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REVIEW

Syndecan-1 – A New Piece in B-cell Puzzle+

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Syndecans are transmembrane proteoglycans, with core proteins mainly decorated with heparan sulfate chains. Syndecan-1 is expressed in a tissue-, cell- and differentiation-specific manner. Its extracellular domain can bind via HS chains to matrix elements, to growth factors (especially "heparin-binding" proteins) and to certain biological agents. The ectodomain released by proteolysis can also be functionally active. The cytoplasmic domain can take part in signaling processes as well as in modifying cell shape. In hematopoietic cells syndecan-1 is expressed in normal pre-B-cells and plasma cells, as well as in plasmocytoid and lymphoplasmocytoid malignancies. According to our study syndecan-1 is expressed in B-CLL cells both in tissue environment and in circulation. (Pathology Oncology Research Vol 3, No 3, 183–191, 1997)

Key words: syndecan-1, heparan sulfate, proteoglycan, hematopoietic cells, B-cells

Introduction

Life is dependent, essentially, on the highly regulated crosstalks and interactions between the cells and their microenvironment (other cells, matrix; including blood vessels). Proteoglycans (PG – where the core protein is decorated with sulfated sugar chains) – either as cellular or matrix elements (*Table 1.*) – are more and more appreciated participants of these interactions.[1-7] The aim of this review is to offer a brief outline on a peculiar family of PGs, the *syndecans*, especially syndecan-1 in hematopoietic cells.

The core protein of PGs is glycanated by glycosaminoglycans (GAG). (The enzymes responsible for GAG biosynthesis are located largely in the Golgi apparatus.) A tetrasaccharide "linkage region" (-glucuronic acid-galatose-galactose-xylose-) attached to a serine residue in the core protein is the starting point for polysaccharide chain elongation. The biosynthesis of heparan sulfate (HS – which is the main GAG of syndecans) starts as alternating D-glucuronic (GlcA) and N-acetyl-D-glucosamine (GlcNAc) units, joined by 1→4 linkages. The structure is further modified, N-deacetylated/N-sulfated, by C5 epimerization (GlcA→IdoA; iduronic acid) and various O-sulfations. The variability of these modifications allows for some 30 different disaccharide sequences.

The binding of HS sequences to proteins is usually ionic, and involves positively charged, generally clustered amino acids in the core protein. The interaction between HS and proteins is dependent on the presence of sulfate groups, but it is difficult to identify the groups actually essential for binding. It is also known that properly spaced sequences along the HS chain may form functional domains (when bound to growth factors or to other elements).[10]

The *syndecan* (greek: syndein + glychos) *family* has four members, whose core protein carries partly heparan sulfate (HS), and partly chondroitin sulfate (CS). These sulfated sugar chains are responsible mainly for the functional activity of syndecans, i.e. to react with widely different molecules, e.g. growth factors, matrix components, proteases and their inhibitors, biological agents, etc.[7-13]

The known members of the family (in vertebrates) are: *syndecan-1* (epithelial syndecan); *syndecan-2* (fibroglycan; connective tissue syndecan); *syndecan-3* (N-syndecan; neural syndecan); *syndecan 4* (amphiglycan, ryudocan; ubiquitous syndecan).[14] The expression of syndecan is regulated at different levels (transcription, translation,

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Table 1. **Proteoglycans** [8,9]

Localization	*Type*	*GAG chain*
Intracellular	serglycin	HS/CS
Membrane		
SLIPS	(syndecan-like integral membrane proteoglycans)	
	syndecan-1	HS/CS
	syndecan-2,-3,-4	HS
GRIPS	(glypican-related integral membrane proteoglycans)	
	glypicans	HS
part-time PGs		
	betaglycan	HS/CS
	CD44	CS
Extracellular		
SLRPS	(small leucin-rich proteoglycans)	
- class I	decorin, biglycan	CS/DS
- class II	fibromodulin, lumican, keratocan	
	PRELP, osteoadherin	KS
- class III	epiphycan	CS/DS
	osteoglycin	KS
Modular PGs		
- hyalectans	(hyaluronan- and lectin binding PGs) versican, aggrecan, neurocan, brevican	
- non-hyaluronan-binding PGs		
	perlecan, agrin, testican	HS/CS

posttranslation) which contributes to the cell-type-, tissue-type- and differentiation-dependent appearance.[15,16] Syndecan-1 is rather characteristic on differentiated epithelial cells, syndecan-2 on fibroblasts,[17] endothelial cells,[18] and hepatocytes,[19,20] syndecan-3 on neural elements (e.g. on Schwann cells),[21,22] while syndecan-4 can be expressed by various cell types.[23-25] The structures of syndecans are very similar. Moreover, the transmembrane and cytoplasmic parts are highly conservative – only the extracellular parts show individual amino acid sequences, including glycanation sites; therefore differences in the degree of glycanation.[8,12,14] (*Fig. 1*). The extracellular part (ectodomain) contains protease-sensitive cleavage site(s).[26]

Syndecan-1

Structure and expression

The syndecan-1 gene was first cloned from mouse mammary epithelial cells.[27] Now the cDNA sequences in human,[28] rat,[29] and hamster cells[30] are also known, together with the whole mouse gene (23 kb), including the promoter region.[31]

In mice the syndecan-1 gene is localized on chromosome 12, in humans on chromosome 2 (2p23–24 – 2p24.1), close to the N-myc gene. In addition, some important genes have been identified in the vicinity (in the same linkage-group): DEAD-box genes, ornithin decarboxylase, ribonucleotid reductase.[33,34] The homology in the mouse and human syndecan-1 gene and protein is rather high, 78% and 77%, respectively.[32-36] The cytoplasmic and transmembrane domains are evolutionarily conserved (suggesting important biological function). (*Fig. 2*). The gene has 5 exons and 4 introns, the first intron being large (17 kb), compared to the others. Exon I contains the signal sequence, exons II–IV the coding sequences for the extracellular domain (with the five potential glycosylation sites), while exon V for the transmembrane and cytoplasmic domains. The exons are situated between two non-translated end-regions. Northern hybridization results in two mRNA bands, 3,4 and 2,6 kb, where the difference is due to the various degree of adenylation at 3' polyadenylation sites.

The promoter region has three transcription-initiation sites. Binding sites for a variety of different transcription factors support the transcription of syndecan-1, both in constitutively and specifically regulated manner. The former is indicated by binding sites (boxes) for AP2-TF and Sp1-TF, which are common in the promoter regions of "house-keeping" genes, while the latter is performed mainly by binding sites for Antp-TF, NFκB-TF, MyoD-TF and C/EBP boxes, which are more responsible for tissue-, cell or differentiation-specific expression.[28,31,37,38] (*Fig. 3*)

The syndecan-1 protein (69kDa) – similarly to other PGs – is glycanated in the Golgi apparatus, and after the

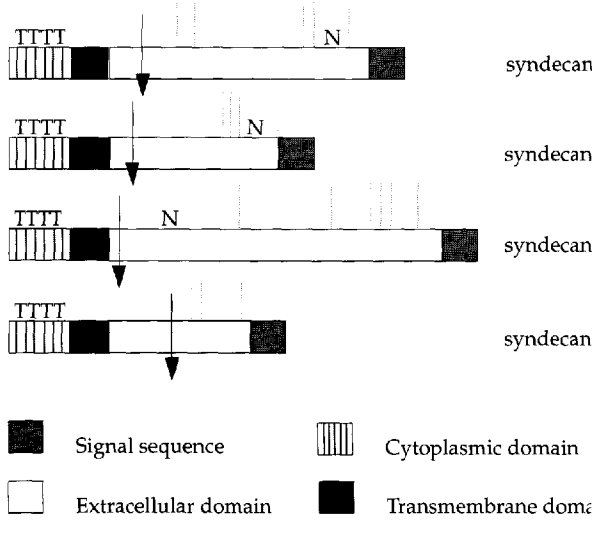

Figure 1. *Protein structures of syndecans. N – glycosylation site; dotted line – GAG-binding sites; arrows – proteolytic cleavage sites; T – tyrosine phosphorylation site*

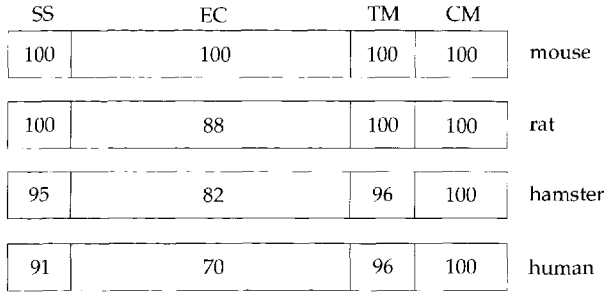

Figure 2. Protein homology of syndecan-1 in various species. Numbers show homology in percentages. SS – signal sequence; EC – extracellular domain; TM – transmembrane domain; CY – cytoplasmic domain

removal of a signal peptide sequence it will reach the cell membrane.[6,12] The N-terminal end carries those amino acid sequences which are able to link covalently to the sugar chains at their serines. In syndecan-1 the DG*S*G*D* and F*S*G*S*GTG sequences can bind primarily HS, while EG*S*G*E* and ET*S*G*E* sequences both HS and CS chains.[39] The glycosylation degree and pattern of the extracellular part can be tissue-specific.[40] The number and length of HS and CS chains, as well as their ratio (HS/CS) ensure the heterogeneity of syndecan-1. The most frequently observed isoforms are: ~100 kDa mainly in squamous

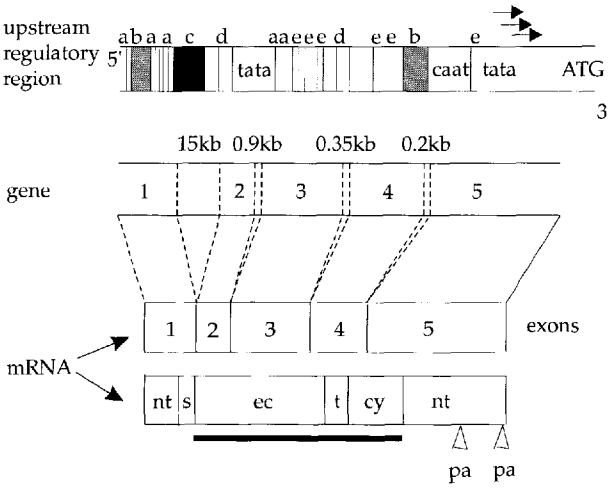

Figure 3. Structure of mouse syndecan-1 gene and mRNA. Upstream regulatory region: binding regions: a – E-box (e.g. MyoD-TF); b – NF-κB; c – tata-like box (Antennapedia TF); d – C/EBP-box (e.g. NF-IL6); e – GC-box (e.g. Sp1-TF, AP2-TF); arrows – transcription initiation sites; Gene: numbered boxes are the exons; the sizes of introns are above the open boxes; mRNS: upper row shows the mature mRNA (exons); the lower row shows the translated and non-translated coding regions. nt – non-translated, s – signal sequence, ec – extracellular domain, t – transmembrane domain, cy – cytoplasmic domain, pa – polyadenylation sites. The thick line shows the translated protein.

cells and plasma cells – localized on the surface by surrounding the cell; ~160 kDa mainly in glandular and single layered epithelial cells – localized especially on the basolateral aspect of the cell; and ~300 kDa mainly in fibroblasts (in vitro) – localized intracellularly.[11,41-47] It has been observed that the various HS/CS ratios allow the binding of different molecules[48] (e.g. on dental mesenchymal cells syndecan-1 can bind tenascin, while mammary epithelial cells with different HS/CS ratio – glycanation pattern – are unable to bind[49]). Syndecan-1 has a rather extended core protein which allows the binding of HS chains at relatively far distances from each other and facilitates interactions of individual HS chains at the same time (e.g. syndecan-1 can be immobilized by one of its HS chains to fibronectin or collagen, and can interact – simultaneously – with bFGF; basic fibroblast growth factor). However, the free HS chains can bind to only one of the two proteins, suggesting much more functional versatility for intact PG than for individual HS chains. The two potential proteolytic sites contribute to the heterogeneity of the extracellular appearance of syndecan-1, since the extracellular part can be cleaved off or endocytosized.[56]

The expression of syndecan-1 can be influenced by hormones (e.g. testosterone, glucocorticoids),[51-53] and by cytokines (*Table 2*). The stimulation of cAMP signals has been described to activate the mRNA pool of syndecan-1 in mouse peritoneal macrophages.[51] Bernfield et al studied the expression of the members of the syndecan family in various cells and tissues, in vitro.[15] They found large amounts of syndecan-1 in epithelial cells, plasma cells and fibroblasts, smaller amounts in neural cells, in some endothelial and pre-B cell lines. Accordingly, the syndecan-1 mRNA expression was high in organs rich in epithelial cells (skin, liver, kidney, lung), and lower, but still significant, in the brain and small intestine. In the mouse embryo the syndecan-1 protein was already present in the four-cell stage, and after gastrulation the expression increased in the ectodermal components.[11,15,56] Differentiation-dependent change of expression has been observed at the interactions of epithelial and mesenchymal cells,[57,58] in different organs (teeth,[59,60] kidney,[61,62] skin, cornea,[63] female genital-tract,[42] lung,[43] skeletal muscle,[64] B-cells,[65]). Interestingly, the expression decreased with the transformation of differentiated epithelial cells (keratinocytes,[66] and epithelial cell lines,[67] *in vitro*), and with the dedifferentiation of epithelial malignancies (head and neck-,[68] cervix-,[69] breast-,[52] colon-carcinoma,[70] hepatocellular carcinoma,[71] teratocarcinoma[72]).

Function

Extracellular domain. – The function of syndecans, similarly to other PGs, is determined mainly by the HS and CS chains of the extracellular domain.[73] Syndecan-1

Table 2. Influence of cytokines on syndecan-1 expression

Cytokine	*Change*	*Expression*	*Cell type*	*Ref*
TGFβ, bFGF	up	mRNA, protein	mouse 3T3 fibroblasts, NMuMg	(55)
TGFβ, bFGF	up	only CS chain	human lung fibroblasts	(54)
PDGF	up	mRNA, protein	rat vascular smooth muscle cells	(64)
TNFα	down	mRNA, protein	mouse endothelial cells	(18)
IL-6	down	protein	human B-cells	(116)

may carry both, but functionally the HS chains seem to be more active (especially by interacting with the "heparin-binding" proteins). HS chains can act as

receptors or co-receptors for different ligands,[74] as

- extracellular matrix components: collagen I–III–V,[75] fibronectin, thrombospondin,[76] tenascin,[77,78] amphotherin and laminin.[79] Essentially, these interactions *encourage the binding of the cell to the matrix* (adherency). It has been shown that transfection of syndecan-1 increased the adherency of lymphoid (Raji) cells and at the same time inhibited the invasive capacity of the cells on collagen I coated surfaces. The interactions between syndecan-1 and the different matrix elements help to fix the cell in a given microenvironment.[80,81] Besides the cell-matrix co-operation, syndecan-1 takes part in *cell-cell adhesion*, either as an adhesion molecule or as the activator of other adhesion factors.
- "heparin-binding" *cytokines, growth factors* (e.g. bFGF, midkine).[82-85] Syndecan-1, acting as an essential co-receptor for bFGF, is expressed on fibroblasts during their differentiation until it is required, i.e.until the fibroblasts need bFGF for differentiation.[11,86] Besides bFGF, a co-expression of TGFβ1 (transforming growth factor-beta; which is also a "heparin-binding" protein) with syndecan-1 was also observed during the development of certain organs. It is highly possible, that these factors and syndecan-1 can influence each others' expression, working as a feed-back regulatory network.[54]
- different *biological agents* as parasites, viruses, bacteria, which can use syndecan-1 as a membrane-receptor helping their binding to the target cells.[87,88]

The *extracellular domain* of syndecan-1 *released by proteolysis*[27] could perform functional activity:

- The release itself could *decrease the anchorage of the cell to the matrix*, promoting detachment of the cell from the matrix and supporting cell mobility.
- Another consequence could be an effect of the accumulated extracellular domain on cellular activities, either in autocrine or paracrine fashion. This is supported by the experiment where the soluble extracellular domain given exogenously *inhibited the proliferation* of certain tumor cells, *in vitro*, without influencing the normal counterparts.[89] The effect could be inhibitory, i.e. the growth factors "trapped" by the released ectodomain.
- It is possible that the released extracellular domain or its negatively charged sulfated sugar chains (especially HS) can *reach the nucleus* and bind to transcription factors or other nuclear proteins which modify/regulate DNA activity.[11]

Cytoplasmic domain. – The cytoplasmic domain is conserved with potential phosphorylation sites (tyrosines) (there is a consensus sequence for the recognition by tyrosine kinase). The role of this domain is still not understood, although some results emphasize its importance:

- The potential tyrosine phosphorylation indicates that syndecans could be cascade elements in *signal transductions*; e.g. the cytoplasmic part of syndecan-2 and -3 are substrates for protein kinase C (but syndecan-1 and -4 are not).
- The change in phosphorylation of syndecan-1 could take part in the *regulation of the release of the extracellular domain*.[90,91] (The cytoplasmic domain is probably activated by phosphorylation, which is regulated mainly by phosphatases. Phosphatase inhibition by orthovanadate and pervanadate released the inhibited tyrosine kinase and the cytoplasmic domain became phosphorylated.)[90,91]
- The cytoplasmic domain can *interact with other cytoplasmic components* (e.g. F-actin filaments) influencing the change in cell shape. It is believed that function is independent from the quality or quantity of the extracellular sugar chains.[22,92,93]
- A significant task for the cytoplasmic domain could be the *guide of the molecule towards the cell membrane*. The localization of a mutant syndecan-1 was changed by deleting the last 12 amino acids from the C'-terminal end. The mutant form appeared not only on the basolateral surface (as the wild form) but apically as well, on MDCK and CHO cells. It is interesting that similar deletion in the cytoplasmic domain did not influence the migration of syndecan-1 to the cell membrane.[92,94]

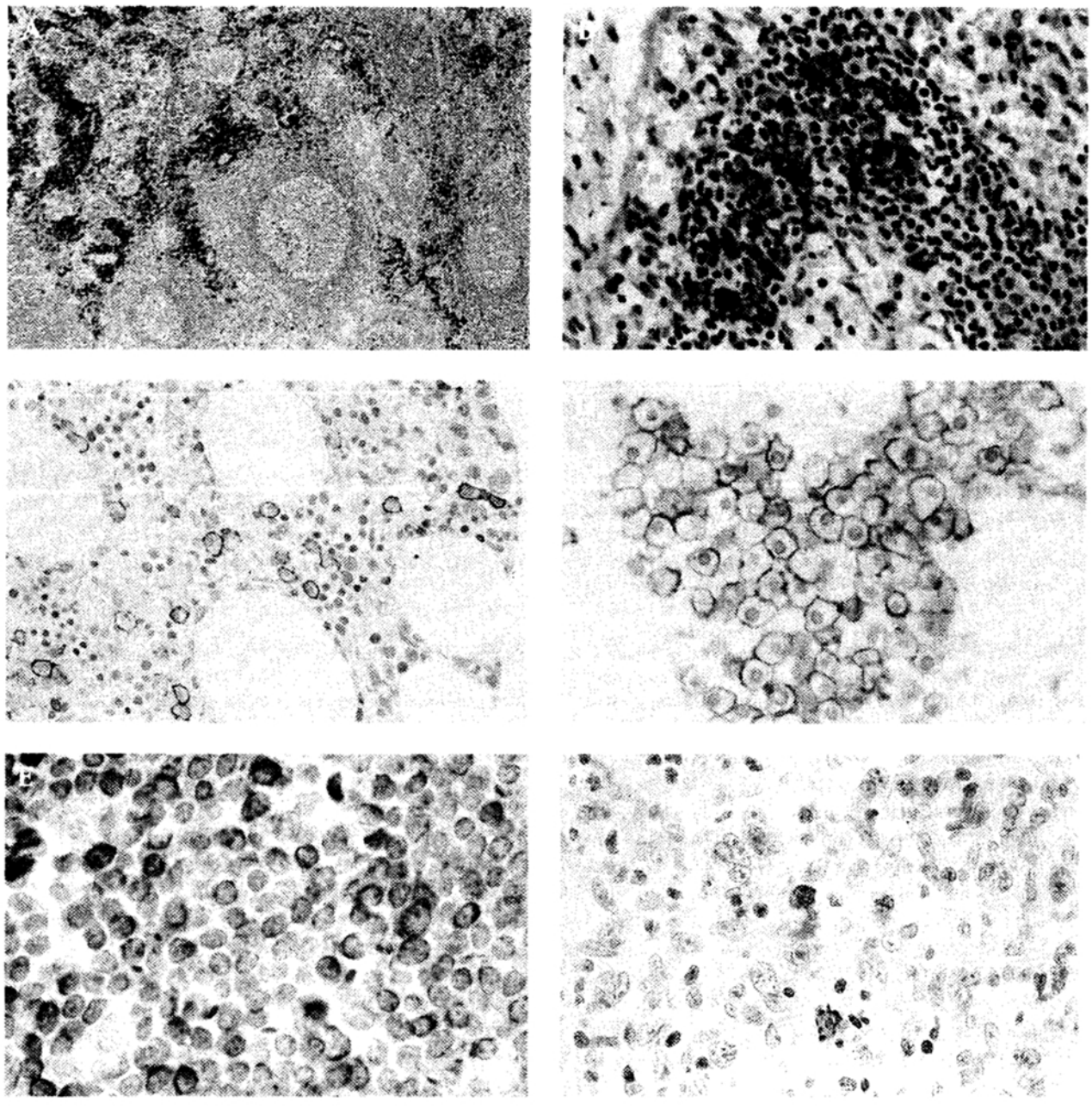

Figure 4. *Expression of syndecan-1. a, b – intensive labelling of plasma cells in lymph node; c – plasma cells in normal bone marrow; d – myeloma cells in bone marrow; e – B-CLL; f – Hodgkin disease (note the positivity of plasma cells and negativity of Hodgkin cells).*

Syndecan-1 and the hematopoietic cells

Bone marrow stem cells and stromal cells - It is known that the differentiation of hematopoietic cells in the bone marrow requires a continuous interaction between stem and/or precursor cells and stromal cells. Many observations support the role of PGs in these interactions: the stromal cells in the bone marrow produce CS and hyaluronic acid, less DS and HS;[95-97] exogenous, purified GAG given to bone marrow stromal cells inhibits GM-CSF activity;[98] HS isolated from bone marrow stromal cells can bind GM-CSF and the biologically active form of IL-3;[99] the removal of HS and CS chains decreases the adhesion between stromal cells and hemopoietic cells.[100]

Endothelial cells – Endothelial cells are normally syndecan-1 negative, but they express different HSPGs upon activation: syndecan-1, -2, -4, glypican and perlecan. This expression is influenced by inflammatory processes, since

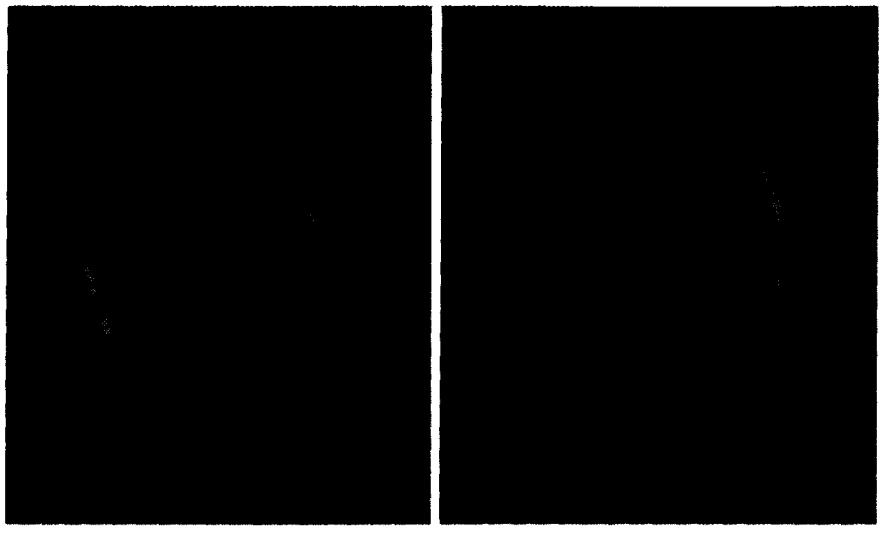

Figure 5. Localization of syndecan-1 on HT58 cultured human NHL cell by confocal microscopy (fluorescent immuncytochemistry with Serotec monoclonal antihuman syndecan-1 antibody after fixation). More than 75 percent of HT58 cells show this in-homogeneous, polarised cell surface positivity of syndecan-1. a – 8-th slide from 16 slides, b – 12-th slide from 16 slides.

GAG production is increased by IL-1, TNFα, and TGFβ, while being decreased by certain injuries (e.g. virus-infection or hypoxia).[101] HS released from the endothelial surface by proteolysis can stimulate the activity of APCs (antigen-presenting cells).[102] It is also known that heparin inhibits the P- and L-selectin mediated "leucocyte rolling" on the endothelial cells.[103]

Lymphoid cells. – In lymphoid cell differentiation the early forms of B-cells have a relatively close relationship with the stromal cells, which is ended by the immunglobulin-gene rearrangements, and finally the B-cells leave the bone marrow and reach the secondary lymphoid organs. Here, antigen stimulus can transform B-cells into antibody-forming plasma cells. Interestingly, these stages are accompanied by changes in syndecan-1 protein expression: it is present on the pre-B-cells in the bone marrow and also on the plasma cells (i.e. when the cells seem to require tissue environments and interactions), while it is missing from the circulating B-cells.[65] Different experiments showed that following activation or repeated immunization, the plasma cells appearing at day 7–10 expressed syndecan-1, but memory cells appearing later, did not.[104-107] Similarly, in mouse spleen the immunization activated antibody-forming cells proved to be syndecan-1 positive.[108] Recently, two new genes were described in relation to maturation of plasma cells: B-lymphocyte-induced-maturation-protein (Blimp) and B-cell-specific-activation-protein (BSAP): their expression changed together with syndecan-1, increased (B-limp and syndecan-1) or decreased (BSAP).[109,110] All these information suggest that syndecan-1 is required for B-cells at certain stages of differentiation, either to contribute to their immobilization in a particular tissue environment and/or to serve as a receptor to bind certain growth/maturation factors. The former possibility is further supported by the findings that cells of plasmocytoma lines were readily attached to collagen,[45,111] and that syndecan-1 participated in the adhesion process of lymphoid cells.[80,112] It should be emphasized again, that the fine structure of HS can differ on identical PG core proteins influencing fundamental cellular properties. E.g. two myeloma lines with almost the same amounts of syndecan-1 and similarly sized core protein and HS chains showed highly different binding to type I collagen.[113]

The question arises that if syndecan takes part in the regulation of B-cell differentiation, how does it change – if at all – in leukemo- or lymphomagenesis. As mentioned, the dedifferentiation of epithelial tumors was accompanied by the decrease or loss of syndecan-1 expression. This is definitely not the case with plasma cells, since the expression of syndecan-1 is maintained in myeloma/plasmocytoma cells, as well as in lymphoplasmocytoid lymphoma cells. In our study – on more than 50 human NHLs – the plasmocytoid or lymphoplasmocytoid tumors also showed positivity *(Figs. 4,5)*. Moreover, practically in all B-CLL cases both circulating leukemic cells and those infiltrating the lymph nodes expressed syndecan-1 (mRNA and protein).[114] These results are opposed to the observation of others' on B-CLL cells as well as on Reed-Sternberg cells[115] (in our Hodgkin lymphoma cases the tumor cells proved to be negative). The differences are probably caused by using different antibodies or different antigene-retrieval techniques.

The biological significance of syndecan-1 expression in hemopoetic cells is still to be undertstood. The puzzle is complicated by the fact that until now none of the other lymphoid cell types – normal or malignant T-cells, as well as B-cell lymphomas except those mentioned above – were found to express syndecan-1. Moreover, if syndecan-1 is expressed only in certain leukemias/lymphomas, is it involved in the pathogenesis of these malignancies, or is it merely "just" an accompanying by-stander?

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