Structural Basis of Type VI Collagen Dimer Formation*

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We have determined the interactive sites required for dimer formation in type VI collagen. Despite the fact that type VI collagen is a heterotrimer composed of α1(VI), α2(VI), and α3(VI) chains, the formation of dimers is determined principally by interactions of the α2(VI) chain. Key components of this interaction are the metal ion-dependent adhesion site (MIDAS) motif of the α2C2 A-domain and the GER sequence in the helical domain of another α2(VI) chain. Replacement of the α2(VI) C2 domain with the α3(VI) domain abolishes dimer formation, whereas alterations in the α2(VI) C1 domain did not disrupt dimer formation. When the helical sequences were investigated, replacement of the α2(VI) sequence GSPGERGDQ with the α3(VI) sequence GEGGERDGV abolished dimer formation. Mutating the Pro-108 to a Lys-108 in this α2(VI) sequence did not influence dimer formation and suggests that, unlike the integrin I-domain/triple-helix interaction, hydroxyproline is not required in collagen VI A-domain/helix interaction. These results demonstrate that the α2(VI) chain position in the assembled triple-helical molecule is critical for antiparallel dimer formation and identify the interacting collagenous and MIDAS sequences involved. These interactions underpin the subsequent assembly of type VI collagen.

Type VI collagen has a ubiquitous distribution throughout connective tissues, and it is thought to link cells and other matrix components. It has three different chains, α1(VI), α2(VI), and α3(VI), each containing a short triple-helical region and globular extensions at NH2 and COOH termini (1, 2). In contrast to most other collagens, type VI collagen undergoes some polymerization prior to secretion. Heterotrimeric association of the α1(VI), α2(VI), and α3(VI) chains constitutes a monomer with a short triple-helical region (100 nm) encompassed by NH2- and COOH-terminal globular regions (3). Dimers are assembled by a staggered antiparallel alignment of two disulfide bonded monomers, resulting in a 75-nm overlap between the two triple helices and alignment of the COOH-terminal globular region of one molecule with the helical domain of the other. In dimers, the triple-helical regions become supercoiled in a left-handed superhelix of pitch 37.5 nm (4, 5). Dimers then align with their ends in register to form tetramers, which are the secreted form. Tetramers then align end-to-end in the extracellular space to form type VI collagen microfibrils (4) (Fig. 1).

The majority of the type VI collagen globular regions comprise domains that have homology to von Willebrand factor A-domains (6). A-domains are found in a number of proteins, including integrins (designated αI-domains) and several collagens, and appear to act as homologous adhesion domains. The crystal structures of several αI-domains reveal a Rossman-type fold, with a six-stranded parallel β-sheet flanked by seven amphipathic α-helices (7). Side chains from three loops closely opposed on the upper surface of the domain coordinate a Mg2+ or Mn2+ ion, to form a three-dimensional metal ion-dependent adhesion site (MIDAS), which is conserved in all αI-domains. Loop 1 contains a contiguous DXIXXS sequence, where D is aspartate, X is any amino acid, and S is serine; loop 2 contains a threonine residue, while loop 3 contains an aspartate residue, located —70 and 100 residues from the DXIXXS sequence, respectively. Mutation of individual MIDAS residues disrupts metal binding and significantly reduces or eliminates ligand binding activity (8–13). Metal ion binding to a MIDAS sequence in the α2Iβ1 I-domain has been shown to be a critical determinant of collagen binding (14).

Integrin heterodimers αIβ1, αIβ2, αIβ3, αIβ5, and αβ1, can bind collagen (15–18). Their binding sequence in the αI-domain surrounding the MIDAS groove creates a groove centered on the metal ion (19). Residues on the upper surface of the αI-domain surrounding the MIDAS groove contribute to the affinity and specificity of collagen binding (7, 20–23). Structural analysis has shown that the collagen triple-helix fits into the αI I-domain binding groove, where a glutamate residue from the collagen coordinates the metal ion of the MIDAS motif (14). Ligand binding induces a conformational change, resulting in the αI-helix unwinding and facilitating collagen adhesion (14). Two triple-helical sequences within type I collagen, GFOGER (24) and GLOGER (25), where O represents hydroxyproline, have been identified as binding motifs for αI- and α2 I-domains. When a GFOGER containing collagen peptide was co-crystallized in complex with a α2 I-domain (14), the collagen glutamate was shown to coordinate the metal ion, while the arginine and phenylalanine residues made contact with the αI-domain. The conservative substitution of the collagen glutamate to aspartate eliminated binding, since the aspartate is too short to coordinate the ion (24). While the αI- and α2 I-domains each contain a conserved MIDAS motif, small structural differences may explain why the αI1-domain has a higher binding affinity to type IV collagen (23, 26).

We have previously shown that the α2C2 A-domain is critical for dimer formation in type VI collagen (27). Consideration of the staggered antiparallel alignment of type VI collagen monomers in dimers suggests that a C2 domain of one monomer interacts with the helical domain of another type VI collagen molecule. In type VI collagen, a MIDAS motif is found in C1

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1 The abbreviation used is: MIDAS, metal ion-dependent adhesion site.
The amplified type VI collagen kit (Strategene, Cambridge, UK) was used to introduce mutations in min at 60 °C, described previously (27), the tertiary oligonucleotides containing the desired mutation (125 ng), 200 μM sequence identity and reading frame integrity were confirmed by dye-termination assembly. Amplified fragments corresponding to the expected sizes were isolated and then purified using a silicon matrix-based purification kit (Qiagen, USA) for 15 min, then the cell pellet was washed three times in g/ml proteinase K (Sigma, Poole, UK) in the presence of 10 mM CaCl₂ for 20 min at 4 °C. RNA was purified using spin columns (Qiagen) and eluted in RNase-free water containing RNase inhibitor. Translation of RNA transcripts was performed using an Expand high fidelity PCR kit (Roche Diagnostics, Germany) to the 5’ end of the 3(VI) chain C2 domain MIDAS motif DGSER (bases 301–339) (1), incorporating the mutations shown underlined. The 2(VI) helix sequence GSPGERDQ (residues 106–111) (1) was mutated to GEPGER (2(VI)/2H) (Fig. 3), using two complimentary oligonucleotides (5’-CGGGGGAGAGGAGGAGGGAGCCAGGGGAGCGA-3’) (bases 307–354) (1), incorporating the mutations shown underlined. The 2(VI) helix sequence GERGDV (residues 106–114) (1) (2(VI)/2H) (Fig. 3) of identical position, using two complimentary oligonucleotides (5’-GGAGGGCAGGGGAGAGGGGAGCCAGGGGAGCGA-3’) (bases 322–360) (1), incorporating the mutations shown underlined. The 2(VI) helix sequence GERGDQ (residues 109–114) (1) was mutated to GERGV (2(VI)/2H) (Fig. 3), using two complimentary oligonucleotides (5’-GGAGGGCAGGGGAGAGGGGAGCCAGGGGAGCGA-3’) (bases 322–360) (1), incorporating the mutations shown underlined.

**EXPERIMENTAL PROCEDURES**

**Generation of 2(VI) Chimera Construct—**A chimeric construct consisting of a signal peptide sequence from the N1, helix, and C1 domains of the 2(VI) chain and C2 domain of the 2(VI) chain was generated by overlap extension PCR. Clone pGEM2zC1, described previously (27), was utilized to amplify the signal peptide sequence and 2(VI) N1, helix, C1 domains, using the signal peptide forward primer (5’-CGGGGGCAGGGGAGAGGGGAGCCAGGGGAGCGA-3’) incorporating a 23-base fragment (bases 2456–2478) (1) to the 3’ end of the 2(VI) C1 domain and a 23-base overlap (bases 7411–7437) (2) to the 5’ end of the 2(VI) C2 domain. Clone pGEM2zC3A, described previously (27), was used to generate an 2(VI)/2H chain C2 domain, using forward primer (5’-CCAGGGGAGCGAGGAGACGTTGGCGCAAGGGGAG-3’) (bases 7411–7437) (2) to the 5’ end of the 2(VI) C2 domain and a 23-base overlap (bases 2456–2478) (1) to the 3’ end of the 2(VI) C1 domain and an 2C2 reverse primer (5’-GTTTACAGGATGTGTTGGTG-3’) (bases 8282–8304) (2) containing a stop codon. PCR was performed using an Expand high fidelity PCR kit (Roche Diagnostics, Lewes, UK). Reaction mixtures (50 μl) consisted of 1 ng of template cDNA, reaction buffer containing 1.5 mM MgCl₂, 200 μM dNTPs, 50 pmol of forward and reverse primers, and 2.6 units of DNA polymerase mixture (thermostable Taq and Pwo). Reaction mixture was incubated for 3 min at 94 °C, immediately followed by 1 min at 94 °C, 2 min at 60 °C, and 5 min at 72 °C for 25 cycles, then 7-min incubation at 72 °C. Amplified fragments corresponding to the expected sizes were isolated and then purified using a silicon matrix-based purification kit (Qiagen, Crawley, UK). Purified short overlap 2C1 2C/H chain (1 ng) and 2C2 domain (1 ng) PCR products were combined in a second round overlap extension PCR. A reaction was performed for 30 s at 94 °C, 2 min at 42 °C, and 1 min at 72 °C for six cycles, in the absence of primers to allow self-anneling of the 2C1 and 2C2 overlap regions. Signal peptide forward primer and 2C2 reverse primer were then added and reaction mixture immediately incubated for 25 cycles of 30 s at 94 °C, 1 min at 60 °C, and 3 min at 72 °C, followed by 7-min incubation at 72 °C. The amplified 2(VI) chimeric construct was isolated, purified, and cloned into TA vector pGEM (Promega, Southampton, UK), then the sequence identity and reading frame integrity were confirmed by dye-termination automated sequencing.

**Mutation of α-Chains—**A QuikChange™ site-directed mutagenesis kit (Strategene, Cambridge, UK) was used to introduce mutations in type VI collagen α-chain constructs cloned into vector pGEM (Promega). A reaction mixture consisted of α-chain clone (10 ng), two complementary oligonucleotides containing the desired mutation (125 ng), 200 μM dNTPs, 2.5 units of Pfu DNA polymerase, and reaction buffer to a final volume of 50 μl. The reaction mixture was incubated for 30 s at 95 °C, immediately followed by 30 s at 95 °C, 1 min at 55 °C, and 12 min 30 s at 68 °C for 18 cycles, cooled to 4 °C, then 10 units of DpnI restriction enzyme added and incubated for 90 min at 37 °C. Mutated DNA was transformed into E.coli BL21-Blue competent cells, then colonies containing the correct mutation were identified by dye-terminator automated sequencing.

**2(VI) C2 Domain MIDAS Mutations—**Using clone pGEM2zC2, described previously (27), the 2(VI) C2 domain MIDAS motif DGERG was mutated to the aligned α3(VI) C2 domain sequence DSAET (residues 2392–2396) (1) (2C2/2H) (Fig. 2), using two complimentary oligonucleotides (5’-GCTTGCTGCTGGACGGAGCTGGACGACCTGGTCGTTG-3’) (bases 2520–2557) (2) containing the mutations shown underlined. The 2(VI) C2 domain MIDAS motif DGGER (residues 818–822) (1) was mutated to DGSESS (2C2/2M) (Fig. 2), using two complimentary oligonucleotides (5’-GCTTGCTGGACGGAGCTGGACGACCTGGTCGTTG-3’) (bases 2520–2557) (2) containing the mutations shown underlined. The 2(VI) C2 domain MIDAS motif TDG (residues 927–929) (1) was mutated to TTG (2C2/2M) (Fig. 2), using two complimentary oligonucleotides (5’-GCTTGCTGGACGGAGCTGGACGACCTGGTCGTTG-3’) (bases 2520–2557) (2) containing the mutations shown underlined. The 2(VI) helix sequence GSPGERDQ (residues 106–114) (1) incorporating the amino-terminal GDR triplet was mutated to the corresponding 2(VI) helix sequence GGERGDV (residues 106–114) (1) (2C2/2H) (Fig. 3) of identical position, using two complimentary oligonucleotides (5’-GGGAGGAAGCAGGGGAGCGAAGGGGAGCGA-3’) (bases 307–354) (1), incorporating the mutations shown underlined.
KH M buffer (100 mM potassium acetate, 20 mM Heps, pH 7.2, 2 mM magnesium acetate). No added mRNA controls were used in these studies (27); in the absence of added mRNA, no translation products were detected. All experiments were shown to be reproducible after repeating a minimum of three times.

**Immunoprecipitation and Detection of a-Chain Assemblies—**Washed cells were incubated for 30 min at 4 °C in NET buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 0.25% (w/v) gelatin, 0.05% (v/v) Nonidet P-40 and 0.02% (w/v) sodium azide), the supernatant was preclared with 10% (v/v) protein A-Sepharose for 1 h at 4 °C, then incubated with type VI collagen polyclonal antibody VIA (kindly donated by Dr. S. Ayad) (29) for 16 h at 4 °C. The supernatant was then incubated with 10% (w/v) protein A-Sepharose for 2 h at 4 °C, centrifuged at 800 × g for 3 min, and the immunoprecipitates were washed three times in NET buffer minus Nonidet P-40 and gelatin and then resuspended in SDS-PAGE sample buffer, with or without 5% β-mercaptoethanol. Type VI collagen α-chains were analyzed using reducing 8% (w/v) polyacrylamide gels, while monomers, dimers, and tetramers were observed using non-reducing 3% (w/v) polyacrylamide 0.4% (w/v) agarose composite gels (27), which were fixed, dried, and imaged using a Fujix BAS2000 phosphorimager.

**Homology Models—**Atomic models for the interaction of a collagen triple helix with a2(VI) C2 domain were built on the crystal structure coordinates of the complex between the A-domain of α1β1 integrin and a collagen peptide containing the GFOGER sequence (14). First, a homology model for a2(VI) C2 was built based on the alignment of its sequence to both von Willebrand factor A-domain (27), and the αA-domain of α1β1 integrin, using the coordinates of the ligand-bound form of the α1β1 A-domain as reference. The program LOOK (Molecular Applications Group, Palo Alto, CA) was used for this homology modeling. Different models for the collagen-a2(VI) C2 interaction were then assembled using collagen triple-helical models with the following sequences: (EAGSOGGERGDQGAR)3 from a2(VI), (PRGEKGERGDVGIRO)6 from α3(VI), and a model with sequence ((PKGDOGAFGLKGEK)) (EAGSOGGERGDQGAR) (PRGEKGERGDVGIRO) to represent an α1n2α3 collagen VI heterotrimer (see “Discussion”). A metal ion was always modeled at the MIDAS site, and a few water molecules were also included in the models to complete the metal coordination sites and to account for the water-mediated hydrogen bonds in the collagen triple helices (30, 31). The complex models thus assembled were subject to energy minimization using the program CNS (32). By analogy with the collagen-integrin A-domain structure, the a2(VI) C2 domain is identified as the “A” chain, and the three chains in the collagen triple helix are identified as “B,” “C,” and “D,” respectively.

**RESULTS**

All DNAs encoding the mutated α-chains were verified by sequencing, then shown by reducing SDS-PAGE to produce a translation product of the expected size and similar abundance to the corresponding non-mutated α-chains (data not shown). Differences in the monomer intensities observed on the agarose composite gels reflect differences in monomer assembly or stability.

**MIDAS Sequence Involvement in Type VI Collagen Assembly—**To delineate the residues of the C2 domain that determined type VI collagen assembly, a chimeric a2(VI) chain was constructed in which the a2(VI) C2 domain was replaced with the a3(VI) C2 domain (see Fig. 2, a2-chimera-normal). When these a2(VI) wild type and a2-chimera chains were translated...
and analyzed using non-reducing agarose/acrylamide composite gels, the wild type chain produced dimers and tetramers, but the chimeric α2(VI) chain produced only low levels of monomers (Fig. 4, lanes 1 and 3). The α3(VI) chain was also unable to form dimers (Fig. 4, lane 2). Replacement of the α2(VI) C2 domain with the α3(VI) C2 domain thus abolished dimer formation.

Manipulation of the MIDAS domain within the α2(VI) C2 domain also was found to abolish dimer formation. Thus, when the α2(VI) C2 domain sequence DGSSER (residues 818–822), homologous to the MIDAS consensus sequence DXSSX, was substituted by site-directed mutagenesis for the corresponding homologous to the MIDAS consensus sequence DXSXS, was DGSER to replace DSAET (Fig. 5, lane 1). This substitution could be re-instated by re-introducing the MIDAS motif, whereas the α3(VI) chain (lane 2, α2(VI) Thr-928 (α2C2/2M mutant) lane 3, α2(VI) Ser-822 (α2C2/3M mutant). Translation products representing lower monomer, higher monomer, dimer, and tetramer are as shown.

The triple-helical sequence GFOGER (where O represents hydroxyproline) within collagen type I has been identified as the minimum recognition motif for integrin α1 and α2 I-domains (24). A GER triplet is present in the α2(VI) chain (residue 822) in the α3(VI) helix by site-directed mutagenesis, the arginine (residue 822) was substituted for a serine (see Fig. 2, a2C2/3M mutant). After 4 h of translation the Arg-822 → Ser-822-mutated α2(VI) chain produced a much lower level of monomer, dimer, and tetramer formation when compared with non-mutated α2(VI) chain (Fig. 5, lanes 1 and 3).

Changing the potential MIDAS sites in the C1 domain of the α2(VI) chain with sequences in the α3(VI) C1 and C2 domains did not prevent dimer and tetramer formation (see Fig. 2, a2C2/4M and a2C2/5M) (data not shown).

Helix Sequence Involvement in Type VI Collagen Assembly—The triple-helical sequence GFOGER (where O represents hydroxyproline) within collagen type I has been identified as the minimum recognition motif for integrin α1 and α2 I-domains (24). A GER triplet is present in the α2(VI) helix sequence at residues 109–111. An glu-110 → Asp-110-mutated α2(VI) chain (Fig. 6, lane 1). This proline (residue 109) in exactly the same position as that found in the α2(VI) helix sequence (residues 109–111). Residues 106–114 (GSPGERGDQ) in the α2(VI) helix were substituted for residues 106–114 (GEKGERGDV) in the α3(VI) helix by site-directed mutagenesis (see Fig. 3, a2C2/2H mutant). The mutated α2 chain produced only low levels of monomer after 4 h of translation (Fig. 6, lane 3).

To delineate which residues within the α2(VI) helix sequence GSPGERGDQ (residues 106–114) are important to type VI collagen assembly, individual constituents were substituted for identically positioned α3(VI) helix residues within the sequence GKEKGERGDV (residues 106–114). The proline (residue 108) is predicted to be hydroxylated (28). Hydroxylation is an important determinant of helical stability, as shown by the addition of dipiridyyl to the translation reaction when, after 4 h of translation, no assemblies corresponding to monomer, dimer, or tetramer were observed (Fig. 6, lane 6). A Pro-108 → Lys-
FIG. 6. Analysis of α2(VI) triple-helical mutations on dimer assembly. Normal or mutated α2(VI) chain RNA was translated for 4 h and the products immunoprecipitated using polyclonal antisera VIA and then separated using a 0.5% agarose 3% polyacrylamide composite gel under non-reducing conditions. Lane 1, α2(VI) chain (normal); lane 2, α2(VI) Asp-110 (α2C2/1H mutant); lane 3, α2(VI) GEKGERGDV (106–114) (α2C2/2H mutant); lane 4, α2(VI) Glu-107 (α2C2/3H mutant); lane 5, α2(VI) Lys-108 (α2C2/4H mutant); lane 6, addition of 0.5 mM α,α′-dipyridyl to the reaction; lane 7, α 2(VI) Val-114 (α2C2/5H mutant). Translation products representing lower monomer, higher monomer, dimer, and tetramer are as shown.

108-mutated α2(VI) chain (see Fig. 3, α2C2/4H mutant) produced monomer, dimer, and tetramer assemblies at a similar level to a non-mutated α2(VI) chain (Fig. 6, lane 5, compare with lane 1). Similarly, an Ser-107 → Glu-107-mutated α2(VI) chain (see Fig. 3, α2C2/3H mutant) produced monomer, dimer, and tetramer assemblies at a comparable level to non-mutated α2(VI) chain (Fig. 6, lane 4). However, a Gln-114 → Val-114-mutated α2(VI) chain (see Fig. 3, α2C2/5H mutant) produced only monomers (Fig. 6, lane 7).

The α3(VI) chain did not form dimers and tetramers even when the α2(VI) helical and C2 domains were inserted (see Fig. 3, α3C2/MH mutant) (data not shown).

DISCUSSION

The elaboration of type VI collagen microfibrils extracellularly is critically dependent on the formation of stable tetramers intracellularly. Little is known about the formation and stabilization of these intracellular assemblies and how dimers form. The observed staggered antiparallel arrangement of monomers to form dimers shows that the COOH-terminal domain must interact with the helical domain of another molecule (4). We previously showed (27) that the C2 domain of the α2(VI) chain is a critical determinant of dimer formation and tetramer elaboration. We have now delineated the molecular basis of this dimer formation by identifying the sequences within the α2(VI) chain that determine dimer formation. The α2(VI) chain provides the residues in the helical portion of one monomer and the MIDAS motif of the C2 domain in another monomer, and these interact in a specific manner to form antiparallel dimers.

Previous studies of A-domain interactions with fibrillar collagen have identified the triple-helical sequence GFOGER (where O represents hydroxyproline) within collagen type I as a recognition motif for integrin α1 and α2 I-domains (24). Studies on the interaction between the integrin αβ1 and fibrillar collagen revealed that the critical residues in the A-domain lay on the three loops that both co-ordinated the metal ions and made direct H bonds and salt bridges to the collagen (14). The authors also suggested that, while the GFOGER motif occurs only in the α1 chains of types I and IV collagen, GxOGER may account for the ability of several loci in collagens to bind to αβ1. The collagenous sequence of the α2(VI) chain contains the homologous sequence GSPGERGQ, which we have shown here by site-directed mutagenesis is required for A-domain mediated dimer formation. Recently, the crystal structure of the A3-domain of von Willebrand factor was determined, and site-directed mutagenesis showed the collagen binding site is close to the bottom face of A3 and not in the top face with the vestigial MIDAS motif (33). Moreover, site-directed mutagenesis of residues on the top face displayed normal collagen binding (34). Homology alignment of the α2(VI) C2 A-domain and the von Willebrand A3-domain shows very little conservation...
in the three short sequences involved in this bottom face collagen binding.

The evidence from our site-directed mutagenesis experiments, the conservation of all but one of the metal binding features on α2(VI) C2 A-domain, and the presence of an essential GxOGER collagenous sequence indicates that the C2-triple helix interaction resembles that of collagen with A-domain integrins. To gain further insights into the molecular interaction between α2(VI) C2 domain and the triple-helical region of type VI collagen, we built atomic homology models based on the collagen-integrin A-domain crystal structure (14) (see "Experimental Procedures"). Fig. 7 shows a model of the interaction of α2(VI) C2 A-domain (A chain) with the triple-helical region of an α2(VI) A-homotrimer. As in the collagen-integrin α1-domain crystal structure (14), this model predicts that the middle strand (C chain in red) accounts for the majority of the interactions with the C2 domain, with fewer from the trailing strand (D chain in yellow) and none from the leading strand (B chain in purple). The middle strand glutamate Gln-C110 completes the coordination of the metal ion in the MIDAS site in a manner completely equivalent to the collagen-integrin interaction. Nevertheless, the model suggests that there might be some significant differences. For example, the next residue in the GER triplet, Arg-C111 (not shown in Fig. 7), does not seem to have a suitable interaction partner in the collagen-integrin structure (14). Our model places Arg-C111 main chain in contact to Phe-893 side chain on the middle strand (no interaction with C2) and α3 the trailing strand, as shown in Fig. 8c. In fact, the model built with a heterotrimer sequence predicts even more favorable interactions, such as Lys-D108 in the trailing strand with Glu-821 from the DGSER motif (Fig. 8c). Thus, the need to provide binding specificity to the C2 domain seems to dictate the way in which the three chains of collagen VI need to assemble together to form multimerization-competent heterotrimers.

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