect of LNs. The general absence of a capsule may have

consequences for trafficking patterns that could differ in TLOs from what is seen in LNs, in which the DCs and T cells migrate through the peripheral medullary sinus to the parenchyma TLOs arise in several instances of chronic inflammation, including autoimmunity, chronic graft rejection, persistent infection summarized in ref. They can be induced experimentally by tissue-specific expression of certain inflammatory mediators summarized in ref. As noted above, lymphoid chemokines regulate trafficking of lymphocytes and DCs to and within LNs, and their expression 20 , 30 is one criterion that defines TLOs. TLOs likely function as local sites of antigen presentation and lymphocyte activation, including somatic hypermutation and class switching in B cells 31 , which suggests that they facilitate local antimicrobial responses as well as epitope spreading 32 , 33 and autoimmune exacerbation. TLOs can progress from a relatively benign to a destructive phase and lose their lymphoid organ characteristics. For example, in the non-obese diabetic NOD mouse model of type 1 diabetes mellitus T1DM , initial pancreatic infiltrates are characterized by HEV development and minimal islet destruction, whereas later stages demonstrate frank islet destruction and diabetes The presence of high proportions of regulatory T cells in some TLOs 25 , 35 suggests that immune regulation occurs in these locations. They are also found in TLOs associated with some tumors The functions of the LVs in TLOs have not been thoroughly investigated but are worthy of analysis with regard to fluid balance and transport of antigen and naive, activated, and memory lymphocytes. Fluid balance is a critical function of LVs in the body. Since edema is a frequent occurrence in acute inflammation, it is likely that LVs associated with that process serve a drainage function. Lymphangiogenesis accompanies acute inflammation with enhanced lymph flow Seeger and colleagues suggest that inflammation occurs before lymphangiogenesis and gives rise to that process Lymphangiogenesis at early times after immunization or during acute inflammation may be the result of the presence of excess fluid, but the LVs are unable to transport APCs 13 due to defects in lymphatic contraction Thaunat and colleagues have suggested that the existence of edema in an injured tissue results in an insufficient lymphatic outflow that then gives rise to chronic inflammation at the local site They suggest that defective lymphatic drainage is a prerequisite for the development of TLOs and have provided data supporting this concept in chronic graft rejection. Techniques to measure fluid accumulation are available 46 but have not been employed in the local region of a TLO. Future research could take advantage of measurements of interstitial fluid pressure in the local vicinity of a TLO to evaluate whether edema occurs and the LVs are functional. This may be more feasible and meaningful in a clinical setting, in which a relatively accessible TLO such as the joint in rheumatoid arthritis RA provides a logical study site. For example, proteins such as insulin in the pancreatic islet are in immediate proximity to or even a part of the TLO in T1DM. Thus, the necessity for antigen transport to the TLO through an extensive LV system might not be necessary, and the LVs may not serve that function. The presentation of self-antigen in LNs 19 that has been suggested as a mechanism for self-tolerance has not been investigated in TLOs and is an important area for future research. LVs that are packed with lymphocytes are prominent in some TLOs ref. Figure 2 Diagrammatic rendering of actual staining of a TLO from a mouse salivary gland. A Giemsa staining of TLO reveals the presence of leukocytes. TLO-associated LVs may also function in an efferent capacity by transporting activated lymphocytes to the periphery. This is only effective if the mice have already developed pancreatic TLOs Treatment results in additional accumulation of lymphocytes in the pancreatic TLOs, which is reversed upon cessation, resulting in rapid islet destruction and diabetes 23 , These data are also consistent with the observation that FTY also prevents egress from inflamed tissues into afferent lymphatics 55 , 56 and raise the exciting possibility that inhibitors of LV function could prevent diabetes and other autoimmune diseases systemically by preventing trafficking from the TLO to the LNs. The involvement of additional cell types is suggested by the existence of lymphangioblasts, which are distinct from blood endothelial cells, in developing tadpoles Studies in chickens 61 , 62 and mice 63 â€” 65 support a role for mesodermal cells that express macrophage and lymphatic markers that become, integrate into, or support LVs through their production of VEGFs. Regulation of lymphangiogenesis in TLOs is poorly understood. Angiogenesis occurs in inflammation and platelets are present, which indicates that the important players in embryonic lymphangiogenesis may participate. Thus, the possibility, though remote, exists that a recapitulation of the developmental program could occur â€” that is, that LVs in inflammation could arise from veins as they do in

development. On the other hand, the presence of blood vessels and their nearby LVs in TLOs suggests that lymphangiogenesis in inflammation occurs by sprouting from existing LVs. But what are the cells that signal these events? DCs, macrophages, and T and B cells have been implicated in the regulation of LVs in acute inflammation 13 , 66 â€” Different cells may be important at different times in various tissues. For example, B cells appear to be important in the lymphangiogenesis that occurs in LNs during inflammation, but only at the early stages after immunization 13 , The participation of macrophages in lymphangiogenesis in acute inflammation has been well documented, although the precise nature of their role is a subject of considerable controversy. Data in a model of corneal transplant lymphangiogenesis suggest that macrophages can actually transdifferentiate into LECs 70 ; that is, that macrophages themselves are precursors to LECs 61 , 62 , 64 , The expression of LYVE1 by macrophages could be interpreted as evidence that this is the case. On the other hand, the expression of this marker on both cell types may be a red herring. Kerjaschki and colleagues demonstrated the presence of host bone marrowâ€”derived precursors in association with LVs in the TLOs of chronically rejecting kidneys Osteoclast precursors, which include cells with macrophage properties, participate in lymphangiogenesis in a model of TNF transgeneâ€” and serum-mediated RA During low-dose, streptozotocin-induced pancreatic inflammation, there is a marked increase in macrophages in and around the islets. Lineage-tracing experiments might resolve this controversy. Cytokines contribute to lymphangiogenesis in acute inflammation, although there have been few studies evaluating their roles in the chronic inflammationâ€”associated TLOs. The question of LT participation is of particular interest given both its crucial role in lymphoid organ development and its ability to induce TLOs. The plasticity of LVs is a reflection of their environment, which influences their function, especially in the case of inflammation. CCL21 is particularly sensitive to inflammation. Immunofluorescence and microarray studies that compare LECs from acutely inflamed and resting mouse skin reveal increased expression of CCL21 and several other inflammatory genes Interestingly, there is downregulation of other genes, including Vegfr3 and Prox1. Extension of these studies to LVs in TLOs may reveal differences due to the chronic nature of stimulation, and data from a mouse corneal model of recurrent inflammation suggest that this is the case The authors suggest that, in chronic inflammation, LVs retain memory in their accelerated development of a network of functional LVs The ability to isolate LVs on the basis of their antigen expression 77 or transgene induced fluorescence 79 will allow their molecular analysis and comparison to vessels from resting LNs, activated LNs, and TLOs. As noted above, new techniques allowing isolation, purification, and single-cell in situ analysis will provide the tools for determination of gene expression. Are there any genes that are differentially expressed in LVs from TLOs compared with those in the rest of the body? If so, it will be possible to preferentially affect those vessels with inhibitors of their function while leaving remaining LVs intact. Analysis of lymphocyte, DC, and antigen-trafficking patterns in TLOs in real time in vivo is now possible with the use of mice that express fluorescent markers for HEVs 80 and LVs 79 , Although the technique of in vivo imaging is well established for analysis of trafficking in LNs 82 , addressing this issue in TLOs is a greater challenge. The key is to study TLOs in tissues that are amenable to these techniques, which will allow the evaluation of questions concerning LV insufficiency, memory, and plasticity in LVs in TLOs, and on a functional level, to determine whether valves and muscles occur in these vessels. The analysis of TLOs in mice whose LVs are conditionally deleted or induced through PROX1 regulation will provide information regarding the importance of fluid drainage functions of LVs in this context. Finally, the influence of the local environment on the LVs in TLOs in different organs must be analyzed. Clinical implications Elucidation of LV regulatory mechanisms in TLOs will contribute to the development of therapies to either promote or inhibit their formation, but we must keep in mind that LVs may be beneficial or detrimental depending on their context. Inhibition of TLO LVs may be beneficial in autoimmunity, since they contribute to exacerbation by epitope spreading; this could occur through their transport of naive lymphocytes and APCs to the local site. Treatments that discourage LV development, such as inhibition of macrophages clodronate , cytokines antibodies or receptor blockers , and growth factors e. The identification of markers preferentially expressed or expressed at a high level on TLO LVs would allow for their preferential inhibition.

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4: JCI - Lymphatic vessels and tertiary lymphoid organs

1) primary lymphatic organs are the sites where stem cells divide and become immunocompetent; 2)secondary lymphatic organs and tissues are the sites were most immune responses occur. Lymphatic organs and tissues are classified into two groups.

Bomba1, Zhen Gu1, 2, 3 1. How to cite this article: Theranostics ; 7 Despite these advances, therapy with natural immune cells or lymphoid organs is relatively expensive and time-consuming. Alternatively, biomimetic materials and strategies have been applied to develop artificial immune cells and lymphoid organs, which have attracted considerable attentions. In this review, we survey the latest studies on engineering biomimetic materials for immunotherapy, focusing on the perspectives of bioengineering artificial antigen presenting cells and lymphoid organs. The opportunities and challenges of this field are also discussed. Emerging trends and clinical challenges in this field are also discussed. Figure 1 The major interactions between T cells and DCs and the three signals leading to activation and expansion of T cells. Signal 1 is antigen presentation by interaction between the peptide-MHC complex and TCR; Signal 2 is co-stimulation by co-stimulatory molecule interaction. Signal 3 is release of cytokines, which are essential for T cell expansion and differentiation. Artificial antigen presenting cell system Antigen-presenting cells APCs act as a link between the innate and adaptive immune responses. For example, in adoptive cell transfer ACT , tumor-specific T cells are isolated then expanded ex vivo to obtain a large number of cells for transfusion. Moreover, the isolation and culture of DCs is a time-consuming process that obstructs the translation of T cell based therapy. Since these aAPCs are ready-to-use to the patients, this strategy is becoming a common tool in immunology and clinical applications. Signal 2 is provided by co-stimulatory molecules, which are upregulated on APCs; this leads to the complete activation of T cell. Co-stimulatory agonists, such as the anti-CD28 monoclonal antibody mAb , are known to provide the necessary co-stimulatory signals to T cells. Lastly, signal 3 involves cytokines produced by either APCs or T cells, which are essential for T cell expansion and differentiation. Other cytokines such as IL-7, IL and IL have been investigated and may promote better expansion or differentiation into more optimal T cell phenotypes. It is another strategy to treat autoimmune diseases and allograft rejection. Lipid based aAPC The dynamic lipid bilayer is essential for the molecular interactions in the natural systems. It indicated the role of the lipid membrane as a scaffold supporting MHC-restricted antigen presentation. Therefore, Ding et al. Similarly, Giannoni et al. The described aAPCs were based on artificial membrane bilayers containing T cell ligands membrane microdomains. They showed that preclustering of MHC molecules triggered a higher degree of T cell activation than soluble tetramers and aAPCs with MHC molecules uniformly distributed in artificial bilayer membranes. The authors found that the nanoporous silica particles showed increased membrane fluidity compared to the protocells formed from nonporous solid silica nanoparticles or unsupported liposomes. In another example, using silica beads coated with a lipid bilayer was shown to be more efficient than liposomes to boost CTL responses. This technology presents the potential to synthesize particles that are coated with natural DC membranes for aAPCs preparation. The cancer cell membrane along with its associated antigens were coated onto PLGA polymeric nanoparticle cores. The resulting CCNPs was used to deliver tumor-associated antigens to antigen presenting cells or to homotypically target the source cancer cells. B Transmission electron micrographs TEM of cancer cell membrane-coated nanoparticles. Reprinted with permission from ref. Copyright American Chemical Society. Click on the image to enlarge. Non-biodegradable sepharose or polystyrene beads were the first synthetic bead-based platforms used to activate T cells. Figure 3 Biodegradable polymeric artificial antigen-presenting cells. Encapsulated cytokines were released from particles in a time-dependent manner. B SEM imaging of the microparticle. D Expansion of T cells after various treatment as indicated. The film-stretching method was used for controlling the shape of PLGA microparticles to generate ellipsoidal aAPCs with varying long axis lengths and aspect ratios. After systemic administration, these nanoellipsoidal aAPCs stimulated stronger in vivo immune cell responses comparable to previously reported spherical aAPCs at a reduced overall protein dose. Moreover, the authors

found that these nanoellipsoidal aAPCs had enhanced pharmacokinetic properties, properly due to their resistance to hepatic and splenic elimination. In addition to PLGA, a new class of semi-flexible and filamentous polymers comprising of poly isocyano dipeptide and oligo ethylene oxide side chains were developed by Rowan and coworkers. This enhanced activity can be attributed to the structural flexibility and multivalency of these polymers, assisting in the formation of TCR nanoclusters on the T cell surface. In addition, these semi-flexible and filamentous polymers were biocompatible and non-toxic, highlighting their promise for the induction of both ex vivo and in vivo T cell responses. Inorganic aAPCS Synthetic aAPCs may also contain superparamagnetic parts for further separation from cells by the magnetic field before transfusion into patients. Magnetic particles are of particular interest for ex vivo T cell expansion. In addition to magnetic beads, magnetic nano-aAPCs were recently developed. After binding to the TCR, the magnetic field was used to drive aggregation of these magnetic nano-aAPCs, resulting in TCR clustering and increased T cell expansion in vitro and after adoptive transfer in vivo. Magnetic field-enhanced nano-aAPC stimulation is a novel approach to drive receptor clustering. In another example, a magnetic field was used for the enrichment of rare tumor-specific T cells and activate them to induce proliferation. Yu and co-workers[ ] designed a magnetic Janus microparticle to control T cell activation remotely. One side of these particles was decorated with a thin film of magnetically responsive materials, and on the other side coated with stimulatory ligand anti CD3 for T cell activation. By simultaneously controlling the rotation and locomotion of the Janus particles, the authors demonstrated the initiation of T cell activation in single-cell precision. The high-surface-area carbon nanotubes have been widely used as in aAPCs for ex vivo T cell expansion[-]. A potential mechanism for the enhanced stimulation response with treated single-walled nanotubes SWNTs surface may be due to the local clustering of the antibody stimuli in defect regions combined with the chemical nature of the environment surrounding these clusters. In the following work, a carbon nanotube-polymer composite CNP was developed to expand T cells ex vivo Figure 4. These CNPs could remarkably activate the T cells ex vivo. Meanwhile, the magnetic properties of the PLG nanoparticles allowed for separation of CNPs from the expanded T cells after activation ex vivo. After adoptively transferred into the tumor bearing mice, the expanded T cells induced a significant delay in tumor growth in a murine melanoma model and increased T cell infiltration in tumor sites. Artificial Lymphoid Organs Lymphoid organs such as the thymus, spleen, and lymph nodes are essential for the immune response. Various scaffold materials, including natural proteins such as fibroin[ ], spidroin[ ], alginate[ ] and collagen[ ], synthetic polymers including PLG polylactate-co-glycolate , PLA polylactate , and PGA polyglycolate ,[ ] and inorganic mesoporous silica rods[ ] have been applied for constructing scaffolds. Figure 4 A carbon nanotube-polymer composite for T-cell therapy. Copyright Nature Publishing Group. Lymph node The artificial lymph nodes that imitate the structure of a lymph node organ have been developed. First, several in vitro models of lymph node were created. In one approach, the researchers developed a bioreactor that imitated human cell microenvironment and homeostasis of primary follicles. Both the T and B lymphocytes and dendritic cells formed clusters within the matrix, indicating their potential functionality. Additionally, this system represented some of the processes in a lymph node, for example, the migration and interaction of lymphocytes with dendritic cells. In another example, Matloubian et al. It was found that lymph flow affected not only the expression of the chemokines but also the rate of cell division, indicating that increased lymph flow may act as an early inflammatory cue to enhance efficient immune response. Recently, Purwada et al. The described approach is promising for artificial production of antigen specific antibodies. Furthermore, in vivo models of artificial lymph nodes have been demonstrated. Irvine and co-workers[ ] designed injectable DCs-carrying alginate gels. An in vivo self-gelling formulation of alginate was designed, which was obtained by mixing calcium-loaded alginate microspheres with soluble alginate solution and dendritic cells. Meanwhile, some of the inoculated DCs moved to the draining lymph nodes. Watanabe and co-authors[,] developed a system based on a collagen matrix. It has been found that the transplants, which were infiltrated frequently, contained many T cell and B cell clusters. Moreover, these T cells and B cells had similar organization to that of the normal lymph node. They also demonstrated that several high endothelial venule HEV markers of secondary lymphoid organs and blood vessel-like structures were detected in the matrix, suggesting they had become

organized tissues in mice. Similar results were also demonstrated in immunodeficient SCID mice. Another therapeutic strategy is the implantation of cell-free systems saturated with immunomodulators to reprogram the specific lymphocytes. The enhanced efficacy of this vaccine could be a result of the promoted local activity of DCs induced by danger signals and antigens at the vaccination site. The same group recently reported cryogel-based whole-cell cancer vaccines for cancer immunotherapy. These cryogels were then subcutaneously injected into mice, leading to significant anti-tumor T cell responses in a melanoma model. In addition, inorganic mesoporous silica rods MSRs with a high-aspect ratio were found to assemble in vivo after subcutaneous injection, forming macroporous structures. The authors found that the MSR scaffolds could greatly increase the number of recruited cells compared to polymer scaffolds. Thymus Other artificial lymphoid organs, such as an artificial thymus, are also highly attractive targets because they also play important roles in immune system. Although in vivo models have yet been reported, artificial thymic organoids have been developed in vitro. This work provides opportunity of applying thymus transplantation to boost immune function, which is an essential step towards bioengineering of an artificial thymus Figure 7. In addition, immunological function of the implanted spleen was also demonstrated. Similarly, mucosal immune tissue has also been demonstrated through neointestine synthesis. These constructs were transplanted into syngeneic adult recipients. After 20 weeks, intraepithelial and lamina propria immunocyte were detected in transplanted intestines, suggesting their capacity to form a mucosal immune system. Figure 5 Generation of a synthetic lymphoid tissue-like organoid in mice. A Fluorescence imaging of transplant tissues. B Immunohistochemical staining of spleen and transplant tissues.

LYMPHOID ORGANS 15. pdf

5: Doctors Gates: lymphoid organs (Organs of the Immune System)

Which of the following is a primary lymphoid organ? Which of the following are the secondary, or peripheral lymphoid organs? Study aids. Related quizzes.

Classification[edit] ILCs can be divided based on the cytokines that they can produce, and the transcription factors that regulate their development and function. For each newly discovered branch of the ILC family, it will be important to determine whether a cell type represents a stable lineage or just a stage of differentiation or activation. In a nomenclature and classification system was proposed that divides the known ILCs into three groups. ILC1s are analogous to Th1 cells, and share the common transcription factor of T-bet. NK cells play a role in tumor surveillance and the rapid elimination of virus-infected cells. NK cells, discovered in , are the prototypical innate lymphoid cell, and have been described as large granular lymphocytes that lack the T cell receptor. ILC2s also termed natural helper cells, nuocytes, or innate helper 2 cells [9] play the crucial role of secreting type 2 cytokines in response to helminth infection. They have also been implicated in the development of allergic lung inflammation. After stimulation with Th2 polarising cytokines e. ILC2s are critical for primary responses to local Th2 antigens e. They are found mainly in mucosal tissues and particularly in the intestinal tract. They are essential for development of lymphoid organs during embryogenesis and after birth regulate the architecture of lymphoid tissue. On top of that, they have been linked to the maintenance of T cell memory. Transcriptional repressor ID2 appears to antagonize B and T cell differentiation , yielding an ID2-dependent precursor that can further differentiate with lineage-specific transcription factors. There is evidence that the different branches of ILCs share a common precursor. The development of ILCs is not completely understood. Their ability to rapidly secrete immunoregulatory cytokines allows them to contribute early on in immune responses to infection. They often reside at mucosal surfaces , where they are exposed to infectious agents in the environment. Helminth infection[edit] ILC2 cells play a crucial role in the protection against helminthic infection. They are a major early source of IL , which can activate T cells and induce physiological responses that will help expel a parasite. These physiological responses include stimulating goblet cell mucus secretion and contraction of smooth muscle. In addition, they secrete signals that recruit and activate mast cells and eosinophils , and which stimulate B cell proliferation. They also secrete Amphiregulin , a member of the epidermal growth factor family, that stimulates tissue repair. This can function to enhance the barrier function of the epithelium and slow pathogen entry. In response to inflammatory signals from the dendridic cells and gut epithelium, they produce IL which increase the production of antimicrobial peptides and defensins. ILC3s also assist in immune responses to extracellular bacteria by maintaining the homeostasis of epithelia. Therefore, when malfunction appears, these cells may participate in the development of inflammatory bowel diseases IBD. Their function is regulated by signals from stimulatory and inhibitory receptors. In this way, they act in a complementary manner with the cytotoxic T cells that recognize and kill tumor cells which present a foreign antigen on MHC class I. ILC1 influence tumor microenvironment by production of several cytokines e. IFNg and TNFa which at the beginning of immune response polarize other immune cells into inflammatory phenotype, e. ILC2 produce cytokines that promote anti-inflammatory immune response e. This microenvironment leads to tumor development and progression and contribute for better survival of cancer cells. ILC2s are critical in energy homeostasis by producing methionine-enkephalin peptides in response to IL This production promotes the emergence of beige adipocytes in white adipose tissue. The process of beiging leads to increased energy expenditure and decreased adiposity. They produce a profile of signals in response to pro-allergenic cytokines IL and IL that is similar to those produced in response to helminthic infection. Their contribution to this signaling appears to be comparable to that of T cells. In response to allergen exposure in the lungs, ILC2s produce IL, a necessary cytokine in the pathogenesis of allergic reactions. This response appears to be independent of T and B cells. Further, allergic responses that resemble asthma-like symptoms have been induced in mice that lack T and B cells using IL It has also been found that ILC2s are present in higher concentrations in tissues where allergic symptoms are present, such as in the nasal polyps of patients with

chronic rhinosinusitis and the skin from patients with atopic dermatitis. The integration of information collected through these numerous inputs allows NK cells to maintain self-tolerance and recognize self-cell stress signals. NK cell dysregulation has been implicated in a number of autoimmune disorders including multiple sclerosis , systemic lupus erythematosus , and type I diabetes mellitus. Some researchers suggest that the definition should focus more on the germline-coding of receptors in the innate immune system versus the rearranged receptors of the adaptive immune system. Annual Review of Immunology.

6: Chapter Lymphatic System (Mastering) Flashcards | Easy Notecards

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7: Innate lymphoid cell - Wikipedia

lymphoid organs The spleen, lymph nodes, thymus, Peyer patches, and tonsils, where more than 98% of T lymphocytes are found. See: T cell See also: organ lymphoid resembling or.

8: Lymphatic system - Wikipedia

15 The Lymphatic System â€¢Lymph nodes -Largest lymphoid organ in body -Located in upper left quadrant of abdomen -Often injured by trauma to abdomen.

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