13 *ABSTRACT*

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Regulatory Role of Carbohydrate Ligands for Selectins in the Homing of Lymphocytes

profile

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Graduated Kyoto University School of Medicine in 1974, and obtained his Ph.D. from Kyoto University Graduate School of Medicine in 1982. Started his professional career in the laboratory of Prof. Sen-itiroh Hakomori at Fred Hutchinson Cancer Research Center, Program of Biochemical Oncology, Seattle, Washington, USA (1980-1982), then became assistant professor at Kyoto University School of Medicine (1982-1985) and then a lecturer there (1985-1991). Presently chief of the Division of Molecular Pathology at Aichi Cancer Center Research Institute. He received the Young Investigator Award from the Japanese Biochemical Society in 1985, and from the Japanese Association for Cancer Research in 1986. His research interests include cell-to-cell interaction and recognition, biochemistry of carbohydrates, and medical oncology.

Key words Cell adhesion, Transcriptional regulation, Carbohydrate sulfation, Chemokine, Cyclic sialic acid

Selectin-mediated cell adhesion is involved in the routine homing of lymphocytes, inflammatory mobilization of leukocytes and tissue infiltration of malignant cells. Recently it has become increasingly clear that selectin-mediated cell adhesion is principally regulated by the expression of specific carbohydrate ligands. Two kinds of carbohydrate ligands for selectin are so far noted in humans: one is conventional sialyl Lewis^x, and the other is sulfated sialyl Lewis^x as represented by sialyl 6-sulfo Lewis^x.[1-4] Conventional sialyl Lewis^x is preferentially involved in the recruitment of leukocytes in inflammation, while sialyl 6-sulfo Lewis^x primarily mediates the routine homing of leukocytes, as schematically shown in Figure 1.

Sialyl Lewis^x is constitutively expressed on granulocytes and monocytes, while it is absent on most resting peripheral lymphocytes. Activation of lymphocytes by inflammatory stimuli strongly induces surface expression of sialyl Lewis^x. This lineage-specific, at times constitutive and at other times inducible expression of sialyl Lewis^x is governed mainly by the transcriptional regulation of the gene for fucosyltransferase VII, the rate-limiting enzyme in sialyl Lewis^x synthesis in leukocytes.[5,6] The 5′-regulatory region of the fucosyltransferase VII gene lacks the conventional TATA box, but has an initiator element juxtaposed by the Sp1 consensus site, which is critical in initiating transcription. The regulatory region is equipped also with multiple binding sites for important activators of transcription, including a distinct CRE-consensus motif, a binding site for T-*bet*, GATA-3 and MZF-1-binding site. These may well play essential roles in the strongly inducible sialyl Le^x expression on activated Th1 lymphocytes, its attenuated expression on Th2 lymphocytes, and its constitutive expression on granulocytes and monocytes.

The sialyl 6-sulfo Lewis^x determinant is expressed on high endothelial venules of peripheral lymph nodes, where it mediates the L-selectin-dependent homing of naïve T lymphocytes. The determinant is also exhibited on HEVs of Peyer's patches, appendices and GALT (gut-associated lymphoreticular tissue), where it mediates the gut-homing of a distinct subset of helper memory T lymphocytes, which express L-selectin, CCR9 and $\alpha_4\beta_7$-integrin. A small subset of resting helper memory T lymphocytes in peripheral blood of healthy individuals also express the determinant. The subset strongly co-expresses PSGL-1 and CCR4, but not $\alpha_4\beta_7$-integrin, indicating that these cells are skin-homing helper memory T lymphocytes, which home to the skin by interacting with E- and P-selectins on dermal endothelial cells.[7] It is noteworthy that the sialyl 6-sulfo Le^x is preferentially involved in the routine homing process of various subsets of helper T-lymphocytes under non-inflammatory conditions.

A peculiar feature of sialyl 6-sulfo Lewis^x is that its selectin-binding activity is strictly regulated by a distinct post-translational modification of the terminal sialic acid moiety,[6, 8-10] which is specifically observed with the sulfated ligand, but not with non-sulfated conventional sialyl Lewis^x. When intracellular mobilization of calcium ion is triggered, the terminal sialic acid moiety of sialyl 6-sulfo Lewis^x is converted to cyclic sialic acid by sialic acid cyclase, and the ligand loses its selectin-binding activity. The conversion of the active selectin ligand to the inert ligand is a very rapid process that is completed within 5 minutes after stimulation, thereby preventing excessive accumulation of leukocytes in routine homing processes. This kind of rapid modulation accompanied by a physiologically significant functional consequence has gone virtually unnoticed in connection with cell surface carbohydrates. Proteins and nucleic acids are generally believed to be indispensable functional molecules, but the role of carbohydrates as the third functional molecules has long remained obscure, and great physiological significance has been attributed to aglycones such as core proteins rather than to carbohydrate portions of the ligands even in the field of selectin research. In any case, the present results further confirm that carbohydrate ligands are substantial functional molecules that figure most in the regulation of selectin-mediated cell adhesion; they are not mere supporting cast for membrane core proteins that carry carbohydrate chains.

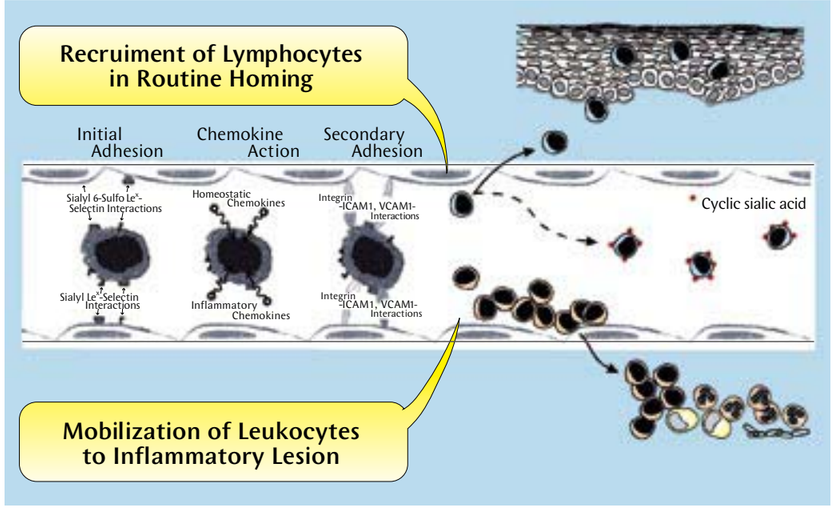

Figure 1. Roles of sulfated and non-sulfated carbohydrate ligands for selectins in the recruitment of lymphocytes. Lymphocytes home at a slow and steady speed, avoiding excess accumulation of cells at vascular beds in the routine homing process. This slow and steady homing is maintained by the negative feedback system employing post-translational modification of the ligand sialyl 6-sulfo Lewisx via the cyclic sialic acid pathway. In contrast, massive accumulation of lymphocytes at an inflammatory lesion is mediated mainly by non-sulfated conventional sialyl Lewisx, the expression of which is augmented by transcriptional activation of the fucosyltransferase VII gene.

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