Review paper

Selectins in dermatology

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Post Dermatol Alergol 2011; XXVIII, 6: 514–521

Abstract

In the course of an inflammatory reaction an inflow of cells takes place to the site of inflammation. At the beginning of the process the main role is played by selectins, the group of three proteins responsible for initiation of leukocyte adhesion to endothelial cells. Selectins are present on the cell surface while serum and body fluids contain their soluble forms. In the course of several inflammatory diseases alterations in intensity of E-selectin expression or in concentration of their soluble forms were detected. We have devoted our attention to the problem of selectins in dermatology.

Key words: selectins, ligands, selectins in dermatology.

Introduction

Tissue leukocyte infiltrate represents one of the exponents of an inflammatory infiltrate [1]. Adhesion molecules participate in the inflammatory reaction of the body. They include selectins, integrins, immunoglobulin-like molecules, sialomucins and cadherins. The process of leukocyte migration itself may be separated into five stages: marginalization, rolling, activation, strict adhesion and diapedesis [2]. Introduction to the extravasation involves contact between a circulating lymphocyte and endothelial surface. The process is possible due to binding of selectins to their ligands. In the sequels, the blood flow pushing the lymphocyte from behind causes its rotatory motion [1]. In immunological nomenclature the phenomenon is termed rolling [1]. The motion of a lymphocyte over the endothelial surface has a constant pace [1]. At that time the lymphocyte is subjected to the action of various chemotactic substances. Subsequently, lymphocytic integrins bind to immunoglobulin-like molecules and fix the lymphocyte to the endothelium. Activated leukocytes produce proteolytic enzymes, which decompose proteins of the extracellular matrix and endothelium basement membrane, which allows for diapedesis [1, 2]. After penetrating the tissue interior the lymphocyte fulfils its effector functions.

Concentration of soluble forms of adhesion molecules, including selectins, is elevated in various inflammatory diseases encountered in dermatology [3]. Inhibition of adhesion molecule activities in treatment of inflammatory diseases by application of antibodies or peptide fragments which block their interactions opens up considerable potential of developing modern therapeutic methods in various branches of medicine [4-7].

Selectins

Selectins are glycoproteins of a common structural scheme (Figure 1). Their N-terminal fragment of the extracellular portion is formed by a calcium-dependent lectin domain [1, 8]. Next to it, a fragment exists with a structure resembling that of epithelial growth factor, termed the epithelial growth factor (EGF)-like fragment [1, 8]. Depending on the type of selectin, subsequently a variable number of domains can be distinguished, manifesting structure similar to proteins involved in complement system regulation (CSR) [1, 8]. Every selectin also contains a trans-membrane fragment, passing through the entire cell membrane thickness. The terminal component involves a relatively short intracellular fragment [1, 8]. The lectin domain plays a mediatory role in binding a ligand while the EGF-like domain and CSR domain control affinity of selectins to ligands, the transmembrane fragment provides anchorage in the cell membrane for the entire selectin molecule, while its intracellular portion is responsible for transmission of a signal for molecule internalization [9, 10]. Three types of selectins can be distin-

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guished: endothelial E-selectin, leukocytic L-selectin and platelet P-selectin. The type of selectin is determined by its extramembranous part, specifically by the number of CSR repeats; thus E-selectin contains six repeats of CSR, L-selectin contains two, while P-selectin has as many as nine CSR repeats [1].

Soluble forms of selectins may arise due to shedding of the molecule fragments from the cell surface and also due to alternate splicing of the gene product [11-13]. Increased concentration of selectins, and of E-selectin in particular, is considered to represent a marker of endothelial cell activity [14, 15].

E-selectin, also termed CD 62 E, is produced *de novo* in endothelial cells following their stimulation by, e.g., interleukin 1, tumour necrosis factor β (TNF-β) or lipopolysaccharide [11, 16]. As compared to other selectins, it manifests an intermediate molecular weight (115 kD), resulting from its content of 6 CSR domains [1]. Its earlier employed domains include endothelium leukocyte adhesion molecule 1 (ELAM-1) and leukocyte-endothelial adhesion molecule 2 (LECAM-2) [17]. Expression of E-selectin may be noted exclusively at the site of an ongoing inflammatory process, and because it is produced by endothelial cells only, it can be regarded as representing a marker of activity of the cells and be used in monitoring of diseases with vascular engagement [2, 5, 10]. Its expression cannot be detected until a few to more than 10 h following activation. Preceded by cell stimulation by cytokines or endotoxins, E-selectin is synthesized *de novo* and then supplied to the cell membrane [10]. The process takes 2 to 4 h. Following its short exposure, within 24 h E-selectin becomes decomposed in cellular lysosomes [10, 17]. The principal function of E-selectin involves transition of the leukocyte rolling stage to strict adhesion. This can happen since E-selectin may slow down movement of cells rolling on the surface of endothelium [18]. Its soluble form, still active, seems to represent the extracellular fragment, deprived of integrin transmembrane and intracellular portions. It exerts chemotactic activity toward neutrophils and it activates integrins β2. Mean concentration of the soluble E-selectin in sera of healthy individuals ranges from 10 ng/ml to 112 ng/ml [19-21].

L-selectin, also termed CD 62 L, contains only two CSR domains, and thus represents the smallest molecule among the discussed group. Its molecular weight is appraised at 74-100 kDa [1]. Its synonyms include leukocyte-endothelial adhesion molecule 1 (LECAM-1) and leukocyte adhesion molecule 1 (LAM-1) [6]. The protein is constitutively expressed on the surface of monocytes, granulocytes, lymphocytes, haemopoietic progenitor cells as well as on immature platelets. L-selectin is also present on the surface of high endothelium venules, typical for blood vessels of lymph nodes, thus playing an important role in lymphocyte recruitment to the organs [3]. Following cell activation, a proteolytic reaction and then shedding of the extracellular P-selectin portion from the cell surface takes place. This form remains active and, at high concentrations, it inhibits binding of leukocytes to endothelium [9, 22]. Various isoforms of the soluble L-selectin exist, depending on the cell type from which the molecule was shed [9]. However, the principal source of the soluble L-selectin form involves leukocytes accumulated in the site of inflammation [17]. According to the recent literature data in healthy individuals the mean serum concentration of the soluble L-selectin form ranges between 379 ng/ml and 2400 ng/ml [9, 22]. In turn at concentrations of 8000 ng/ml to 15000 ng/ml, adhesion of lymphocytes to endothelium is fully blocked [9]. In the course of inflammation, L-selectin cooperates with P-selectin, and therefore absence of either of them does not markedly affects the rolling process [17]

P-selectin, also termed CD62P, represents the largest of selectins since it contains 9 CSR domains. The molecular mass is 140 kDa. Other, less frequently used names include granule membrane protein 140 (GMP-140), platelet activation dependent granule-external membrane protein (PADGEM) and leukocyte-endothelial adhesion molecule 3 (LECAM-3) [1, 17]. The protein is present in granules α of blood platelets and in Weibel-Palade bodies of endothelial cells. Within a short time after cell activation (a few seconds or minutes) expression of P-selectin molecules takes place on the cell surface, with the maximum noted after 20-30 min [10]. The translocation of P-selectin from granules to cell membrane takes place under the effect of thrombin, histamine, complement components or tumour cells [1, 10, 23]. Its expression on the cell surface is transient and therefore it can be employed as an index allowing evaluation of early interaction between endothelial cells and lymphocytes [23-25]. Termination of activation is followed by re-internalization of a P-selectin molecule fragment in granules of blood platelets and Weibel-Palade bodies of endothelial cells. P-selectin alone is capable of starting leukocyte motility during an inflammatory reaction and it can compensate for the absence of E-selectin [26]. In parallel, E-selectin can successfully substitute for P-selectin. The soluble form of P-selectin, still functionally active, exhibits pro-coagulative properties, and thus it plays a significant role in thrombosis in blood vessels [23, 27]. Two forms of soluble P-selectin exist: the first results from proteolysis beyond the 9th CSR repeat; the other results from alternate splicing of the gene product [24]. In turn, Dunlop *et al*. list three types of soluble P-selectin: two carrying different numbers of SCR repeats, and the third one differing from the former two by absence of transmembrane and intracellular portions [28]. Mean concentrations of the soluble P-selectin in healthy individuals range, according to references, between 36 ng/ml and 300 ng/ml [24, 27-29].

All of the above described selectins recognizing specific carbohydrate determinants bind to ligands on the cell surface of leukocytes, blood platelets and endothelial cells [1]. The linkages activate leukocyte migration (dia-

pedesis) through the wall of blood vessels to the injured tissue or to the site of the developing inflammatory process. The ligands involve sialylated and fucosylated lactosoaminoglycans, situated on a protein core. The core is responsible, most probably, for maintenance of a correct framework for sugar groups [1]. Mucins represent the most accurately recognized L-selectin ligands [1]. They include the most typical blood group antigen, sialylated LewisX (sLe^x CD 15s) and its sLe^a form (CD15a) [1, 11].

The leading ligand for E-selectin is E-L-selectin ligand-1 (ESL-1), present on the surface of lymphocytes during chronic inflammatory processes and on skin-homing lymphocytes. The other ligand, similarly to P-selectin, is PSGL-1. In this way, as mentioned above, function of the selectins can overlap in part and absence of one of them may be compensated by activity of the other one [5, 17].

So far, three ligands of L-selectin have been distinguished: mucosal addressin cell adhesion molecule (MAdCAM-1) manifested mainly on the endothelial surface in mucosal blood vessels; glycosylation-dependent cell adhesion molecule (GlyCAM-1) "suspended" in the glycocalyx of endothelial cells; and CD34 molecule, "anchored" in endothelial cell membrane of blood vessels in lymphoid organs [1, 6, 11].

The main ligand for P-selectin is P selectin glycoprotein ligand-1 (PSGL-1), present on the surface of leukocytes [17]. The other ligand is CD24 (*O-linked oligosaccharide modified glycoprotein*), also termed head stable antigen (HSA), present mainly on neutrophils [1, 8, 11, 17].

The soluble forms of ligands exert an inhibitory action on selectins, blocking them [12]. Conversely, soluble forms of selectins may bind to appropriate ligands and thus may restrict binding of selectins to target cells [12].

Selectins in dermatology

The aspect of adhesion molecules, including selectins, was considered most broadly in psoriasis. Elevated concentrations of E-selectin soluble form were detected in various varieties of psoriasis, including regular psoriasis, generalized pustular psoriasis, pustular psoriasis of palms and soles, and psoriatic erythroderma, and its mean concentrations ranged between 35.1 ng/ml and 139 ng/ml [30-35]. In addition, Yamamoto *et al.* found no significant differences in serum concentration of the protein between patients with ordinary psoriasis and those with pustular psoriasis [32]. Significance of E-selectin in pathogenesis of psoriasis is accentuated by the fact that the applied treatment, e.g., with tars, vitamin D_3 derivatives, systemic glucocorticoids, cyclosporin A, phototherapy, and clinical improvement, was accompanied by a decrease in serum concentration of the soluble form [31, 33, 34, 36]. Nevertheless, Carmona *et al*. noted that despite the lowered concentration of selectin soluble form following treatment of ordinary psoriasis with cyclosporin A, as compared to its pre-treatment levels, its concentration continued to be higher than that noted in a healthy control group. The authors suggested that the persisting high concentrations of E-selectin soluble form (after treatment) may reflect the still persisting activity of endothelial cells and this phenomenon may cause psoriasis relapses [31]. In turn, Groves *et al*. detected no relationship between serum concentration of E-selectin soluble form and exponents of inflammatory conditions, such as ESR or WBC level [30]. In immunohistochemical studies, elevated expression of E-selectin was demonstrated in endothelial cells of skin samples obtained from psoriasis patients [37-40]. Interesting results were presented by Pestelli *et al*., who demonstrated significantly depressed E-P-selectin expression in endothelial cells of psoriatic patients following treatment with cetirizine. The study was controlled by a double blind sample [41]. Serum concentration of P-selectin soluble form was supposed to be higher in patients with psoriasis and its mean values ranged from 76.96 ng/ml to 144.58 ng/ml [36, 42, 43]. In parallel, it should be noted that according to Garbaraviciene *et al*. the values were found to manifest a correlation with intensity of the disease, expressed as PASI (*Psoriasis Area and Severity Index*) [42]. Interestingly, however, no decrease in concentration of P-selectin soluble form was found to follow the applied treatment even if in the same groups the treatment resulted in decreased concentrations of E-selectin soluble form [36]. Aside from P-selectin soluble form, Garbaraviciene *et al.* demonstrated by flow cytometry also its augmented expression in activated blood platelets. In this case the values showed a correlation with PASI [42]. In patients with psoriasis serum concentration of L-selectin soluble form was also examined, disclosing mean values of 1030 ng/ml to 2290 ng/ml, i.e. higher than those noted in a healthy control group. However, the concentration showed no correlation with PASI [36, 44, 45]. Interestingly, Long *et al*. demonstrated that concentration of L-selectin soluble form (similarly to mean serum concentration of P-selectin soluble form) showed no decrease following phototherapy although a decrease was noted in E-selectin soluble form [36]. Expression of L-selectin molecule concentration on the surface of circulating lymphocytes CD4+ and CD8+, monocytes and neutrophils was evaluated by Inaoki *et al*. in patients with benign, moderately severe or severe psoriasis. In the severe form of psoriasis expression of L-selectin proved to be significantly lower on lymphocytes CD4+ as compared to the healthy controls and it showed a negative correlation with PASI. A similarly lower expression of L-selectin molecule was presented also by the remaining inflammatory cells but the difference proved to be insignificant. The results might point to a possible role of lymphocytes CD4+m in pathogenesis of psoriasis [45].

Also in the other forms of eczema, including erythroderma, and in contact dermatitis elevated values of serum concentration of E-selectin soluble form were noted. The mean values were 41.2 ng/ml to 151.5 ng/ml and showed

no significant differences from those noted in psoriasis [30, 46]. Fujita *et al.* stressed in addition that the molecule carries particular significance at early phases of the disease [46]. Nevertheless, no correlation with ESR or WBC levels was found [30]. In turn, Ludwig *et al*. showed by flow cytometry an elevated expression of P-selectin molecule on blood platelets, as compared to a healthy control group [47]. Also in atopic dermatitis elevated, as compared to a healthy control group, serum concentrations of E-selectin soluble form were observed, with its mean levels ranging from 7.7 ng/ml to 167.7 ng/ml [19, 20, 48]. Significantly, a positive correlation was found between serum concentration of the molecule and degree of disease intensity and total serum concentration of IgE [20]. Reich *et al*., in turn, noted elevated serum concentration of E-selectin, only in those patients with atopic dermatitis in whom air-borne allergy was detected to birch pollen and house dust mites but not to grass pollen [48].

Chronic urticaria involves another dermatosis in the course of which elevated serum concentrations of E-selectin soluble form were detected. In this case its mean values ranged from 12.3 ng/ml to 83.22 ng/ml [19, 20, 49] and were supposed to decrease upon therapy with anti-histaminic drugs [49]. Higher expression of E-selectin on endothelial cells was also observed in the course of chronic urticaria [50]. Sera of patients with chronic urticaria proved to contain also higher concentrations of P-selectin soluble form, with mean values of 182.91 ng/ml to 327.91 ng/ml, which were supposed to decrease after use of anti-histaminic drugs [49]. In addition, Garbaraviciene *et al.* observed its increased expression on activated platelets [42].

Equivocal results were obtained in patients with systemic lupus erythematosus (SLE). According to some investigators, in such patients serum concentration of E-selectin soluble form is elevated and correlates with severity of the disease course, expressed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [51, 52], but other investigators failed to detect such a correlation [53, 54] and even detected a decreased concentration of the molecule [55]. The latter observation was explained by the phenomenon of blocking of the ligands for selectin, which was supposed to restrict extravasation of inflammatory cells to tissues [55]. In turn, studies of Reefman *et al.* provided proof for augmented expression of E-selectin in patients with SLE in immunohistochemical studies of skin samples from early lesions, which appeared following intentional exposure to ultraviolet B light [56]. Also an elevated serum concentration of L-selectin soluble form was detected in sera of SLE patients [53, 57]. In the subgroup of patients with involvement of the central nervous system the concentration was elevated also in the cerebrospinal fluid [58]. In parallel, its decreased expression was detected on neutrophils of SLE patients [59]. In the group of patients an elevated serum concentration of P-selectin soluble form was also observed [60, 61]. Interestingly, the concentration in patients with renal lupus was supposed to be higher than in SLE patients with no kidney involvement [60]. Flow cytometry also allowed augmented expression of P-selectin on the surface of blood platelets to be demonstrated [62].

Elevated serum concentrations of E-selectin have also been recorded in patients with other diseases, involving in principle vascular inflammation, including patients with Wegener's granulomatosis, Takayasu's disease or Kawasaki's disease [3, 63]. In patients with the latter condition also significantly elevated levels of L-selectin soluble form were documented [22].

The role of selectins has provided a frequent topic of studies on diseases of the scleroderma group. In systemic sclerosis on several occasions significantly elevated serum levels of E-selectin soluble form were noted. Its levels ranged from 53.9 ng/ml to 120.2 ng/ml [21, 64-67]. In addition, concentration of E-selectin soluble form decreased significantly following immunosuppressive treatment (with application of cyclophosphamide and prednisone), although it remained higher than levels noted in healthy individuals of the control group [21]. In some cases, however, the elevated levels of the molecule proved to be insignificant [68]. In turn, Dziankowska-Bartkowiak *et al.* using immunohistochemistry of skin samples obtained from systemic sclerosis patients demonstrated augmented expression of E-selectin on the surface of endothelial cells and of neutrophils [69]. In the discussed group of patients elevated serum levels also of P-selectin soluble form were detected [67, 68, 70], as well as its increased expression on endothelial cells in skin samples [70]. Moreover, both the above-mentioned expression and the elevated serum levels of P-selectin were suggested to show a correlation with early phases of the disease [70]. On the other hand, no elevated concentrations of L-selectin soluble form could be noted [70] even if its elevated expression was noted on lymphocytes, macrophages and neutrophils [69]. On the other hand, Shimada *et al*. detected a significantly higher serum concentration of L-selectin soluble form and lower expression of L-selectin on lymphocytes CD8+ in cytometric studies in patients with systemic sclerosis [71]. Elevated concentrations of E-selectin and P soluble forms were also detected in morphea patients [67, 72]. Similarly, elevated levels of E-selectin were noted in sera of patients with graft-versus-host disease. Interestingly, both in the acute and in the chronic form of the disease its concentration showed a correlation with early phases of the disease and the increased levels were preceded by manifestation of clinical signs/symptoms [73].

In the group of autoimmune bullous diseases a significantly elevated serum concentration of E-selectin soluble form was noted in pemphigus vulgaris and bullous pemphigoid. Significantly, an improvement in patient clinical condition in the course of its treatment showed a correlation with concentration of the molecule [74]. In turn, immunohistochemical studies on skin samples from the

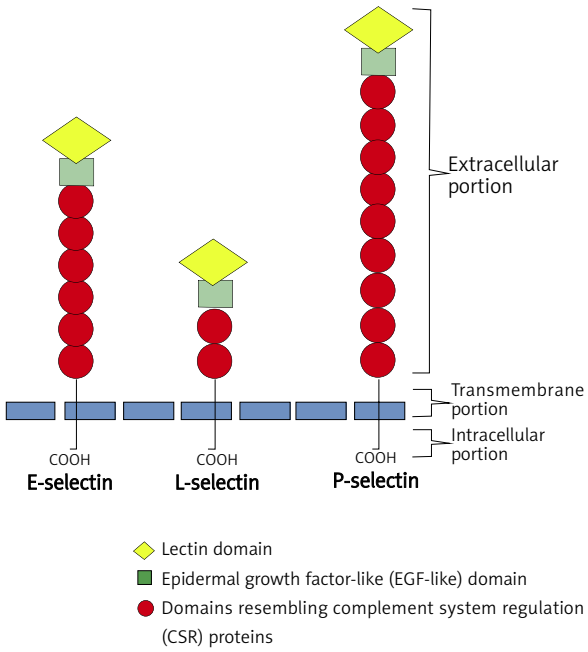

Fig. 1. Schematic structure of selectins. 1) Intracellular fragment consisting of: a) lectin domain, dependent on calcium ions and positioned at molecule N terminus, b) epidermal growth factor (EGF)-like domain, c) homologous domain with complement system regulation (CSR) proteins, which vary in number (2 to 9) depending on type of selectin. 2) Transmembrane fragment, penetrating the cell membrane and anchoring in it the entire selectin molecule. 3) A relatively short intracellular fragment

lesions conducted in a group of patients with herpetiform dermatitis demonstrated increased expression of E-selectin on endothelial cells and of L-selectin on lymphocytes, macrophages and neutrophils [13, 75]. Expression of both selectins was detected mainly within the basal cell layer of the epidermis [75].

In turn, elevated levels of P-selectin soluble form were detected in lichen planus, including lichen planus of mucous membranes [76]. On the other hand, Regezi *et al.* in immunohistochemical studies on oral mucosa samples obtained from patients with the mucosal form of lichen planus recorded increased expression of E-selectin and P-selectin within fine blood vessels of the lamina propria and elevated expression of L-selectin on the surface of most cells in inflammatory infiltrate, including dendritic cells [77].

In turn, in alopecia areata an increased serum concentration was noted of E-selectin soluble form, although the change was on the verge of statistical significance [78], while in histochemical examination of skin samples from the foci of alopecia, increased expression of E-selectin was detected on the surface of endothelial cells [79-83].

Selectins and therapeutic perspectives

Attempts are made to take advantage of the knowledge of the molecular basis of leukocyte migration in treatment of certain diseases. Blocking of adhesion molecules represents a new approach to therapy of autoimmune diseases, complications of burns, in prolongation of allogenic graft survival or in reduction of necrotic foci following ischaemic stroke or myocardial infarction [1, 84]. The search for such drugs is time-consuming and expensive. They should be stable in the body, manifest few undesirable effects and, first of all, they should warrant a clinical and laboratory improvement.

In the last few years, preclinical and clinical trials of the 1st and 2nd phase have been conducted on inhibitors of selectins. Schön *et al.*, in *Lewis* rats with artificially induced uveitis, used intraconjunctival administration of P-selectin inhibitor [84]. Such treatment resulted in decreased expression of P-selectin on the cell surface and in an improved clinical condition. Similar studies were conducted by Whitcup *et al.* introducing endotoxin of *Salmonella typhimurium* to conjunctival sacs of female C3H/HeJ mice, and then administering intraperitoneally monoclonal antibody, which blocked selectins E and P or one of them [86]. They found that blockade of both selectins significantly decreased inflammatory infiltrate while inhibition of one of the selectins insignificantly decreased intensity of the inflammatory infiltrate in histopathological studies on mouse conjunctiva. Bhushan *et al.*, in turn, attempted to block function of E-selectin using monoclonal antibodies in patients with psoriasis [87]. However, the applied treatment brought no significant improvement to the dermatological condition. Hardtke *et al.* also failed to achieve success blocking L-selectin in patients with psoriasis using human monoclonal antibody [88]. The above studies confirmed the suspicions of investigators that selective blocking of individual selectins cannot inhibit an inflammatory process. However, low-molecular weight compounds exist which bind to more than one selectin type. An example is provided by efomycin. It represents a group of non-carbohydrate macrolides, among which efomycin M manifests ability to inhibit leukocyte adhesion by blocking selectins E and P [5, 17]. In turn, efomycins *E*, *G* and *O* manifest lower affinity to selectins while efomycins S and T manifest no biological activity [5, 17]. Schön *et al.* following administration of *efomycin M* detected a significantly inhibited rolling of leukocytes along capillary walls in skin transplanted to mice from psoriasis patients [5]. Some other promising preclinical studies have suggested that blocking of the three selectins in parallel brought the best results. Hick *et al.* demonstrated in their early clinical studies high efficacy of bimosiamose, the inhibitor of three selectins, in treatment of psoriasis [89]. Significantly, in recent years several studies have been conducted on drugs blocking also ligands for selectins or enzymes participating in their synthesis, for example on fucosyl-

transferases IV and VII [90, 91]. It is also suggested that selectins may provide a target for novel therapeutic procedures. Such procedures could be aimed at, e.g., supplying the active substance exactly to the site of the ongoing inflammatory process. The studied objects include liposomes, a potential carrier of such drugs. The spherical structures, formed from a double lipid layer and containing in their envelope, e.g., additional proteins, antigens or other biological substances, might transport inside them a therapeutic substance, affecting specific tissue with augmented expression of a given selectin due to the pathological process progressing in it [8, 17].

The clinical and biological significance of selectin forms present in serum has not yet been clearly defined. The proteins may both amplify and inhibit interactions between leukocytes and cell surface molecules. They may fulfil regulatory functions, modulating an inflammatory response. Concentration of adhesion molecule soluble forms, including selectins, is elevated in various dermatoses, such as lupus erythematosus, atopic dermatitis, psoriasis, lichen planus, graft-versus-host disease, and contact dermatitis [13, 15, 32, 72, 74]. According to some authors, they may serve as an index enabling one to estimate disease activity [14, 19, 21, 31, 42, 73]. They seem to represent an interesting target element of the inflammatory reaction for modern therapeutic approaches.

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