Cell. Mol. Life Sci. 64 (2007) 66–76
1420-682X/07/010066-11
DOI 10.1007/s00018-006-6255-8

Cellular and Molecular Life Sciences

Review

Receptor communication within the lymphocyte plasma membrane: a role for the thrombospondin family of matricellular proteins

A. Forslöw, Z. Liu and K.-G. Sundqvist*

Department of Laboratory Medicine, Division of Clinical Immunology, Karolinska Institute at Karolinska University Hospital Huddinge, SE-141 86 Stockholm (Sweden), Fax: +46 8 585 81 39 0, e-mail: Karl.Sundqvist@hs.se

Received 1 June 2006; received after revision 28 June 2006; accepted 11 October 2006
Online First 8 December 2006

Abstract. Lymphocytes, the principal cells of the immune system, carry out immune surveillance throughout the body by their unique capacity to constantly reposition themselves between a free-floating vascular state and a tissue state characterized by migration and frequent adhesive interactions with endothelial cells and components of the extracellular matrix. Therefore, mechanisms co-ordinating adhesion and migration with signals delivered through antigen recognition probably play a pivotal role for the regulation of lymphocyte behaviour and function. Endogenous thrombospondin-1 (TSP-1) seems to be the hub in such a mechanism for autocrine regulation of T cell adhesion and migration. TSP-1 functions as a mediator of *cis* interaction of vital receptors within the T lymphocyte plasma membrane, including integrins, low density lipoprotein receptor-related protein, calreticulin and integrin-associated protein.

Keywords. Thrombospondin; lymphocyte; extracellular matrix; adhesion; integrin-associated protein; antigen-presenting cell.

Cell surface receptors are important tools for cellular recognition and interaction with components on other cells and the extracellular matrix (ECM). In lymphocytes, the principal cells of the adaptive immune system, cell surface receptors play a pivotal role for antigen recognition and for the unique capacity of these cells to reposition themselves within the organism through adhesive interactions and controlled migration. Accordingly, the T lymphocyte antigen receptor, TCR/CD3, forms a complex cellular structure, termed the immunological synapse (IS), with appropriate peptide-major histocompatibility complexes (MHC) on antigen-presenting cells [1]. Integrins mediate adhesion of lymphocytes and other cells to basement membranes and the surrounding ECM and cell-cell adhesion. T cells express integrins of the $\beta1$, $\beta2$ and $\beta7$ sub-families where $\alpha4\beta1$, $\alpha5\beta1$ and $\alpha L\beta2$ mediate T cell adhesion to endothelial cells and the ECM component fibronectin (FN) [2, 3]. T cell motility is further regulated via $\alpha1\beta1$, $\alpha2\beta1$ and $\alpha6\beta1$ receptors for collagens and laminin (LN) [4, 5] and during T cell activation, $\alpha L\beta2$ is an important part of the IS [6]. Lymphocytes in the blood thus extravasate by a series of adhesive interactions with vascular endothelial cells involving integrins, selectins and chemokines [7–9]. An additional example of cellular recognition is the clearance of apoptotic cells through calreticulin (CRT) activation of lipoprotein receptor-related protein (LRP) on phagocytes [10].

As well as interacting with molecules on neighbouring cells or ECM, cell surface receptors can also form *cis* associations with other receptors on the same cell. LRP/CD91, a large, multifunctional, endocytic cell surface receptor expressed in a variety of tissues, functions as a co-

* Corresponding author.

receptor with other cell surface and integral membrane proteins including amyloid precursor protein (APP), platelet-derived growth factor receptor-β (PDGFR-β), urokinase plasminogen activator receptor (uPAR) and CRT [11, 12]. Interactions in *cis* between integrins and other receptors within the same plasma membrane recruit signalling molecules to sites of cell-cell or cell-matrix adhesion, such as the IS, focal complexes or focal adhesions. Examples of integrin-associated cell surface receptors include integrin-associated protein (IAP/CD47), members of the transmembrane-4 superfamily, CD44 and proteins within the peripheral region of the IS [13–17]. TCR-mediated antigen recognition and signal transduction require interaction with CD3 that contain intracellular signalling domains coupling the TCR/CD3 complex to the downstream signalling machinery and are facilitated by proteins that segregate to the central area of the IS including the co-receptors CD4 and CD8 [16, 18–20].

This review discusses a possible mechanism for regulation of *cis* interactions between receptors within the same plasma membrane through ligands with multiple binding sites for cell surface components, thus enabling cross-linking and aggregation of separate receptors. Such ligands may be either of environmental or exogenous origin, but a prerequisite for putative ligand candidates to be interesting as cross-linkers is that they can induce functional responses in their host cells and are available in the context of cellular recognition and activation. The thrombospondin (TSP) family of glycoproteins with five distinct members identified so far, namely TSP-1, TSP-2, TSP-3, TSP-4 and TSP-5 (cartilage oligomeric matrix protein), fulfil several criteria to be functionally important cell surface ligands. The members of the TSP family show a widespread distribution in various organs in the embryonic as well as the adult organism [21–23].

TSP-1 is a multifunctional ECM glycoprotein that displays distinct biological activities in different cell types and has been implicated in cancer cell invasion as an inhibitor of angiogenesis and tumour growth, activates transforming growth factor (TGF)-β and is necessary for maintenance of normal pulmonary homeostasis [24–27]. TSP-1 is a major component of platelet α-granules released in response to thrombin and binds to the platelet surface [28]. The expression of TSP is up-regulated in proliferating cells, in inflammation and in wound healing, and increased TSP expression has been linked to disease states including tumour progression, atherosclerosis and arthritis [29–37]. While ECM glycoproteins like FN, collagen, vitronectin (VN) or LN generate a structural scaffold which enables cellular organization and as such regulates adhesion, survival and differentiation of attached cells, TSP-1 and -2 together with tenascin C, osteopontin, the cysteine-rich 61/connective tissue growth factor/nephroblastoma overexpressed (CCN) family and SPARC (serum protein acidic and rich in cystein)/osteonectin belong to a different class of ECM molecules, the matricellular proteins, known to modify cell-ECM interactions. Matricellular proteins function as both soluble and insoluble proteins and do not contribute directly to tissue integrity but are capable of modulating cell function. When presented in mixed substrata, the matricellular proteins can anatagonize the pro-adhesive activities of other matrix proteins and cause deadhesion when presented in soluble form to cells in a strong adhesive state [38, 39]. TSP-1 in soluble form has primarily anti-adhesive effects characterized by a reorganization of stress fibres and loss of focal adhesion plaques [40]. This effect is mediated through interactions of the NH_2 terminal domain of TSP-1 with the NH_2 terminal domain of cell surface CRT and its co-receptor LRP/CD91 [11, 40, 41].

TSP structure and receptor-binding sites indicate the capacity to cross-link cell surface receptors

Matricellular proteins are expressed during development and in areas of tissue repair as well as inflammatory sites [42]. In contrast to ECM glycoproteins which induce cell adhesion, matricellular proteins can act as antagonists of cell-ECM interaction if presented in a soluble form but generally support weak cell adhesion in a bound form [43]. Furthermore, the presence of several distinct cell- and ECM-binding sites on the same protein sequence enables interaction with multiple receptors on the same cell, on separate cells and binding to both cell surface receptors and ECM components. In addition, sites on matricellular proteins that mediate association with growth factors, proteases and cytokines may serve to increase locally the concentration of molecules that regulate growth, survival and motility [38, 44–46].

The TSP are usually divided into two sub-groups, A and B, according to their structure and oligomerization (Fig. 1). Group A comprises two members, TSP-1 and TSP-2, with a molecular mass of about 170 kDa for each monomer on reducing gels and 420 kDa in a trimeric non-reduced form. Each monomer consist of an NH_2-terminal heparin-binding domain, a pro-collagen and connecting domain, type 1, type 2 and type 3 repeats and a COOH-terminal cell-binding domain (Fig. 1). Three monomers are covalently linked through disulphide bonds in the coiled-coil oligomerization region close to the NH_2-terminal domain. Group B are pentamers comprising TSP-3, TSP-4 and TSP-5, and consist of monomers of about 100 kDa. The TSP members of group B do not have the connecting and pro-collagen domain and no type I repeat but have four copies of the type 2 repeat [47–51]. Generally, all TSPs have different numbers of type II epidermal growth factor (EGF)-like domains followed by seven type III repeats followed by a highly conserved COOH-ter-

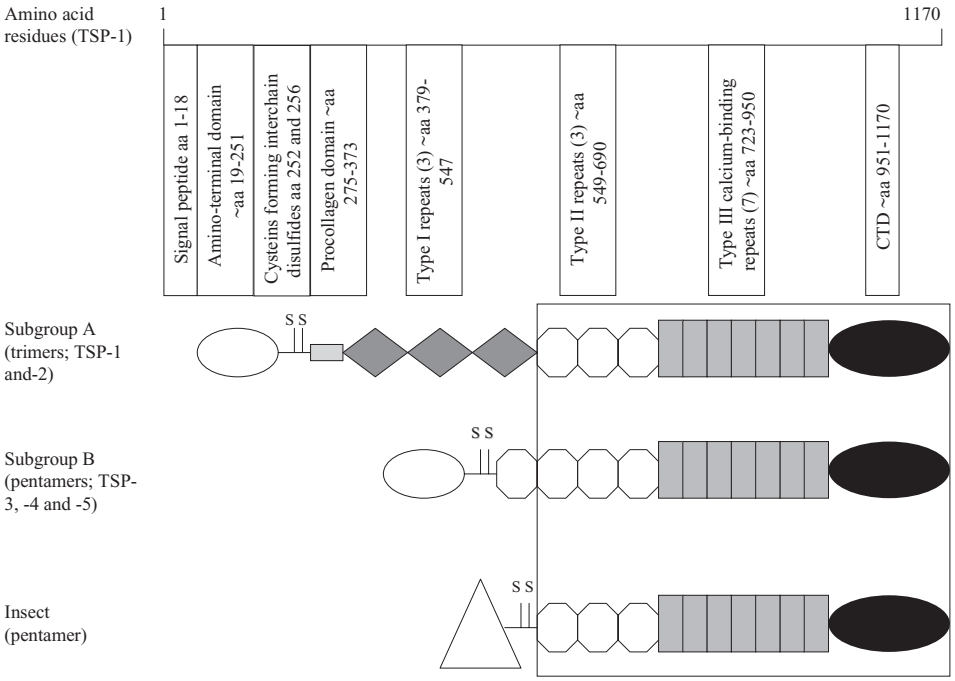

Figure 1. Schematic domain structure of TSPs. [modified from ref. 53]

minal cell-binding domain that is involved in the regulation of cell adhesion and proliferation [52]. TSP-1 and TSP-2 have type I properdin domains that bind CD36 and glycosaminoglycans. TSP-3, TSP-4 and TSP-5 lack properdin repeats and thus CD36-binding capacity [53]. The N-terminal heparin-binding domains of TSP-1 and TSP-2 show low sequence similarities, with only 32% amino acid sequence identity [54]. However, the deadhesive activity of both TSP-1 and TSP-2 is dependent on signalling events mediated through binding to CRT and LRP [55]. Furthermore, TSP-1 and TSP-2 compete with each other for endocytosis and degradation via binding to LRP [56]. N-terminal binding of TSP-1 and TSP-2 to integrin $\alpha 4\beta 1$ stimulates T cell adhesion and chemotaxis [57]. However, the physiological roles of TSP-1 and TSP-2 are probably different. Whereas TSP-1 null mice have epithelial and smooth muscle cell hyperplasia and inflammation of the lung, TSP-2 null mice show increased angiogenesis, bleeding diathesis and reduced fibroblast adhesion [25, 58, 59].

The different domains of TSP-1 subunits display binding sites for various cell surface receptors including the integrins $\alpha v\beta 3$, $\alpha 3\beta 1$, $\alpha 4\beta 1$, $\alpha 5\beta 1$ and $\alpha 6\beta 1$ and CRT/CD91, CD36 and CD47 [60–66]. TSP-1 is involved in multiple functional activities through these receptors, such as adhesion, angiogenesis and cell injury [67, 68] (Table 1). TSP-1 can also bind other extracellular proteins including plasminogen, fibrinogen, fibronectin, heparin and urokinase [45, 69, 70].

The same TSP-1 molecule in soluble form or bound to the ECM or to artificial substrata may cross-link separate cell surface receptors. Cross-linking of surface receptors generally increases the capacity of ligands to induce functional responses in target cells, which is well illustrated by the 'capping phenomenon' induced by antibodies to surface antigens on lymphocytes and other cells [71, 72]. It is also reasonable to assume that free soluble TSP-1 molecules may attach to a cell surface through co-operative binding via their binding sites for integrins, CRT/CD91 and CD47. In support of this idea, TSP-1 can be detected on the lymphocyte surface and appears to be bound to CRT/CD91 [73, 74]. Based on predictions from its structure, each TSP-1 molecule may cross-link separate receptors on the cell surface. Accordingly, one TSP-1 molecule may cross-link three CD47 receptors through its COOH-terminal binding sites although the flexibility of the molecule may limit the cross-linking capacity. One TSP-1 molecule may also cross-link CRT/CD91, integrins and CD47 on the same cell surface. The potential capacity of TSP-1 to cross-link separate receptors on the cell surface implies that ligation of a TSP-1-associated cell surface receptor, such as $\alpha 4\beta 1$, by an ECM ligand (fibronectin in the case of $\alpha 4\beta 1$) influences the cell surface localization and proximity of other TSP-associated receptors, particularly CD47, facilitating functional interactions [57, 75]. Alternatively, TSP-1 may have a basic cell surface association to one major receptor, for example CRT and its co-receptor CD91, and as a consequence of integrin ligation or chemokine stimulation, other receptor binding sites within the TSP molecule are brought into contact with cell surface receptors such as CD47 with a capac-

Table 1. List of TSP-1 sequences related to known functions [modified from ref. 7].

TSP-1 domains	Sequences	Receptors	Functions	Reference
Amino-terminal domain	QNV	$\alpha 3\beta 1$	cell adhesion to TSP-1 haemostasis	62, 107
	RKGSGRR/KKTR	HSPG-LRP-gp330 syndecan sulphated glycolipid	endocytosis	108–112
	ELTGAARKGSGR RLVKGPD (Hep1)	calreticulin heparin	focal adhesion disassembly inhibition of T cell motility	40, 73, 113
	MKKTRG	decorin	inhibits cell adhesion	114
	LDVP	$\alpha 4\beta 1$	promotes cell adhesion and chemotaxis	57, 65
	LALERKDHSG	$\alpha 6\beta 1$	endothelial cell binding to TSP-1 and TSP-2 and laminin	66
	25-kDa peptide	?	stimulates angiogenesis	115
Oligomerization domain			multimerization	
Procollagen homology domain	NGVQYRN		angiogenesis inhibition chemotaxis inhibition	116
Type I repeat domains (1–3)	RFK	LTGF-β	activation of latent TGF-β	117, 118
	WSHWSPW	protein glycosaminoglycan	activation of latent TGF-β	119, 120
	CSVTCG	HIV gp120 HSPG, CD36	anti-angiogenesis cell adhesion	121–123
	GVQxR	CD36	endothelial cell migration	124
Type II repeat domains (1–3)				
Type III repeat domains (1–7)	RGD	$\alpha v\beta 3$ αIIb$\beta 3$ $\alpha 5\beta 1$	cell adhesion	57, 60, 65, 125
			calcium binding	64
	NCPFHYNP NCQYVNV	cathepsin G, elastase		38
Carboxy-terminal domain (CTD)	RFYVVM IRVVM	CD47	chemotaxis cell proliferation apoptosis	63, 126

ity to trigger functional responses such as spreading and proliferation [57, 75].

TSPs and the function of the immune system

TSP-1-deficient mice show aberrant cutaneous wound healing, decreased macrophage recruitment and a disturbance in pulmonary homeostasis [59]. The lungs of these mice exhibit acute and chronic inflammatory infiltrates and increased fibroblastic and epithelial cell proliferation, matrix deposition and haemorrhages in alveoli. These lesions may be specific to the lungs because TSP-1 is normally expressed at high levels in the lung. Crossing strains of integrin $\beta 6$ null and TSP-1 null mice and comparing the double-null mice showed that these exhibited pneumonia and also a significantly higher incidence of inflammation in tissues other than the lung, including hepatitis, polyarteritis nodosa, colitis, pyometra, conjunctivitis, pancreatitis and peritonitis [76]. The conclusion by the authors was that TSP-1 is involved in the regulation of the immune system. However, it remains to be clarified whether infections due to an aberrant adaptive immune system could arise from the TSP deficiency and thus be responsible for the inflammation in multiple organs.

The phenotype of the TSP-2 null mouse implicates TSP-2 in the regulation of adhesion and migration of mesenchymal cells [77]. TSP-2 deficiency in mice leads to increased and prolonged delayed-type hypersensitivity reactions as compared with wild-type mice [78]. The TSP-2-deficient mice also display significantly increased leucocyte adhesion to the endothelium of cutaneous blood vessels. These

results show that TSP-2 plays an important role in limiting inflammatory cell infiltration.

T lymphocytes express TSP-1 with a high turnover and the intracellular storage form of TSP-1 can apparently be mobilized and expressed onto the cell surface as a consequence of appropriate adhesive cellular interactions and during migration in three-dimensional substrata [73, 79]. This points to the possibility that TSP-1 plays a role in the function of the immune system.

The inflammation of joints in rheumatoid arthritis is characterized by infiltration and in situ expansion of lymphocytes. It has been speculated that TSP-1 may augment the inflammation in rheumatoid arthritis since the molecule is exposed on synoviocytes and acts as a co-stimulator of T cells by engaging the receptor CD47 [80]. CD47-TSP-1 interaction may thus be a key element of a regulatory circuit that perpetuates the inflammatory process in the rheumatoid joint.

TSP-induced T cell responses through integrins and CD47

Several studies involving exogenous TSP-1, TSP peptides or antibodies to cellular TSP receptors have shown that TSP-1 can influence T cells and that these effects are mediated through interactions with integrins and CD47. CD4+ T cells adhere to TSP-1 via three distinct receptors – an adhesion-independent receptor that controls adhesion of resting T cells, and the $\alpha 4\beta 1$ and $\alpha 5\beta 1$ integrins, which mediate increased adhesion upon activation [65]. A binding site for $\alpha 4\beta 1$ integrin has been localized to the NH_2-terminal domain of TSP-1 and TSP-2 [57]. Adhesion of Jurkat T cells to TSP-1 or TSP-1-derived peptides stimulate CD3-induced Ras activation and tyrosine phosphorylation of several T cell proteins and transduced signals to the nucleus [81]. ERK phosphorylation was dependent on a $\beta 1$ integrin receptor, MAPK phosphorylation was dependent on CD47 and a heparin peptide-binding receptor was shown to provide a MAPK-dependent nuclear pathway. Insoluble antibodies to CD47 induce co-stimulation or kill T cells in response to CD3 activation, and a synergy between CD47 and TCR ligation is found in early T cell activation [75, 82–84]. In contrast, soluble anti-CD47 antibodies inhibit the allogeneic mixed lymphocyte reaction indicating that the presentation of CD47-binding ligands is critical for the functional effect [85]. Co-stimulatory activity of TSP-1 through interaction with CD47 has also been implicated in synoviocyte-mediated expansion of inflammatory T cells in rheumatoid synovitis [80]. Ligation of CD47 associated with membrane rafts was demonstrated to induce T cell spreading, and actin polymerization and simultaneous ligation of CD47 and CD3 led to additive effects on F-actin [86, 87].

CD47 is not only a receptor for induction of proliferative responses in T cells but has also been shown to be a receptor for induction of T cell anergy in human naive T cells using anti-CD47 antibodies [88]. Whether TSP-1 may induce T cell anergy is still unknown. Intact TSP-1 has been found to inhibit TCR-mediated early T lymphocyte activation and this inhibition depended on CD47 and integrin-associated protein heparan sulphate proteoglycans [89].

CD47 is also a receptor for signal regulatory proteins (SIRPs α and γ), which are expressed at the cell surface of myeloid, haematopoetic and neuronal cells (SIRPα) and on T cells and natural killer (NK) cells (SIRPγ) [90–94]. SIRPα has a transmembrane domain, which contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs) known to interact with the Src-homology 2 domain-containing phosphatases (SHP)-1 and -2, which inhibit tyrosine kinase-coupled signalling pathways [95, 96]. The function of SIRPα is inhibitory during dendritic cell activation and macrophage phagocytosis [97, 98] whereas it plays a positive role in mediating CD47-dependent migration of neutrophils across epithelium [99]. SIRPγ(also named SIRPβ2) does not have a transmembrane signalling domain and mediates adhesion between CD47-expressing antigen-presenting cells and SIRPγ-expressing T cells, thereby promoting T cell activation and proliferation [93, 94]. TSP-1 on the T cell surface might compete in a *cis* manner with SIRPγ for binding to CD47 on the antigen-presenting cell, generating altered or impaired T cell activation.

T lymphocytes may encounter TSP-1 or TSP-1 fragments at inflammatory sites. The demonstration that exogenous TSP-1 could modulate TCR-induced T cell responses through distinct cell surface receptors and elicit both stimulatory and inhibitory signals implies that TSP-1 or TSP-1 fragments may be considered as physiological regulators of T cell function [80, 89]. This has a bearing on normal immune responses to infectious agents as well as on pathological situations such as autoimmune and allergic diseases and graft rejection.

Autocrine regulation of T cell adhesion and motility by TSP-1

T lymphocytes express endogenous TSP-1 with a high turnover [73, 79]. CRT and its co-receptor CD91 seem to function as a cell surface receptor for the NH_2-terminal domain of TSP-1 [74]. Adhesion to ICAM-1 or ECM components via $\beta 1$ and $\beta 2$ integrins brings cell surface TSP-1, which is anchored to CRT/CD91 via the NH_2-terminal domain, in contact with CD47 through its COOH-terminal domain, and up-regulates TSP turnover from a low level in non-adherent cells. CD47 is essential for TSP turnover and adhesion through interaction with the

COOH-terminal domain of TSP-1 in response to triggering signals delivered at the NH_2-terminal. In support of these conclusions, the TSP-1-binding site in CRT, within residues 19–36, markedly enhances integrin-dependent adhesion and cytoplasmic spreading of T cells. 4N1K, the CD47-binding sequence in TSP-1, prevents the increased adhesion induced by CRT 19–36 as well as the basal integrin-dependent adhesion. 4N1K also significantly inhibits the turnover of TSP-1 on fibronectin and ICAM-1, while a scrambled control peptide does not affect TSP expression, and as a result cell surface TSP-1 expression is increased. These results indicate that endogenous TSP-1 connects CRT/CD91 and integrins to CD47 and that this cross-bridging stimulates T cell adhesion. Interestingly, CD3 stimulation seems to inhibit TSP turnover through interference with CD91/CRT-mediated internalization, suggesting that the T cell antigen receptor participates in the control of T cell adhesion via CRT/CD91. β2 integrin clustering is a key event in leucocyte adhesion to the endothelium during the inflammatory response. CD91 has been shown to be a partner for β2 integrins at the leucocyte surface that is essential for integrin clustering and adhesion, as indicated by blocking antibody experiments and inhibition of adhesion by antisense oligonucleotides to down-regulate CD91 [100]. This provides further evidence for a previously unrecognized link between CD91 and leucocyte function [100]. Noteworthy in this context is that the CD91 co-receptor CRT has been shown to be involved in adhesion of non-lymphoid and lymphoid cells to ECM substrata and in the regulation of TSP-1-dependent T cell migration [15, 40, 41, 73, 74, 79, 101–104]. Endogenous TSP-1 also seems to play a role in the migration of T cells into three-dimensional collagen gels and CRT and CD47 participate in the TSP-dependent migration [73]. One possible explanation for the participation of TSP-1 in both adhesion and migration is that the TSP molecule has a common functional role in these two processes. However, an alternative, more plausible explanation is that TSP-1 exerts distinct effects on adhesion and migration on different substrata. Accordingly, the TSP molecule is probably handled differently in cells adherent to two-dimensional ECM substrata or other cells than in cells crawling in three-dimensional collagen matrices, since the lymphocytes crawl through the collagen in a non-adhesive fashion and do not perturb the collagen organization [105, 106].

A model for *cis* receptor communication within the plasma membrane

Figure 2 presents a tentative model for *cis* receptor communication between CRT/CD91, integrins and CD47 within the lymphocyte plasma membrane through endogenous TSP-1. This mechanism is triggered by integrin ligands but may also be triggered by CRT, since the TSP-binding site in CRT is capable of stimulating CD47 via TSP-1 [74]. This means that TSP-1 regulates integrin-dependent T cell functions, such as adhesion and migration, and is consequently important for the capacity of T cells to migrate between separate compartments of the organism. This is consistent with the findings that the turnover of TSP-1 is up-regulated by the integrin ligands FN and ICAM-1 and that TSP turnover depends on interactions with CD47. In non-adherent cells, TSP-1 is probably attached only to CD91/CRT and/or to integrins, and integrin ligation brings TSP-1 into contact with CD47 thus generating a signal that supports adhesion and spreading. These collaborative interactions of TSP-1, via its COOH- and NH_2-terminal domains, with CD47, CRT/CD91 and integrins are further enhanced by up-regulation of TSP turnover through CD91-dependent internalisation and the appearance of new TSP. Based on the evidence that stimulation of CD3 augments TSP expression [74], one may postulate that TSP-1-dependent communication between CRT/CD91, integrins and CD47 is down-

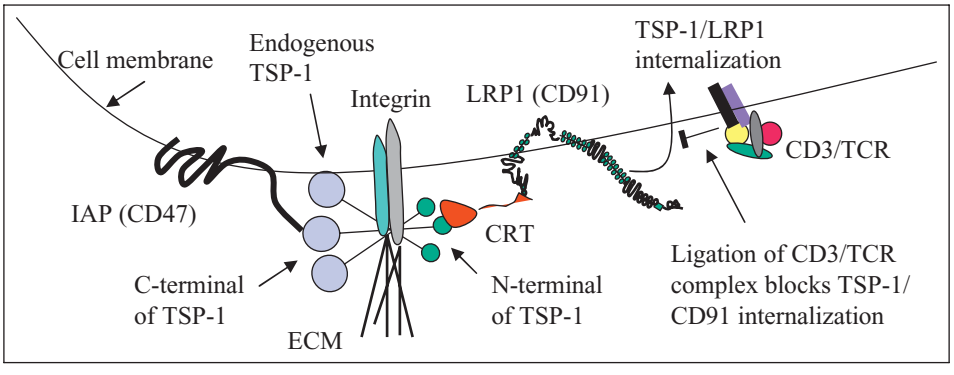

Figure 2. Model of T cell TSP-1 and its interactions with cell surface receptors. TSP-1 is associated with CRT/CD91 and/or integrin before adhesion. Adhesive interactions with ECM components or ICAM-1 via integrins trigger interaction of the COOH-terminal domain of TSP-1 with CD47 and up-regulate TSP turnover. Ligation of TCR/CD3 inhibits internalization of TSP-1, CRT and CD91 and focuses TSP-1 onto its cell surface receptors.

regulated in quiescent, fresh T cells from the blood of healthy individuals. In contrast, this receptor interaction would be up-regulated during normal immune responses and during the course of autoimmune and allergic diseases. Accordingly, TSP-1 may determine an important receptor interaction on the lymphocyte surface and it is conceivable that abrogation of this interaction owing to lack of ligand or blocking of receptors is critical for the control of T cell activity. Interestingly, ligation of TCR/CD3 seems to cause a rapid inhibition of TSP turnover while maintaining TSP expression at a high level, suggesting that a vital molecule for the recognition of antigens and development of immune responses is involved in the regulation of the TSP-dependent mechanism for receptor communication within the T lymphocyte plasma membrane.

The interactions between TSP-1, integrins, CRT/CD91 and CD47 and the effects on these interactions by integrin ligation and stimulation of TCR/CD3 provide potential targets for interference of lymphocyte proliferation and infiltration as well as for prevention of tissue damage in various inflammatory conditions caused by the immune system. This applies to diseases of autoimmune and allergic origin as well as to rejection of transplants. Thus, it may be possible to tailor treatment to combat T cell infiltration through interference with binding sites in the TSP-1 molecule or by blocking its receptors. T cell TSP-1 may play a role in protective immunity to infectious agents. Accordingly, it is possible that the lack of TSP-1 may impair T cell responses to infectious agents and account for the increased circulating white blood cell count and inflammatory infiltrates seen in the lungs of TSP-1-deficient mice and the significantly higher incidence of inflammation in tissues other than the lung in the integrin $\beta 6$ and TSP-1 double-null mice [25, 59, 76]. The identification of a putative mechanism for integrated control of interactions between surface receptors involved in adhesion, migration, growth and survival is thus of great potential interest with respect to understanding the function of the immune system.

Conclusion

TSP-1 is a matricellular protein present in the ECM only at specific stages of development or in association with specific pathological conditions. Studies involving exogenous TSP-1, TSP peptides or antibodies to cellular TSP receptors have shown that TSP-1 can influence T cell adhesion and proliferation and that these effects are mediated through interactions with integrins and CD47. T lymphocytes also express endogenous TSP-1 with a high turnover and this TSP-1 together with integrins, LRP/CD91, CRT and IAP/CD47 seems to play a pivotal role in a mechanism for autocrine regulation of T cell adhesion and motility.

Acknowledgements. This study was supported by the Swedish Cancer Foundation project 1940.

1 Dustin, M. L. (2005) A dynamic view of the immunological synapse. Semin. Immunol. 17, 400–410.
2 Pribila, J. T., Quale, A. C., Mueller, K. L. and Shimizu, Y. (2004) Integrins and T cell-mediated immunity. Annu. Rev. Immunol. 22, 157–180.
3 Szekanecz, Z., Humphries, M. J. and Ager, A. (1992) Lymphocyte adhesion to high endothelium is mediated by two beta 1 integrin receptors for fibronectin, alpha 4 beta 1 and alpha 5 beta 1. J. Cell. Sci. 101, 885–894.
4 Hemler, M. E. (1990) VLA proteins in the integrin family: structures, functions, and their role on leukocytes. Annu. Rev. Immunol. 8, 365–400.
5 Shimizu, Y., Van Seventer, G. A., Horgan, K. J. and Shaw, S. (1990) Regulated expression and binding of three VLA (beta 1) integrin receptors on T cells. Nature 345, 250–253.
6 Grakoui, A., Bromley, S. K., Sumen, C., Davis, M. M., Shaw, A. S., Allen, P. M. and Dustin, M. L. (1999) The immunological synapse: a molecular machine controlling T cell activation. Science 285, 221–227.
7 Schaerli, P. and Moser, B. (2005) Chemokines: control of primary and memory T-cell traffic. Immunol. Res. 31, 57–74.
8 Sackstein, R. (2005) The lymphocyte homing receptors: gatekeepers of the multistep paradigm. Curr. Opin. Hematol. 12, 444–450.
9 Ley, K. (2001) Pathways and bottlenecks in the web of inflammatory adhesion molecules and chemoattractants. Immunol. Res. 24, 87–95.
10 Gardai, S. J., McPhillips, K. A., Frasch, S. C., Janssen, W. J., Starefeldt, A., Murphy-Ullrich, J. E., Bratton, D. L., Oldenborg, P. A., Michalak, M. and Henson, P. M. (2005) Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Cell 123, 321–334.
11 Orr, A. W., Pedraza, C. E., Pallero, M. A., Elzie, C. A., Goicoechea, S., Strickland, D. K. and Murphy-Ullrich, J. E. (2003) Low density lipoprotein receptor-related protein is a calreticulin coreceptor that signals focal adhesion disassembly. J. Cell Biol. 161, 1179–1189.
12 Lillis, A. P., Mikhailenko, I. and Strickland, D. K. (2005) Beyond endocytosis: LRP function in cell migration, proliferation and vascular permeability. J. Thromb. Haemost. 3, 1884–1893.
13 Brown, E. J. and Frazier, W. A. (2001) Integrin-associated protein (CD47) and its ligands. Trends Cell Biol. 11, 130–135.
14 Porter, J. C. and Hogg, N. (1998) Integrins take partners: cross-talk between integrins and other membrane receptors. Trends Cell Biol. 8, 390–396.
15 Coppolino, M. G. and Dedhar, S. (2000) Bi-directional signal transduction by integrin receptors. Int. J. Biochem. Cell Biol. 32, 171–188.
16 Lin, J. Y., Jacobus, B. H., SanMiguel, P., Walling, J. G., Yuan, Y., Shoemaker, R. C., Young, N. D. and Jackson, S. A. (2005) Pericentromeric regions of soybean (*Glycine max* L. Merr.) chromosomes consist of retroelements and tandemly repeated DNA and are structurally and evolutionarily labile. Genetics 170, 1221–1230.
17 Steeber, D. A., Venturi, G. M. and Tedder, T. F. (2005) A new twist to the leukocyte adhesion cascade: intimate cooperation is key. Trends Immunol. 26, 9–12.
18 Manes, S. and Viola, A. (2006) Lipidrafts in lymphocyte activation and migration. Mol. Membr. Biol. 23, 59–69.
19 Call, M. E. and Wucherpfennig, K. W. (2005) The T cell receptor: critical role of the membrane environment in receptor assembly and function. Annu. Rev. Immunol. 23, 101–125.
20 Kuhns, M. S., Davis, M. M. and Garcia, K. C. (2006) Deconstructing the form and function of the TCR/CD3 complex. Immunity 24, 133–139.

21 Corless, C. L., Mendoza, A., Collins, T. and Lawler, J. (1992) Colocalization of thrombospondin and syndecan during murine development. Dev. Dyn. 193, 346–358.
22 Iruela-Arispe, M. L., Liska, D. J., Sage, E. H. and Bornstein, P. (1993) Differential expression of thrombospondin 1, 2, and 3 during murine development. Dev. Dyn. 197, 40–56.
23 O'Shea, K. S. and Dixit, V. M. (1988) Unique distribution of the extracellular matrix component thrombospondin in the developing mouse embryo. J. Cell Biol. 107, 2737–2748.
24 Crawford, S. E., Stellmach, V., Murphy-Ullrich, J. E., Ribeiro, S. M., Lawler, J., Hynes, R. O., Boivin, G. P. and Bouck, N. (1998) Thrombospondin-1 is a major activator of TGF-beta1 *in vivo*. Cell 93, 1159–1170.
25 Lawler, J., Sunday, M., Thibert, V., Duquette, M., George, E. L., Rayburn, H. and Hynes, R. O. (1998) Thrombospondin-1 is required for normal murine pulmonary homeostasis and its absence causes pneumonia. J. Clin. Invest. 101, 982–992.
26 Sargiannidou, I., Zhou, J. and Tuszynski, G. P. (2001) The role of thrombospondin-1 in tumor progression. Exp. Biol. Med. 226, 726–733.
27 Jimenez, B., Volpert, O. V., Crawford, S. E., Febbraio, M., Silverstein, R. L. and Bouck, N. (2000) Signal leading to apoptosis-dependent inhibition of neovascularization by thrombospondin-1. Nat. Med. 6, 41–48.
28 Lawler, J. W., Slayter, H. S. and Coligan, J. E. (1978) Isolation and characterization of a high molecular weight glycoprotein from human blood platelets. J. Biol. Chem. 253, 8609–8616.
29 Narizhneva, N. V., Razorenova, O. V., Podrez, E. A., Chen, J., Chandrasekharan, U. M., DiCorleto, P. E., Plow, E. F., Topol, E. J. and Byzova, T. V. (2005) Thrombospondin-1 up-regulates expression of cell adhesion molecules and promotes monocyte binding to endothelium. FASEB J. 19, 1158–1160.
30 Frangogiannis, N. G., Ren, G., Dewald, O., Zymek, P., Haudek, S., Koerting, A., Winkelmann, K., Michael, L. H., Lawler, J. and Entman, M. L. (2005) Critical role of endogenous thrombospondin-1 in preventing expansion of healing myocardial infarcts. Circulation 111, 2935–2942.
31 McLaughlin, J. N., Mazzoni, M. R., Cleator, J. H., Earls, L., Perdigoto, A. L., Brooks, J. D., Muldowney, J. A. 3rd, Vaughan, D. E. and Hamm, H. E. (2005) Thrombin modulates the expression of a set of genes including thrombospondin-1 in human microvascular endothelial cells. J. Biol. Chem. 280, 22172–22180.
32 Gao, L., Qiu, W., Wang, Y., Xu, W., Xu, J. and Tong, J. (2006) Sublytic complement C5b-9 complexes induce thrombospondin-1 production in rat glomerular mesangial cells via PI3-k/Akt: association with activation of latent transforming growth factor-beta1. Clin. Exp. Immunol. 144, 326–334.
33 Naumov, G. N., Bender, E., Zurakowski, D., Kang, S. Y., Sampson, D., Flynn, E., Watnick, R. S., Straume, O., Akslen, L. A., Folkman, J. and Almog, N. (2006) A model of human tumor dormancy: an angiogenic switch from the nonangiogenic phenotype. J. Natl. Cancer Inst. 98, 316–325.
34 Jou, I. M., Shiau, A. L., Chen, S. Y., Wang, C. R., Shieh, D. B., Tsai, C. S. and Wu, C. L. (2005) Thrombospondin 1 as an effective gene therapeutic strategy in collagen-induced arthritis. Arthritis Rheum. 52, 339–344.
35 Vallejo, A. N., Mugge, L. O., Klimiuk, P. A., Weyand, C. M. and Goronzy, J. J. (2000) Central role of thrombospondin-1 in the activation and clonal expansion of inflammatory T cells. J. Immunol. 164, 2947–2954.
36 Liu, C., Kong, W., Xu, K., Luan, Y., Ilalov, K., Sehgal, B., Yu, S., Howell, R. D. and Di Cesare, P. E. (in press) ADAMTS-12 associates with and degrades cartilage oligomeric matrix protein. J. Biol. Chem.
37 Adams, J. C. (2001) Thrombospondins: multifunctional regulators of cell interactions. Annu. Rev. Cell Dev. Biol. 17, 25–51.
38 Bornstein, P. (1995) Diversity of function is inherent in matricellular proteins: an appraisal of thrombospondin 1. J. Cell Biol. 130, 503–506.
39 Wenk, M. B., Midwood, K. S. and Schwarzbauer, J. E. (2000) Tenascin-C suppresses Rho activation. J. Cell Biol. 150, 913–920.
40 Goicoechea, S., Orr, A. W., Pallero, M. A., Eggleton, P. and Murphy-Ullrich, J. E. (2000) Thrombospondin mediates focal adhesion disassembly through interactions with cell surface calreticulin. J. Biol. Chem. 275, 36358–36368.
41 Goicoechea, S., Pallero, M. A., Eggleton, P., Michalak, M. and Murphy-Ullrich, J. E. (2002) The anti-adhesive activity of thrombospondin is mediated by the N-terminal domain of cell surface calreticulin. J. Biol. Chem. 277, 37219–37228.
42 Bornstein, P. and Sage, E. H. (2002) Matricellular proteins: extracellular modulators of cell function. Curr. Opin. Cell Biol. 14, 608–616.
43 Sage, E. H. and Bornstein, P. (1991) Extracellular proteins that modulate cell-matrix interactions. SPARC, tenascin, and thrombospondin. J. Biol. Chem. 266, 14831–14834.
44 Schultz-Cherry, S., Lawler, J. and Murphy-Ullrich, J. E. (1994) The type 1 repeats of thrombospondin 1 activate latent transforming growth factor-beta. J. Biol. Chem. 269, 26783–26788.
45 Silverstein, R. L., Nachman, R. L., Pannell, R., Gurewich, V. and Harpel, P. C. (1990) Thrombospondin forms complexes with single-chain and two-chain forms of urokinase. J. Biol. Chem. 265, 11289–11294.
46 Bein, K. and Simons, M. (2000) Thrombospondin type 1 repeats interact with matrix metalloproteinase 2: regulation of metalloproteinase activity. J. Biol. Chem. 275, 32167–32173.
47 Bornstein, P., Devarayalu, S., Edelhoff, S. and Disteche, C. M. (1993) Isolation and characterization of the mouse thrombospondin 3 (Thbs3) gene. Genomics 15, 607–613.
48 Lawler, J., Duquette, M., Whittaker, C. A., Adams, J. C., McHenry, K. and DeSimone, D. W. (1993) Identification and characterization of thrombospondin-4, a new member of the thrombospondin gene family. J. Cell Biol. 120, 1059–1067.
49 Oldberg, A., Antonsson, P., Lindblom, K. and Heinegard, D. (1992) COMP (cartilage oligomeric matrix protein) is structurally related to the thrombospondins. J. Biol. Chem. 267, 22346–22350.
50 Qabar, A. N., Lin, Z., Wolf, F. W., O'Shea, K. S., Lawler, J. and Dixit, V. M. (1994) Thrombospondin 3 is a developmentally regulated heparin-binding protein. J. Biol. Chem. 269, 1262–1269.
51 Vos, H. L., Devarayalu, S., de Vries, Y. and Bornstein, P. (1992) Thrombospondin 3 (Thbs3), a new member of the thrombospondin gene family. J. Biol. Chem. 267, 12192–12196.
52 Adams, J. and Lawler, J. (1993) Extracellular matrix: the thrombospondin family. Curr. Biol. 3, 188–190.
53 Adams, J. C. and Lawler, J. (2004) The thrombospondins. Int. J. Biochem. Cell Biol. 36, 961–968.
54 Bornstein, P. (1992) Thrombospondins: structure and regulation of expression. FASEB J. 6, 3290–3299.
55 Orr, A. W., Elzie, C. A., Kucik, D. F. and Murphy-Ullrich, J. E. (2003) Thrombospondin signaling through the calreticulin/LDL receptor-related protein co-complex stimulates random and directed cell migration. J. Cell. Sci. 116, 2917–2927.
56 Chen, H., Sottile, J., Strickland, D. K. and Mosher, D. F. (1996) Binding and degradation of thrombospondin-1 mediated through heparan sulphate proteoglycans and low-density-lipoprotein receptor-related protein: localization of the functional activity to the trimeric N-terminal heparin-binding region of thrombospondin-1. Biochem. J. 318, 959–963.
57 Li, Z., Calzada, M. J., Sipes, J. M., Cashel, J. A., Krutzsch, H. C., Annis, D. S., Mosher, D. F. and Roberts, D. D. (2002) Interactions of thrombospondins with alpha4beta1 integrin

and CD47 differentially modulate T cell behavior. J. Cell Biol. 157, 509–519.
58 Yang, Z., Kyriakides, T. R. and Bornstein, P. (2000) Matricellular proteins as modulators of cell-matrix interactions: adhesive defect in thrombospondin 2-null fibroblasts is a consequence of increased levels of matrix metalloproteinase-2. Mol. Biol. Cell 11, 3353–3364.
59 Agah, A., Kyriakides, T. R., Lawler, J. and Bornstein, P. (2002) The lack of thrombospondin-1 (TSP1) dictates the course of wound healing in double-TSP1/TSP2-null mice. Am. J. Pathol. 161, 831–839.
60 Adams, J. C. and Lawler, J. (1993) Diverse mechanisms for cell attachment to platelet thrombospondin. J. Cell. Sci. 104, 1061–1071.
61 Asch, A. S., Liu, I., Briccetti, F. M., Barnwell, J. W., Kwakye-Berko, F., Dokun, A., Goldberger, J. and Pernambuco, M. (1993) Analysis of CD36 binding domains: ligand specificity controlled by dephosphorylation of an ectodomain. Science 262, 1436–1440.
62 DeFreitas, M. F., Yoshida, C. K., Frazier, W. A., Mendrick, D. L., Kypta, R. M. and Reichardt, L. F. (1995) Identification of integrin alpha 3 beta 1 as a neuronal thrombospondin receptor mediating neurite outgrowth. Neuron 15, 333–343.
63 Gao, A. G., Lindberg, F. P., Finn, M. B., Blystone, S. D., Brown, E. J. and Frazier, W. A. (1996) Integrin-associated protein is a receptor for the C-terminal domain of thrombospondin. J. Biol. Chem. 271, 21–24.
64 Lawler, J., Weinstein, R. and Hynes, R. O. (1988) Cell attachment to thrombospondin: the role of ARG-GLY-ASP, calcium, and integrin receptors. J. Cell Biol. 107, 2351–2361.
65 Yabkowitz, R., Dixit, V. M., Guo, N., Roberts, D. D. and Shimizu, Y. (1993) Activated T-cell adhesion to thrombospondin is mediated by the alpha 4 beta 1 (VLA-4) and alpha 5 beta 1 (VLA-5) integrins. J. Immunol. 151, 149–158.
66 Calzada, M. J., Sipes, J. M., Krutzsch, H. C., Yurchenco, P. D., Annis, D. S., Mosher, D. F. and Roberts, D. D. (2003) Recognition of the N-terminal modules of thrombospondin-1 and thrombospondin-2 by alpha6beta1 integrin. J. Biol. Chem. 278, 40679–40687.
67 Sid, B., Sartelet, H., Bellon, G., El Btaouri, H., Rath, G., Delorme, N., Haye, B. and Martiny, L. (2004) Thrombospondin 1: a multifunctional protein implicated in the regulation of tumor growth. Crit. Rev. Oncol. Hematol. 49, 245–258.
68 Thakar, C. V., Zahedi, K., Revelo, M. P., Wang, Z., Burnham, C. E., Barone, S., Bevans, S., Lentsch, A. B., Rabb, H. and Soleimani, M. (2005) Identification of thrombospondin 1 (TSP-1) as a novel mediator of cell injury in kidney ischemia. J. Clin. Invest. 115, 3451–3459.
69 Mosher, D. F., Misenheimer, T. M., Stenflo, J. and Hogg, P. J. (1992) Modulation of fibrinolysis by thrombospondin. Ann. N.Y. Acad. Sci. 667, 64–69.
70 Silverstein, R. L., Leung, L. L., Harpel, P. C. and Nachman, R. L. (1985) Platelet thrombospondin forms a trimolecular complex with plasminogen and histidine-rich glycoprotein. J. Clin. Invest. 75, 2065–2073.
71 Taylor, R. B., Duffus WPH, Raff, M. C., de Petris, S. (1971) Redistribution and pinocytosis of lymphocyte surface immunoglobulin molecules induced by anti-immunoglobulin antibody. Nat. New Biol. 233, 225–229.
72 Sundqvist, K. G. (1972) Redistribution of surface antigens – a general property of animal cells? Nat. New Biol. 239, 147–149.
73 Li, S. S., Forslow, A. and Sundqvist, K. G. (2005) Autocrine regulation of T cell motility by calreticulin-thrombospondin-1 interaction. J. Immunol. 174, 654–661.
74 Li, S. S., Liu, Z., Uzunel, M. and Sundqvist, K. G. (in press) Thrombospondin-1 is a cell surface ligand for regulation of integrin dependent T lymphocyte adhesion. Blood
75 Ticchioni, M., Deckert, M., Mary, F., Bernard, G., Brown, E. J. and Bernard, A. (1997) Integrin-associated protein (CD47) is a comitogenic molecule on CD3-activated human T cells. J. Immunol. 158, 677–684.
76 Ludlow, A., Yee, K. O., Lipman, R., Bronson, R., Weinreb, P., Huang, X., Sheppard, D. and Lawler, J. (2005) Characterization of integrin beta6 and thrombospondin-1 double-null mice. J. Cell. Mol. Med. 9, 421–437.
77 Kyriakides, T. R., Zhu, Y. H., Smith, L. T., Bain, S. D., Yang, Z., Lin, M. T., Danielson, K. G., Iozzo, R. V., LaMarca, M., McKinney, C. E., Ginns, E. I. and Bornstein, P. (1998) Mice that lack thrombospondin 2 display connective tissue abnormalities that are associated with disordered collagen fibrillogenesis, an increased vascular density, and a bleeding diathesis. J. Cell Biol. 140, 419–430.
78 Lange-Asschenfeldt, B., Weninger, W., Velasco, P., Kyriakides, T. R., von Andrian, U. H., Bornstein, P. and Detmar, M. (2002) Increased and prolonged inflammation and angiogenesis in delayed-type hypersensitivity reactions elicited in the skin of thrombospondin-2-deficient mice. Blood 99, 538–545.
79 Li, S. S., Ivanoff, A., Bergstrom, S. E., Sandstrom, A., Christensson, B., van Nerven, J., Holgersson, J., Hauzenberger, D., Arencibia, I. and Sundqvist, K. G. (2002) T lymphocyte expression of thrombospondin-1 and adhesion to extracellular matrix components. Eur. J. Immunol. 32, 1069–1079.
80 Vallejo, A. N., Yang, H., Klimiuk, P. A., Weyand, C. M. and Goronzy, J. J. (2003) Synoviocyte-mediated expansion of inflammatory T cells in rheumatoid synovitis is dependent on CD47-thrombospondin 1 interaction. J. Immunol. 171, 1732–1740.
81 Wilson, K. E., Li, Z., Kara, M., Gardner, K. L. and Roberts, D. D. (1999) Beta 1 integrin- and proteoglycan-mediated stimulation of T lymphoma cell adhesion and mitogen-activated protein kinase signaling by thrombospondin-1 and thrombospondin-1 peptides. J. Immunol. 163, 3621–3628.
82 Reinhold, M. I., Lindberg, F. P., Kersh, G. J., Allen, P. M. and Brown, E. J. (1997) Costimulation of T cell activation by integrin-associated protein (CD47) is an adhesion-dependent, CD28-independent signaling pathway. J. Exp. Med. 185, 1–11.
83 Pettersen, R. D., Hestdal, K., Olafsen, M. K., Lie, S. O. and Lindberg, F. P. (1999) CD47 signals T cell death. J. Immunol. 162, 7031–7040.
84 Mateo, V., Lagneaux, L., Bron, D., Biron, G., Armant, M., Delespesse, G. and Sarfati, M. (1999) CD47 ligation induces caspase-independent cell death in chronic lymphocytic leukemia. Nat. Med. 5, 1277–1284.
85 Waclavicek, M., Majdic, O., Stulnig, T., Berger, M., Baumruker, T., Knapp, W. and Pickl, W. F. (1997) T cell stimulation via CD47: agonistic and antagonistic effects of CD47 monoclonal antibody 1/1A4. J. Immunol. 159, 5345–5354.
86 Green, J. M., Zhelesnyak, A., Chung, J., Lindberg, F. P., Sarfati, M., Frazier, W. A. and Brown, E. J. (1999) Role of cholesterol in formation and function of a signaling complex involving alphavbeta3, integrin-associated protein (CD47), and heterotrimeric G proteins. J. Cell Biol. 146, 673–682.
87 Rebres, R. A., Green, J. M., Reinhold, M. I., Ticchioni, M. and Brown, E. J. (2001) Membrane raft association of CD47 is necessary for actin polymerization and protein kinase C theta translocation in its synergistic activation of T cells. J. Biol. Chem. 276, 7672–7680.
88 Avice, M. N., Rubio, M., Sergerie, M., Delespesse, G. and Sarfati, M. (2001) Role of CD47 in the induction of human naive T cell anergy. J. Immunol. 167, 2459–2468.
89 Li, Z., He, L., Wilson, K. and Roberts, D. (2001) Thrombospondin-1 inhibits TCR-mediated T lymphocyte early activation. J. Immunol. 166, 2427–2436.
90 Seiffert, M., Cant, C., Chen, Z., Rappold, I., Brugger, W., Kanz, L., Brown, E. J., Ullrich, A. and Buhring, H. J. (1999)

Human signal-regulatory protein is expressed on normal, but not on subsets of leukemic myeloid cells and mediates cellular adhesion involving its counterreceptor CD47. Blood 94, 3633–3643.

91 Seiffert, M., Brossart, P., Cant, C., Cella, M., Colonna, M., Brugger, W., Kanz, L., Ullrich, A. and Buhring, H. J. (2001) Signalregulatory protein alpha (SIRPalpha) but not SIRPbeta is involved in T-cell activation, binds to CD47 with high affinity, and is expressed on immature CD34(+)CD38(–) hematopoietic cells. Blood 97, 2741–2749.

92 Adams, S., van der Laan, L. J., Vernon-Wilson, E., Renardel de Lavalette, C., Dopp, E. A., Dijkstra, C. D., Simmons, D. L., van den Berg, T. K. (1998) Signalregulatory protein is selectively expressed by myeloid and neuronal cells. J. Immunol. 161, 1853–1859.

93 Brooke, G., Holbrook, J. D., Brown, M. H. and Barclay, A. N. (2004) Human lymphocytes interact directly with CD47 through a novel member of the signal regulatory protein (SIRP) family. J. Immunol. 173, 2562–2570.

94 Piccio, L., Vermi, W., Boles, K. S., Fuchs, A., Strader, C. A., Facchetti, F., Cella, M. and Colonna, M. (2005) Adhesion of human T cells to antigen-presenting cells through SIRPbeta2-CD47 interaction costimulates T-cell proliferation. Blood 105, 2421–2427.

95 Kharitonenkov, A., Chen, Z., Sures, I., Wang, H., Schilling, J. and Ullrich, A. (1997) A family of proteins that inhibit signalling through tyrosine kinase receptors. Nature 386, 181–186.

96 Fujioka, Y., Matozaki, T., Noguchi, T., Iwamatsu, A., Yamao, T., Takahashi, N., Tsuda, M., Takada, T. and Kasuga, M. (1996) A novel membrane glycoprotein, SHPS-1, that binds the SH2-domain-containing protein tyrosine phosphatase SHP-2 in response to mitogens and cell adhesion. Mol. Cell Biol. 16, 6887–6899.

97 Latour, S., Tanaka, H., Demeure, C., Mateo, V., Rubio, M., Brown, E. J., Maliszewski, C., Lindberg, F. P., Oldenborg, A., Ullrich, A., Delespesse, G. and Sarfati, M. (2001) Bidirectional negative regulation of human, T. and dendritic cells by CD47 and its cognate receptor signal-regulator protein-alpha: down-regulation of IL-12 responsiveness and inhibition of dendritic cell activation. J. Immunol. 167, 2547–2554.

98 Oldenborg, P. A., Gresham, H. D. and Lindberg, F. P. (2001) CD47-signal regulatory protein alpha (SIRPalpha) regulates Fcgamma and complement receptor-mediated phagocytosis. J. Exp. Med. 193, 855–862.

99 Liu, Y., Buhring, H. J., Zen, K., Burst, S. L., Schnell, F. J., Williams, I. R. and Parkos, C. A. (2002) Signalregulatory protein (SIRPalpha), a cellular ligand for CD47, regulates neutrophil transmigration. J. Biol. Chem. 277, 10028–10036.

100 Spijkers, P. P., da Costa Martins, P., Westein, E., Gahmberg, C. G., Zwaginga, J. J. and Lenting, P. J. (2005) LDL-receptor-related protein regulates beta2-integrin-mediated leukocyte adhesion. Blood 105, 170–177.

101 Fadel, M. P., Dziak, E., Lo, C. M., Ferrier, J., Mesaeli, N., Michalak, M. and Opas, M. (1999) Calreticulin affects focal contact-dependent but not close contact-dependent cell-substratum adhesion. J. Biol. Chem. 274, 15085–15094.

102 Coppolino, M. G., Woodside, M. J., Demaurex, N., Grinstein, S., St-Arnaud, R. and Dedhar, S. (1997) Calreticulin is essential for integrin-mediated calcium signalling and cell adhesion. Nature 386, 843–847.

103 Coppolino, M. G. and Dedhar, S. (1999) Ligand-specific, transient interaction between integrins and calreticulin during cell adhesion to extracellular matrix proteins is dependent upon phosphorylation/dephosphorylation events. Biochem. J. 340, 41–50.

104 Kwon, M. S., Park, C. S., Choi, K., Ahnn, J., Kim, J. I., Eom, S. H., Kaufman, S. J. and Song, W. K. (2000) Calreticulin couples calcium release and calcium influx in integrin-mediated calcium signaling. Mol. Biol. Cell 11, 1433–1443.

105 Haston, W. S., Shields, J. M. and Wilkinson, P. C. (1982) Lymphocyte locomotion and attachment on two-dimensional surfaces and in three-dimensional matrices. J. Cell Biol. 92, 747–752.

106 Wolf, K., Muller, R., Borgmann, S., Brocker, E. B. and Friedl, P. (2003) Amoeboid shape change and contact guidance: T-lymphocyte crawling through fibrillar collagen is independent of matrix remodeling by MMPs and other proteases. Blood 102, 3262–3269.

107 Guo, N., Templeton, N. S., Al-Barazi, H., Cashel, J. A., Sipes, J. M., Krutzsch, H. C. and Roberts, D. D. (2000) Thrombospondin-1 promotes alpha3beta1 integrin-mediated adhesion and neurite-like outgrowth and inhibits proliferation of small cell lung carcinoma cells. Cancer Res. 60, 457–466.

108 Godyna, S., Liau, G., Popa, I., Stefansson, S. and Argraves, W. S. (1995) Identification of the low density lipoprotein receptor-related protein (LRP) as an endocytic receptor for thrombospondin-1. J. Cell Biol. 129, 1403–1410.

109 Mikhailenko, I., Kounnas, M. Z. and Strickland, D. K. (1995) Low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor mediates the cellular internalization and degradation of thrombospondin: a process facilitated by cell-surface proteoglycans. J. Biol. Chem. 270, 9543–9549.

110 Yang, Z., Strickland, D. K. and Bornstein, P. (2001) Extracellular matrix metalloproteinase 2 levels are regulated by the low density lipoprotein-related scavenger receptor and thrombospondin 2. J. Biol. Chem. 276, 8403–8408.

111 Ferrari do Outeiro-Bernstein, M. A., Nunes, S. S., Andrade, A. C., Alves, T. R., Legrand, C. and Morandi, V. (2002) A recombinant NH(2)-terminal heparin-binding domain of the adhesive glycoprotein, thrombospondin-1, promotes endothelial tube formation and cell survival: a possible role for syndecan-4 proteoglycan. Matrix Biol. 21, 311–324.

112 Roberts, D. D. (1996) Regulation of tumor growth and metastasis by thrombospondin-1. FASEB J. 10, 1183–1191.

113 Murphy-Ullrich, J. E., Gurusiddappa, S., Frazier, W. A. and Hook, M. (1993) Heparin-binding peptides from thrombospondins 1 and 2 contain focal adhesion-labilizing activity. J. Biol. Chem. 268, 26784–26789.

114 Merle, B., Malaval, L., Lawler, J., Delmas, P. and Clezardin, P. (1997) Decorin inhibits cell attachment to thrombospondin-1 by binding to a KKTR-dependent cell adhesive site present within the N-terminal domain of thrombospondin-1. J. Cell Biochem. 67, 75–83.

115 Taraboletti, G., Morbidelli, L., Donnini, S., Parenti, A., Granger, H. J., Giavazzi, R. and Ziche, M. (2000) The heparin-binding 25 kDa fragment of thrombospondin-1 promotes angiogenesis and modulates gelatinase and TIMP-2 production in endothelial cells. FASEB J. 14, 1674–1676.

116 Tolsma, S. S., Volpert, O. V., Good, D. J., Frazier, W. A., Polverini, P. J. and Bouck, N. (1993) Peptides derived from two separate domains of the matrix protein thrombospondin-1 have anti-angiogenic activity. J. Cell Biol. 122, 497–511.

117 Ribeiro, S. M., Poczatek, M., Schultz-Cherry, S., Villain, M. and Murphy-Ullrich, J. E. (1999) The activation sequence of thrombospondin-1 interacts with the latency-associated peptide to regulate activation of latent transforming growth factor-beta. J. Biol. Chem. 274, 13586–13593.

118 Schultz-Cherry, S., Chen, H., Mosher, D. F., Misenheimer, T. M., Krutzsch, H. C., Roberts, D. D. and Murphy-Ullrich, J. E. (1995) Regulation of transforming growth factor-beta activation by discrete sequences of thrombospondin 1. J. Biol. Chem. 270, 7304–7310.

119 Guo, N. H., Krutzsch, H. C., Negre, E., Vogel, T., Blake, D. A. and Roberts, D. D. (1992) Heparin- and sulfatide-binding peptides from the type I repeats of human thrombospondin promote melanoma cell adhesion. Proc. Natl. Acad. Sci. USA 89, 3040–3044.

120 Hofsteenge, J., Huwiler, K. G., Macek, B., Hess, D., Lawler, J., Mosher, D. F. and Peter-Katalinic, J. (2001) C-mannosylation and O-fucosylation of the thrombospondin type 1 module. J. Biol. Chem. 276, 6485–6498.

121 Asch, A. S., Silbiger, S., Heimer, E. and Nachman, R. L. (1992) Thrombospondin sequence motif (CSVTCG) is responsible for CD36 binding. Biochem. Biophys. Res. Commun. 182, 1208–1217.

122 Tuszynski, G. P., Rothman, V. L., Papale, M., Hamilton, B. K. and Eyal, J. (1993) Identification and characterization of a tumor cell receptor for CSVTCG, a thrombospondin adhesive domain. J. Cell Biol. 120, 513–521.

123 Crombie, R., Silverstein, R. L., MacLow, C., Pearce, S. F., Nachman, R. L. and Laurence, J. (1998) Identification of a CD36-related thrombospondin 1-binding domain in HIV-1 envelope glycoprotein gp120: relationship to HIV-1-specific inhibitory factors in human saliva. J. Exp. Med. 187, 25–35.

124 Dawson, D. W., Volpert, O. V., Pearce, S. F., Schneider, A. J., Silverstein, R. L., Henkin, J. and Bouck, N. P. (1999) Three distinct D-amino acid substitutions confer potent antiangiogenic activity on an inactive peptide derived from a thrombospondin-1 type 1 repeat. Mol. Pharmacol. 55, 332–338.

125 Chandrasekaran, S., Guo, N. H., Rodrigues, R. G., Kaiser, J. and Roberts, D. D. (1999) Pro-adhesive and chemotactic activities of thrombospondin-1 for breast carcinoma cells are mediated by alpha3beta1 integrin and regulated by insulin-like growth factor-1 and CD98. J. Biol. Chem. 274, 11408–11416.

126 Graf, R., Freyberg, M., Kaiser, D. and Friedl, P. (2002) Mechanosensitive induction of apoptosis in fibroblasts is regulated by thrombospondin-1 and integrin associated protein (CD47). Apoptosis 7, 493–498.