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Review

How Endothelial Cell Organo-Specificity Mediates Circulating Cell Homing

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Abstract. Normal and transformed cells home into tissues from the circulation in a very selective way thanks to highly complex molecular mechanisms that govern cell-to-cell interactions and drive the homing of circulating cells so that it is achieved properly. Because this is characterized by a resulting high selectivity, it constitutes a template for targeted drug-, gene- or cell-therapy strategies. Designing a mimetic-based therapy requires the identification of the responsible selective molecules, but also their mechanisms of action and interactions with their ligands together with their biological modulation and regulation. This homing/invasion event is decisive at the level of the endothelium that lines the vessel walls. Since cell-to-cell interactions mean a double recognition process, this review will illustrate the part played by the endothelial cells (ECs) and their adhesion molecules: the protein as well as the glycan point of view, the chronology, and the environmental modulation of EC adhesion molecule expression. These characteristics should provide keys to understanding the resulting overall specificity of cell localization. Taking into account the cytokine microenvironment, a fundamental role was recently documented for locally secreted chemokines which act through their restricted presentation by endothelial cells. As such, chemokines contribute to illustrating the concept of endothelial organo-specificity which is approached here, uncovering the role of glycoconjugate signaling as the hallmark of refined cellular recognition, and discussed in the context of potential drug design against site-directed diseases such as metastases, inflammatory leukocyte recruitment, and tumor/inflammation-induced angiogenesis…

Key words: adhesion; chemokines; endothelial cell; lectins/glycoconjugates.

Introduction

Since the demonstration by Gowans and Knight in 1964 that circulating leukocytes enter secondary lymphoid organs at specialized endothelial sites[77], it was shown that T memory lymphocytes were able to recirculate to the tissues where they had come from; further on, B immunoblasts were shown to migrate preferentially into mucosal tissues (for a review see [55]). This contributed to building the concept of homing tissue specialization and tissue-specific lymphocyte recirculation fundamental to acquired immunity. The regio-selectivity is indeed favorable to performing an immune response[25]: it helps the meeting of antigens and lymphocytes which carry the antigen-specific receptor, reducing cross reactivity and allowing site specialization of the immune responses. Indeed, integration and control of systemic immune responses depend on the regulated trafficking of lymphocytes. The homing process

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disperses the immunological repertoire, directs lymphocyte subsets to the specialized microenvironments that control their differentiation, regulates their survival, and targets immune effector cells to sites of antigenic or microbial invasion.

The exquisite specificity of lymphocyte homing is determined by combinatorial "decision processes" involving the multistep sequential engagement of adhesion molecules and signaling receptors as described by SPRINGER[92, 93].

These homing-related interactions are seamlessly integrated into the overall interaction of the lymphocyte with its environment and participate directly in the control of lymphocyte function, life span, and population dynamics.

Lymphocyte homing and recirculation processes represent a natural model for targeted trafficking, the specificity of which results from a refined regulation due to the controlled expression of adhesion molecules, cytokines and chemokines receptors on the one hand (circulating cells), while the counterpart cells, i.e. the endothelial cells (ECs), express the corresponding ligands and present them in a proper way at the proper time. Similar molecular mechanisms are used in pathological situations and precious information can be gained from the comparison of homing/metastases localization, recirculation/tumor cell escape[90], and tumor--mediated and inflammation-mediated angiogenesis[1, 11].

Indeed, blood-borne circulating cells recognize and are recognized by vascular ECs. The latter allow circulating cells to extravasate in a tissue-specific manner and contribute to defining the cell homing selectivity, which is fundamental in physiologically normal, as well as pathological processes (inflammation, autoimmune diseases, metastasis). These properties led to the expression of the endothelial organo-specificity concept. Consequently, knowing how ECs are able to sort the circulating cell subpopulations, arrest them and make them enter a tissue, is a key to immunotherapy[58, 111], targeted drug therapy[94] and cellular therapy designs. This review will focus on examples of biological processes that need EC organo-specificity to be accomplished, thus demonstrating it.

EC Organo-Specificity Is a Concept that Highlights the Molecular Mechanisms of Cell Recruitment and Invasion

The structural and functional heterogeneity of the endothelium has long been recognized[75, 99]. Indeed, the microvascular endothelium controls the body's compartmentation and homing of lymphocytes into lymphoid[38] and non-lymphoid sites in a tissue-specific manner (see the review [25]). Microvascular ECs recognize blood-borne circulating cells and allow them to extravasate in a tissue-specific manner. As this property determines the selectivity of lymphocyte homing, it is fundamental in physiological as well as pathological processes: inflammation[34], autoimmune diseases[49], and metastasis[90]. These studies pointed out the existence of molecules that should distinguish one endothelium from another one and the mechanisms of their regulation. Such molecules are key to understanding the selectivity mechanism. Indeed, homing was shown to be mediated by the spatio-temporarily regulated sequential expression of specific cell adhesion molecules, called homing receptors, present both on the circulating leukocytes and on ECs[12]. The requirement for multiple protein-protein interactions allows a genetically limited receptor-ligand repertoire to be used combinatorially to control the recirculation of different leukocytes and other circulating cell subsets. The observed final specificity results generally from several steps in the process, which is selective and distinct for a tissue site. This combination of several selective steps results in a high degree of specificity.

Because recirculation begins with blood lymphocytes interacting transiently and reversibly with the vascular endothelium, an early step of the adhesion cascade is a decisive contact between circulating cell and microvascular EC, mediated by inducible EC adhesion molecules: E-selectin and P-selectin on the ECs[13, 19, 26, 29, 36, 39, 57, 78]. Later steps involve other adhesion molecules, e.g. intercellular adhesion molecule-1 (ICAM-1)[35, 41, 86, 92, 93, 103, 109]. Specific recognition mediated by the leukocyte L-selectin[8, 14, 42] becomes regio-selective despite its large distribution. This is attributed to the vascular addressins restricted expression among ECs according to the tissues and vessels. Addressins are mucin-type or mixed mucin/immunoglobulin-type glycoproteins[14, 15, 43, 66, 106, 116]; they are differentially expressed on the endothelium, depending upon their tissue origin[65, 66, 101, 105], and their structure is highly modulated by the microenvironment at the posttranslational level[32]. To become high-affinity L-selectin ligands, they must undergo "decoration" with the appropriate sugar residues, especially with the most common sugar epitopes recognized by L-selectin: sialyl Lewis X (sialyl Le^x; CD15s) and its sulphated form, presented by appropriate mucin-type proteins (GlyCAM-1, MAdCAM-1 or CD34). In the mouse, typical peripheral lymph node addressins (PNAds): GlyCAM-1[45, 101], CD34 and Sgp200 (sulphated glycoprotein of

200 kDa), are recognized by MECA79 antibody[12, 16, 101]. In humans, the corresponding glycosylated epitopes of PNAds, recognized by MECA79 and by JG-1.2 monoclonal antibodies[15], are presented on podocalyxin-like, CD34 and Sgp200 sialomucins[82, 84, 85]. Specific mucosa-associated addressin, MAdCAM-1, was found first in mouse[12, 32, 69, 79] and later in human ECs[23]. In additional to its being recognized by L-selectin through its sialomucin sugar residues[15, 23, 68], the MAdCAM-1 molecule possesses an immunoglobulin-like domain which interacts with the $\alpha_4\beta_7$ integrin homing receptor of lymphocytes[18]. Selectin binding epitopes are also present on other mucin-type glycoproteins, such as P-selectin ligand-l[33, 56, 64, 67, 72, 81, 104, 108], E-selectin ligand-1[97, 122], and cutaneous leukocyte antigen[17]. It must be emphasized that cellular glycoconjugates participate not only in selectin/addressin interactions[15, 16], but also in other lectin/glycoconjugate-mediated recognition phenomena in homing and invasion[17, 53, 54].

ECs and Metastases Localization

As described above, endothelial cells play fundamental roles in normal processes, but also in pathological ones, such as wound healing and inflammation[6, 7, 27, 63, 88, 98 115]. Moreover, they are the soil for the seeding of secondary tumoral foci (metastases)[76] and their capacity for making angiogenesis in the proximity and under the influence of a tumor[48] makes them 1) mediate tumor survival and 2) provide the tumor cells with a means to escape from the primary site into the circulation[51, 76, 107, 120].

In this context, ECs are the first target to aim for in antiadhesion[114, 118] and/or gene targeting[30, 73] therapies. In order to elaborate clinical protocols for such therapies, adequate cellular models with preserved regio--specificity are necessary[5, 100]. Microvascular EC lines were established from primary cell cultures prepared and further immortalized in a similar way. As such, the resulting cell lines were comparable. EC lines preserved tissue-specific phenotypes[41] and they displayed the tissue-specific behavior of lymphoid cells and myeloid cells. This makes them tools for advanced *in vitro* studies on the molecular mechanisms of cell--cell interactions.

Adhesive interactions are involved in the control of proliferation, migration, differentiation and other cell functions. The discriminative recognition and adhesion between leukocyte subpopulations and ECs built up interest aimed at understanding organ-selective cancer metastasis. As mentioned earlier, most information concerning adhesive molecules and their ligands involved in the adhesion process comes from research dealing with normal leukocytes. It is noticeable that similar adhesive molecules and mechanisms could be involved in metastasis and other invasive pathologies.

Along this line of evidence, addressins (and selectins) are actively studied because they are significant adhesion and organ-selective molecules expressed on ECs and highly dependent upon microenvironmental biological conditions. For example, the addressins that allow T lymphocytes to discriminate peripheral lymph node and mucosal tissues are respectively PNAd and MAdCAM-1[96, 102].

During inflammation, selectin molecules appear rapidly on the EC surface (P-selectin, E-selectin) and the expression of others increases (as ICAM-1) to mediate competent cells influx into tumor-inflamed tissue[96].

E-selectin seems to be involved in metastasis of colon cancer, since *in vitro* adhesion of several colon cell lines expressing E-selectin ligands: sialyl Le^X and sialyl Le^a, was shown to depend upon the presence of E-selectin on the activated endothelium[71, 112]. It was also shown that colon cancer cell adhesion to E-selectin occurs under flow conditions and leads to their complete arrest[61, 62].

Other lectins, such as galectin-1, expressed on the extra-cellular surface of EC, may be also involved in tumor cell adhesion[59] while galectin-3 [31] displays an inversely correlated distribution among ECs and colon cancer cells as far as invasiveness is concerned.

Such regulated and correlated expressions can be highly significant because some types of cancer metastasize preferentially into selected organs, for example prostate cancer cells into bones[28, 87] or melanoma cells into lungs[9, 47, 83, 119].

We recently described (PAPROCKA et al., submitted) a cytofluorimetric method to demonstrate specific and discriminative cell-to-cell adhesion occurring between human microvascular EC lines of distinct tissue origin and lymphocytes as well as colon carcinoma cells. This quantitative assay has proven useful in studying the molecular mechanisms involved in tissue-specific cell--to-cell interactions. Indeed, the labeling of one adhesion partner with a red fluorescent label, chosen because of its stability and non-exchangeability between cells[44], allowed a further characterization of the adherent cellular partners during this assay. Consequently, this assay is potentially useful in identifying the molecules involved in the adhesion process[74]; it demonstrated *in vitro* the exclusive capacity of ECs in select-

ing the cell population(s) that they are capable of recognizing and sorting.

It can be assumed that such sorting is more precise likely to be *in vivo* because of the microenvironmental controls and regulations, external stimuli to which ECs are extremely reactive. This is part of their main characteristic properties and results in their extreme selectivity.

Adhesion to and invasion of the EC layer by tumor cells is one aspect of this cell-to-cell interactive process. It is further illustrated by the neovascularization that is induced by the tumor environment.

Tumor-Selective Angiogenesis

This is the EC response to tumor-cell factors. Angiogenesis is required for the continual growth of the tumor and provides a gateway for cells to escape the confines of the primary tumor.

As during the adhesion process, an antigenic stimulus triggers a cascade of functional responses, leading to basement membrane dissolution, EC migration, proliferation and microvessel formation[24].

This process is a selective reaction[60, 91] of the ECs to the tumoral factors. These should, consequently, be identified to control the EC response. The genes that are implicated during the EC response are currently being actively studied by DNA array and gene display[50, 91, 95]. New molecules should be identified with these tools as well as with differential gene expression display. With this technique we could identify a new adhesion regulatory molecule expressed on some endothelial cells only (LAMERANT and KIEDA, submitted).

A common feature of the adhesion and invasion processes, the glycoconjugate-to-protein recognition, has to be pointed out. This feature is particularly illustrated during angiogenesis progression by studies aimed at the development of drugs that target the tumor neovasculature in order to inhibit tumor growth. The use of glycoconjugate synthesis inhibitors, such as castanospermine, which blocks the glucosidases that convert protein N-linked high mannose carbohydrates to complex oligosaccharides, resulted in a significant inhibition of tumor growth *in vivo* in nude mice and of basic fibroblast growth factor-induced angiogenesis[80]. Such glucosidase inhibitors prevented the morphological differentiation of ECs *in vitro*. Cell surface oligosaccharides are required for angiogenesis; alterations of these structures on ECs inhibit tumor growth.

HALLORAN et al.[40] have studied ECs not only as key participants in the angiogenic processes that characterize tumor growth, wound repair and inflammatory diseases, such as human rheumatoid arthritis (RA). They have shown that EC lectin molecules, such as soluble E-selectin, mediate angiogenesis and described an EC molecule, Lewis^Y-6/H-5-2 glycoconjugate (Le^Y/H), which shares some structural features with the soluble E-selectin ligand, sialyl Le^X: Le^Y/H is rapidly cytokine inducible, up-regulated in RA synovial tissue (where it is cell bound) and it is up-regulated in a soluble form in angiogenic RA. Soluble Le^Y/H is a potent angiogenic mediator, suggesting a novel paradigm of soluble blood group antigens as mediators of angiogenic responses and implying new targets for therapy of diseases that are characterized by persistent neovascularization[40].

As reviewed[70], the involvement of carbohydrate-binding proteins in angiogenesis is highly significant. The decisive importance of carbohydrate-recognition during angiogenesis stems from the observation that angiogenic factors, such as the fibroblast growth factor family and vascular endothelial growth factors, bind initially to the extracellular matrix proteoglycans before binding to their cognate receptors; some of the adhesion molecules bind to glycoconjugates present on the surface of the ECs.

Considering the EC participation in homing specificity, this glycoconjugate-mediated presentation of adhesion molecules and factors seems to be quite a general means used by EC to handle the molecules that they use for recognition and/or attraction purposes. This has been demonstrated in the case of cytokines and chemokines involved in the selective homing process.

EC Glycoconjugates as Cytokines/Chemokines Presenters and Microenvironment Signaling Intermediates

Among other cytokines (such as IL-6), IL-7 is documented as a lectin-active cytokine that achieves its cytokine role together with a lectin activity[22] by being presented on the endothelial surface upon binding to glycosaminoglycans[2]. This cytokine can function as a cofactor during myelopoiesis, the generation of cytotoxic T cells[113, 121] natural killer (NK), cells[3, 121] and activated monocytes[4], and it promotes the formation of some organs, i.e. Peyer's patch anlage and germinal center organization[117].

BIZOUARNE et al.[20, 21] and DENIS et al.[32] observed that murine ECs from peripheral lymph nodes could be specifically activated by IL-7 to induce expression of en-

dogenous lectin adhesion molecule. Further studies showed in the same model a selective induction of addressin (MECA79 antigen) expression upon IL-7 treatment[32]. We recently demonstrated the presence of IL-7 receptors on endothelial cells (DUS et al., submitted) but the mechanism of EC activation by IL-7 is not yet attributed as a receptor-mediated or glycosaminoglycan-presented one, as further described in the case of the chemokines.

Chemokines are secreted molecules that play a major part in conditioning the endothelial cells. Synthesized by the underlying epithelial tissue cells, they can be taken up by ECs, trancytosed and finally presented on the luminal EC surface, thus constituting a chemotactic gradient for the circulating blood-borne cells. Because they are synthesized in an organ-selective manner, as reviewed[55], they contribute efficiently to the specific character of cell homing. Not only are chemokines preferentially localized in their synthesis, they stimulate ECs in a selective manner to induce EC adhesion capacity towards lymphocytes. This has been mainly illustrated (CROLA et al., submitted) in the case of fractalkine[10, 37, 46] and 6Ckine[52, 89, 110].

Concluding Remarks

Endothelial cell biology is highly directed towards well-defined recognition and interactions with cells and molecules that modulate the immune responses. ECs are indeed the portals where tissue-entry decisions are taken. As such, endothelial cells are studied to find out the molecules that one has to aim for in order to target a site of the body. EC's second main characteristic resides in their sensitivity to microenvironmental signals by selective activation.

As such, EC's react differentially to organ- and tissue-derived factors such as chemokines, and tumor and inflammation factors; they also react to soluble factors in the lumen of the vessel fluids as well as to the cells that come in contact and raise EC activation.

Consequently, the striking organo-specificity of ECs is a property thanks to which ECs are able to mediate cell selection by adhesion, recognition, extravasation and, ultimately, antigen-to-lymphocyte meeting, thus leading to immune response.

The second level of EC selectivity appears in the differential activation and response to the microenvironment in pathological situations that, analogically to normal situations, take advantage of EC selectivity. Cancer metastases and tumor angiogenesis are examples that were illustrated in this review, which, furthermore, pointed out the importance of glycobiology-dependent EC behavior and biological properties.

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