The Superfamily of Proteins With von Willebrand Factor Type A-Like Domains: One Theme Common to Components of Extracellular Matrix, Hemostasis, Cellular Adhesion, and Defense Mechanisms

By Alfonso Colombatti and Paolo Bonaldo

The TERM superfamily defines a set of related sequences that belong to two or more families and whose different proteins may or may not share sequence similarity with all the members of the other families in the set. Notable is the Ig superfamily, whose members have a diversity of sequences and functions but a common denominator in the recognition role at the cell surface.

In recent years a large body of information has emerged regarding the structure and biologic function of various proteins that constitute the extracellular matrix (ECM). New collagen types have been identified and numerous proteoglycans and glycoproteins have been isolated. Cell surface receptors mediating interactions between ECM and different types of cells also have been the subject of intensive investigations. In some cases it was shown that these components are involved in diverse physiologic phenomena, including cell differentiation, cell migration and adhesion, hemostasis, and immune response. These functions are exerted via multiple matrix-matrix and cell-matrix interactions and are mediated through specialized and unique domains identified by in vitro studies and presumably related to true biologic functions in vivo. Structural data obtained by protein sequence analysis and cDNA cloning have also made it clear that several ECM constituents are assembled by selective incorporation of common domains shared with other proteins. For instance, the fibronectin type III repeats constitute more than 50% of this molecule and are responsible for the cell, heparin, and DNA binding functions. These repeats show a high degree of similarity with domains present in another ECM protein, tenascin/lytotactin, involved in neural and non-neural cell-cell interactions and with domains of cytoplasmic and cell surface molecules including the leukocyte common antigen-related protein (LAR) and the neural cell adhesion molecules L1 and F11/contactin.

Another example is represented by a number of proteins that were recently reported to share a high sequence similarity extending into regions composed of about 200 residues that are often duplicated in tandem within a single protein. The prototype molecule, von Willebrand factor (vWF), that was the first in which these sequences were recognized as representing a unique domain, contains three similar regions defined as type A domains. A variable number of the type A units have been found in other molecules. The number of proteins that incorporate type A-like genetic elements is continuously growing and it is now possible to identify a new set of related proteins that can be designated as type A domain superfamily. We will briefly outline a few properties of these members with emphasis on the structure, function, and biologic role of their type A domains, and suggest speculations on possible relationships. For additional information on the individual members the reader is referred to recent comprehensive reviews.

The type A-like domain specifies a common molecular theme that is present in proteins of the: (1) immune system, leukocyte integrins LFA-1, Mac-1, P150-95, and factor B and component C2 of the complement activation pathway; (2) hemostatic system, vWF; (3) cell adhesion machinery, VLA-1 and VLA-2 integrins; and (4) ECM, cartilage matrix protein (CMP) and type VI collagen. Based on the broad distribution and the relative abundance in the tissues and the number of type A repeats present in type VI collagen molecules (15 to 18 considering the three chains), the ECM can be considered, at the moment, the predominant site of expression of type A repeats.

Members of the type A superfamily are involved in ligand recognition so diverse as to include several collagens (types I, II, III, IV, V, and VI), proteoglycan, heparin, fibrinogen, factor X, C3b, IC3b, zymosan, lipopolysaccharide, ICAM-1, and glycoprotein (GP)1b (Table 1). Only a few of these different binding functions have been located with certainty within the type A domains.
Table 1. Members of the Type A Superfamily, Their Ligands, and Function

<table>
<thead>
<tr>
<th>Protein</th>
<th>Ligands</th>
<th>Function</th>
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<tr>
<td>Hemostasis</td>
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<td>GP Ib</td>
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<td></td>
<td>Factor B</td>
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<td>Integrins</td>
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<td></td>
<td>Mac-1</td>
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<td>Factor X</td>
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<td>p150, 95</td>
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<td>ECM</td>
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<td>Collagen VI</td>
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<td>Proteoglycans</td>
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of the members of the superfamily. Nevertheless, there are suggestions (see later text) that several of the above-mentioned functional properties reside in the type A domains of the respective molecules.

MOLECULAR CHARACTERISTICS OF TYPE A REPEATS

At present our understanding of the molecular structure of the type A superfamily members has been deduced in large part from molecular cloning. Figure 1 shows a schematic representation of the structure of the different components. The \( \alpha \) chains of the leukocyte \( \beta 2 \) integrins LFA-1, Mac-1, p150,95 (corresponding to the cluster of differentiation CDlla, CD1 lb, and CDllc, respectively), and of the VLA-1 and VLA-2 (CDw49b) (corresponding to the GPIa subunit of the platelet collagen receptor GPIa-IIa complex) \( \beta 1 \) integrins have one type A-like domain that is located at the N-terminal extracellular part of the molecule embedded within repeated domains, three of which are similar to consensus metal-binding domains. These are the only integral membrane proteins reported to date to bear a type A domain. In the integrins the domain is called \( \alpha \) for \( \alpha \)-chain.

Two components of the complement system (C2 and factor B) have one type A domain each that is bounded on one side by the cleavage site involved in the activation of the zymogen to the active fragment C2b and Bb, and on the other side by the serine protease domain. vWF has three tandemly repeated type A domains approximately in the middle of the molecule. The ECM protein CMP has two type A-like domains that represent about 90% of the protein. Type VI collagen is constituted by three different chains: \( \alpha 1(\text{VI}) \), \( \alpha 2(\text{VI}) \), and \( \alpha 3(\text{VI}) \). The \( \alpha 1(\text{VI}) \) and \( \alpha 2(\text{VI}) \) chains have a similar size and a short collagenous sequence flanked by three type A-like domains, one at the amino end and two at the carboxyl end. The \( \alpha 3(\text{VI}) \) chain is three times larger than the other two chains and most of the additional sequences are represented by an extended amino-terminal end made of six to nine additional type A-like repeats.

Amino acid sequence similarity. With the introduction of few gaps, the overall similarities among the different repeats are in the ranges between 63.6% (repeats A8 and A6 of the \( \alpha 3 \) chain of type VI collagen) and 18.5% (repeats A3 and A2 of the \( \alpha 3 \) chain of type VI collagen), if conservative changes also are considered. Most of the repeats conform to a consensus sequence having a framework of highly conserved residues (Fig 2). In addition, alignment and analysis of all the sequences available show that there are short stretches of sequences which share a much higher degree of similarity. These amino acid residues define several more conserved subregions separated by "variable" or less conserved sequences of different lengths (8 to 40 residues). It could be speculated that most of the conserved subregions of type A domains are providing a stable molecular organization involved in fundamental protein-protein interactions, whereas the "variable" sequences modulate and fine-tune such interactions and confer ligand recognition specificity. The overall protein sequence similarity among the type A-like domains and the short amino acid motifs that recur in some but not in other members make it possible to envision a lineage tree. For instance, the domains that flank the collagenous sequences of type VI collagen (repeats A') can be grouped together: although they show the lowest conservation among themselves they possess unique cysteine residues that might be important in the process of collagen heterotrimer formation. The domains at the N-terminus of the \( \alpha 3(\text{VI}) \) chain and the two domains of CMP form a distinct subfamily. The three leukocyte integrins have a high degree of similarity and together with VLA-1 and VLA-2 belong to a different grouping. The two complement components also are clearly distinct from the other members of the superfamily.

Characteristic of most of the type A-like domains is the
absence or only occasional presence of N-linked glycosyla-
tion sites. In addition, the absence of cysteines in most type
A repeats is notable. The lack of cysteines is particularly
striking in those members that are cysteine-rich in the
regions flanking their type A domains (see Fig 1). When
cysteines are present within the domains they are usually at
the boundaries where they could form an intrachain loop,
with most of the type A domain protruding toward the
outside. These features might allow accessibility to ligand
interaction and flexibility to assume variable conforma-
tions. However, because no data are yet available on the
tertiary structure of the type A containing molecules, this
hypothesis is largely speculative at present.

Genomic structure. The genomic structure of several
members of the superfamily has been elucidated, and a
distinct pattern of organization of the exons encoding the
 alignments of a set of related sequences is made subjectively by hand. Amino acids are indicated by the single letter code. A', the nine repeats of vWF; B-CZ, the two repeats of factor B and component C2 of C'; pl, the flanking the collagenous sequences of type VI collagen; A, the nine repeats of the amino acid (or a gap, indicated by a line) is given if more than 50% of the sequence in a given set (A', A, vWF, pl) or if both sequences (CMP, B-CZ, pl) have the same amino acid (or a gap) in that position. Similar amino acids are grouped as follows: V,1,L,A,M ((6); D,E (B); R,H,K,S (T); Y,F. A dot marks the position where amino acids of related sequences are variable and belong to different groups. If more than 50% (A', A, vWF, pl) or both (CMP, B-CZ, pl) amino acids belong to the same group they are indicated by capital letters of a smaller size. Amino acids from different sequences belonging to the same set are indicated by capital letters of yet another smaller size. Capital letters are in bold type.

Fig 2. Alignment of consensus sequences showing the conserved (marked by solid lines) and variable subregions of type A domains. Multiple alignments of a related sets of reads is made subjectively by hand. Amino acids are indicated by the single letter code. A', the nine repeats flanking the collagenous sequences of type VI collagen; A, the nine repeats of the a3 chain of type VI collagen; CMP, the two repeats of CMP; vWF, the three repeats of vWF, B-CZ, the two repeats of factor B and component C2 of C'; pl, the two repeats of VLA-1 and VLA-2; β1, the three repeats of LFA-1, Mac-1, ~150.95. The consensus is derived from nine (A', A), three (vWF, pl), or five (CMP, B-CZ, pl) different sequences. A consensus amino acid (or a gap, indicated by a line) is given if more than 50% of the sequence in a given set (A', A, vWF, pl) or if both sequences (CMP, B-CZ, pl) have the same amino acid (or a gap) in that position. Similar amino acids are grouped as follows: V,1,L,A,M ((6); D,E (B); R,H,K,S (T); Y,F. A dot marks the position where amino acids of related sequences are variable and belong to different groups. If more than 50% (A', A, vWF, pl) or both (CMP, B-CZ, pl) amino acids belong to the same group they are indicated by capital letters of a smaller size. Amino acids from different sequences belonging to the same set are in bold type.

type A repeats in the different proteins has emerged. Several of the type A domains are encoded within one exon: a single exon encodes A1 and A2 of vWF; four repeats of the a3 chain (A6 through A9); and two A' repeats of the a2 chain of the chicken (B. Trueb, personal communication, 1990) type VI collagen also are each encoded by one exon. Each of the two repeats of CMP is encoded by two exons. However, other repeats are encoded by multiple exons: A3 of vWF and the single type A repeat found in factor B of complement. LFA-1 (T. Springer, personal communication), and p150,95 are each encoded by four or five exons. Furthermore, the gene organization of these homologous genetic regions shows a variation in length and phase class of the introns, and this may contribute to the development of the diverse binding specificities demonstrated or hypothesized for type A domains. vWF and the other members of the superfamily are clearly the results of multiple gene fusions, duplications, and intron insertion and deletions, and the type A repeats have undergone selective pressures in the different environments in which they are located.

Evolutionary relationships. It is still premature to provide a strict lineage or family tree because too few molecules from only three species have been sequenced so far. Nevertheless, it is conceivable that type A repeats originated by duplication and divergence during evolution from a common precursor, whose function might have been to mediate primordial interactions and recognitions. In a general scheme of hypothetical evolution, a precursor gene provided the basis for its incorporation into a wide variety of molecular types with diverse functions. In some molecules, such as vWF, CMP, and type VI collagen, duplication events probably took place by repeated recombinations and gave rise to multiple copies of type A domain within the molecule. Based on functional and structural grounds it could be speculated that the three domains flanking the type VI collagenous sequences arose at earlier times. A collagen monomer is a three-chain molecule, and the joining of a collagenous sequence with one type VI collagenous sequence must have preceded the duplication events that led to the formation of the three genetically different chains of type VI collagen presently known. This concept is further supported by the observation that the A' repeats flanking the collagenous domain of type VI collagen are the least similar to the other
repeats. Lack of phylogenetic data prevents this hypothesis to be verified at the moment. Microfilaments resembling the periodic structures constituted of disulfide-bonded tetramers of type VI collagen, have been detected in chicken and human tissues, as seen in chicken and even in sponges. While not yet proven by sequence data, these findings would indicate a very ancient function also for type A repeats of collagen VI. The other molecules involved in hemostasis, cellular adhesion, and defense mechanisms could have adopted the type A interaction and recognition system at a later time, also acquiring an increased specialization.

FUNCTIONAL ASPECTS

Known functions of molecules in the type A superfamily are given in Table 1. Functions include adhesion and binding between cells and plasma-soluble or ECM components, between soluble and ECM components, and between different ECM components. A key feature is that heterophilic binding seems to be the rule. On the other hand, the current model of type VI collagen supramolecular assembly into microfibrils, based on previous electron microscopic observations and more recent sequence data, suggests the existence of homophilic interactions by an end-to-end association between the globular ends of type VI collagen tetramers that are composed of type A repeats.

VWF. A prominent function of vWF is the binding to the platelet membrane GPIb, which plays a fundamental role in promoting platelet adhesion to perturbed endothelial surfaces. This adhesion takes place at sites of vascular injury through the interaction of vWF with subendothelial collagen or other components. Both monoclonal antibody (MoAb) inhibition of platelet interaction with vWF and competition with fragments of vWF obtained after enzymatic digestion have established that the functional domain of vWF for GPIb binding is located in repeat A1. Furthermore, one of the two binding sites of vWF for heparin has been assigned next to the GPIb binding region in the same repeat, A1. Domain A of vWF for heparin has been assigned next to the GPIb binding region in the same repeat, A1. The domain of vWF responsible for its binding to collagen also has received much attention; although there are still conflicting results on the precise residues involved, the conclusion was reached that the domains A1 and A3 are involved in binding to collagen. It is possible that this interaction is mediated by the individual domains as a whole entity through multiple low-affinity interactions because overlapping synthetic peptides of about 15 amino acids could not inhibit the binding of labeled vWF to collagen I fibrils (Z. M. Ruggeri, personal communication, 1990).

β1 Integrins. Binding to collagen I through type A repeats is a function shared by several components of the superfamily. On the surface of leukocytes there are multiple receptors with the potential capability of binding to collagen: the β1 integrins VLA-1 and VLA-2 might be used for trafficking into and within lymphoid organs and migration in and out inflammatory exudates, and for other functional activities. An interesting inverse relationship between the relative expression of VLA-1 and VLA-2 has been noted during the course of T-cell activation in vitro. Thus, high levels of VLA-1 expression appear on T cells activated by phytohemagglutinin. The presence of VLA-1 on T lymphocytes at the sites of lesions in patients with rheumatoid arthritis and multiple sclerosis and the absence of VLA-1 from their peripheral blood lymphocytes might represent an in vivo correlate of the in vitro activation stage, and adhesion to collagen may be important in T-cell compartmentalization in inflamed synovium. On restimulation there is a marked diminution in the level of VLA-1 that is often accompanied by an increase in the expression of VLA-2. Nonproliferating but activated T cells might bind collagen with the type A domain of VLA-1 whereas more rapidly dividing cells might instead use VLA-2 to interact with ECM components. The interaction of monocytes and macrophages with collagen, probably via VLA-1 and/or VLA-2, has a direct effect on the function of phagocytic cells resulting in an augmented secretion of several cytokines and prostaglandins. In addition, collagen can influence the differentiation of cultured monocytes into macrophage-like cells and alter cytoplasmic functions of differentiated monocytes. That collagen binding via the type A domain of the platelet collagen receptor GPIa-IIa (VLA-2) plays a relevant role in hemostasis stems from the finding that a patient deficient in the α chain of VLA-2 (platelet GPIa) lacks responsiveness to collagen and presents bleeding disorders.

β2 Integrins. All three leukocyte integrins, LFA-1, Mac-1 and p150,95, appear to function as general adhesion proteins for immune interactions, mediate cell signaling and/or activation, and contribute to leukocyte adhesion to endothelial and artificial substrates. Adhesive functions have been investigated for all leukocyte integrins. Several studies have dealt with the blocking of target T-cell-mediated conjugate cytolysis with LFA-1 MoAbs and with the blocking of T-lymphocyte adherence to endothelial, fibroblast, keratinocyte, and synovial cells. The specific ligand of LFA-1, the intercellular adhesion molecule ICAM-1, was identified, and their interaction with purified molecule and MoAb blocking was analyzed. In these latter studies different functional epitopes were defined, but no molecular epitope mapping was given that could unequivocally localize at least some of these functions to the type A inserted domain of LFA-1. In a recent study several MoAbs were identified that bind to the type A domain of Mac-1. At least two of these MoAbs could inhibit cell adhesion to the endothelium (A. Arnaout, personal communication, 1990).

In addition to the intercellular adhesion phenomena, the leukocyte integrins also serve as receptors for numerous soluble ligands. For instance, iC3b, i.e., the major C3 opsonic fragment, favors the binding of phagocytic cells to iC3b-coated targets through the Mac-1 receptor. Through this function Mac-1 might play a role in coagulation by initiating an alternative cascade by binding to endothelial cell-associated factor X and fibrinogen. It is highly probable that the
sites of these interactions of Mac-1 are in the inserted type A domain. Recent data by Angelar et al (in preparation, as quoted in reference 19), making use of COS cells transfected with chimeric Mac-1/p150,95 α subunits, demonstrate that the majority of MoAbs tested are directed against the type A domain of each subunit. In addition, MoAbs directed against epitopes on the type A domain of Mac-1 can inhibit iC3b binding to Mac-1 and therefore allow the assignment of this function to the type A domain (A. Arnaout, personal communication, 1990). Because iC3b, factor X, and fibrinogen mutually inhibit one another for binding to Mac-1,46 this inhibition suggests a spatial proximity of the sites of Mac-1 that mediate interaction with iC3b, factor X, and fibrinogen, and perhaps also the activation-dependent functional epitopes map to the type A domain.

Complement factors. Complement is a major effector of the humoral immune response. It is composed of at least 20 plasma glycoproteins and cell membrane receptors that mediate the biologic effects, such as engulfment or lysis of foreign particles or cells.21,90 Complement can be activated by two pathways, the classical and the alternative, in which C2 and factor B are involved, respectively.

Given the similarity between the type A domain of Mac-1, which is the receptor for iC3b, and factor B (and C2), which binds C3b with the N-terminus 33-Kd fragment containing the type A domain,97 it might follow that C3b binds factor B (and C2) through the type A inserted domain. It is interesting that binding of C3b to factor B requires divalent cations47 as binding of iC3b to isolated Mac-148 and p150,95.98 Although there are no canonical divalent cation binding sites in the type A domains, there are sequence motifs containing DG and GD that could form a functional cation binding site in the three-dimensional structure. In agreement with this hypothesis is the recent observation that the VLA-2-mediated adhesion of platelets to collagen is Mg²⁺-dependent.77

ECM molecule. CMP and type VI collagen participate with their multiple type A repeats in the ECM assembly. CMP is a major noncollagenous protein of the ECM of several cartilages,31 where it associates with chondroitin sulfate proteoglycan, and preliminary data indicate that it binds to collagen.32 Perhaps type VI collagen plays a role in anchoring the basement membrane of nonepithelial cells to the underlying connective tissue and in bridging collagen I and III fibrils with a network of microfilaments.65 Type VI collagen has additional features that point to a more generalized function for this protein of the superfamily: it is found in most connective tissues, including cartilage, and also in the subendothelial spaces where it has been shown to interact with vWF,100 and it is one of the major components of the extracellular matrix. The demonstration that a recombinant fusion protein of the α3(VI) chain containing only type A repeats binds to type I collagen fibrils provided a structural-functional basis at the molecular level for the specific bridging role of type VI collagen in connective tissues.86 Most of the sequence (70%) of type VI collagen is made of type A repeats, and there is evidence that multiple forms of the α3(VI) chain with a variable number of repeats are expressed within the tissues.101 Because type VI collagen is so rich in type A repeats that differ from one another by several amino acid residues, it could be anticipated that additional functions will be ascribed to these repeats. Furthermore, the recent demonstration that multiple forms of the α3(VI) chain can be generated by alternative splicing in type A repeated domains suggests that variable splicing could provide another level of regulation of molecular interactions of this component.74

When there are several type A repeats, as in type VI collagen, the overall affinity of the interaction with collagen I could be affected. Nevertheless, in the VLA-1 and VLA-2 collagen receptors one single repeat is sufficient for the interaction with type I collagen to occur. For this reason it is likely that distinct mechanisms are at work in the binding of type A repeats to collagen I.

CONCLUSIONS AND PERSPECTIVES

The many different molecules bearing type A repeats and the processes in which these domains participate represent an incomplete but already complex picture. It could be speculated that the binding reactivities observed in vitro are consistent with physiologic functions played in tissues by cells expressing integrins with inserted domains; by molecules such as vWF, C2, and factor B; and by structural ECM components such as CMP and type VI collagen.

Although no satisfactory explanation can be offered at the moment to clarify the fine specificity of the multiple ligand interactions of the similar type A repeats, these domains might exhibit a considerable degree of functional plasticity in response to local conditions: (1) Cells coexpressing multiple integrins might vary the ability to interact with the ECM via type A-dependent phenomena by new or increased expression of nontype A-containing integrins.102 (2) Modifications of ligand binding specificity by cell-specific factors: for instance, the platelet collagen receptor VLA-2/GP1a-IIa binds collagen I (via type A repeat) in platelets59,103 and laminin in endothelial cells.104 (3) Conformational changes might add new functions following activation by several means, as it happens when macrophages are stimulated by ADP and acquire the capability of binding fibrinogen and factor X.45,46 (4) Local differences in the concentration of type A-containing components. (5) Expression of molecules with variable numbers of type A repeats as seen with type VI collagen: in this case a change in the ligand specificity is suggested by the distinct anatomical localization of type VI collagen molecules bearing a different number of type A repeats.74

The collagen I binding function is a common feature of vWF,66 VLA-1,75 VLA-2,74,75 CMP,32 and type VI collagen.56

Repeats present in other molecules (ie, β2 integrins) could share the collagen I binding function: adhesion of phagocytic cells to subendothelium and recruitment into inflammatory areas could proceed through a mechanism mediated by binding to collagen fibers via the inserted type
A domain of the leukocyte integrins. It is likely that several adhesion mechanisms had to evolve to accommodate a variety of leukocyte functions, as migration through ECM, homing, and regulatory events and functions mediated via type A repeats of this variety of components are certainly playing a major role. Localization of C2 and factor B complement components to inflammatory sites also could potentially be mediated by adhesion to collagens via type A domains.

At present, several inherited deficiency-state diseases

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**Fig 3.** Schematic representation of a series of events in which type A repeats (shown as small empty boxes [ ]) are playing a functional role. (A) Inflammation and hemostasis shown at lower magnification. The shaded areas (B and C) are shown enlarged in the lower part of the figure. (B) Inflammation. Phagocytic cells migrate through the endothelium, adhere to collagen I fibrils or fibril fragments through VLA-2, and ingest iC3b opsonized bacteria through Mac-1 (CR3) and p150,95. (C) Hemostasis. At the site of injury vWF interacts through its A1 domain with platelet GPIIb and through A1 and A3 domains with subendothelial collagen I. The subendothelial network is also comprised of fibroblasts interacting with collagen I via VLA-1 and VLA-2, and of type VI collagen microfibrils that connect different collagen I fibers through the multiple type A domains of the globular ends. Other type A-related functions that also take place in inflamed tissues and during hemostasis are not shown for the sake of clarity. Similarly, other components that play a role both in inflammation and hemostasis but are not associated with type A-related functions are omitted. The globular ends of type VI collagen tetramers are depicted to highlight the fact that they are constituted of multiple type A repeats. The actual sizes of the various cells and components are different from those shown here. Abbreviations: bact., bacterium; BM, basement membrane; Col, collagen; endoth. c., endothelial cell; fb., fibroblasts; macr., macrophage; mono., monocyte; plat., platelet; PMN, polymorphonuclear leukocyte.
have been recognized to depend on structural defects of type A repeat-bearing molecules. In leukocyte adhesion deficiency (LAD), leukocytes lack expression of all three β2 integrins and suffer from recurrent infections; in von Willebrand disease (vWD), a severe bleeding disorder, both structural and functional alterations of vWF are demonstrated. Other patients were recently reported with hemorrhagic disorders and a severely impaired response to collagen, and this disfunction is associated with the lack of the α chain of VLA-2 or with an autoantibody to VLA-2. In complement C2 component-deficiency states with the absence or decreased levels of C2, both alterations in opsonization function and persistent autoimmune abnormalities are detected. Several disease states are the results of defects in type A repeat-bearing constituents, but at present the only molecular evidence that the underlying cause is due to alterations within the type A domains has been reported for the type IIA vWD. The existence of pseudogenes that have been identified for a number of genes should be kept in mind in interpreting molecular data. A truncated pseudogene coding for the type A repeats of vWF has recently been identified, and it appears that some of the molecular defects proposed to be the cause of type II B vWF disease were the consequence of the inadvertent amplification of pseudogene sequences. Nevertheless, either immunoochemical or molecular biology techniques promise to allow the definition of other molecular defects within the type A domains.

The type A repeat-containing members participate in several biologic events, two of which are schematically illustrated in Fig 3. Much remains to be determined concerning the molecular basis and relevance of type A domain interactions, namely unidentified putative ligands, interactive sites of the molecules and definition of the sequences responsible for the fine specificity of the conserved domains, and participation in normal and pathologic conditions. Finally, given the already widespread occurrence of type A-containing molecules we can anticipate a picture in which other proteins will be found to contain this type of domain.

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The superfamily of proteins with von Willebrand factor type A-like domains: one theme common to components of extracellular matrix, hemostasis, cellular adhesion, and defense mechanisms

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