Endostatin is a C-terminal proteolytic fragment of collagen XVIII that is localized in vascular basement membrane zones in various organs. It binds to heparin/heparan sulfate and to a number of proteins, but its molecular mechanisms of action are not fully elucidated. We have used surface plasmon resonance (SPR) arrays to identify new partners of endostatin, and to give further insights on its molecular mechanism of action. New partners of endostatin include glycosaminoglycans (chondroitin and dermatan sulfate), matricellular proteins (thrombospondin-1 and SPARC), collagens (I, IV, and VI), the amyloid peptide Aβ-(1–42), and transglutaminase-2. The biological functions of the endostatin network involve a number of extracellular proteins containing epidermal growth factor and epidermal growth factor-like domains, and able to bind calcium. Depending on the trigger event, and on the availability of its members in a given tissue at a given time, the endostatin network might be involved either in the control of angiogenesis, and tumor growth, or in neurogenesis and neurodegenerative diseases.

Endostatin is a C-terminal proteolytic fragment of collagen XVIII that is localized in vascular basement membrane zones in various organs. It inhibits angiogenesis and tumor growth (1–3). The effect of endostatin depends on its concentration (4, 5), on the length of exposure (6), on the type of endothelial cells (7), and on the growth factor inducing cell proliferation (fibroblast growth factor 2 or VEGF) (8, 9).

Endostatin binds to several membrane proteins including α5β1 and αvβ3 integrins (10, 11), heparan sulfate proteoglycans (glypic-an-1 and -4) (12), and KDR/Flik1/VEGFR2 (13). We have previously characterized the binding of endostatin to heparan sulfate chains (9), and of endostatin to integrins (11). Furthermore, we have shown that α5β1, αvβ3, and αvβ5 integrins bind to heparin/heparan sulfate (11).

The broad molecular targets of endostatin suggest that multiple signaling systems are involved in mediation of its antiangiogenic action. Endostatin is a broad spectrum angiogenesis inhibitor that suppresses angiogenesis by blocking general mechanisms that govern endothelial cell growth (14), and initiates a complex network of signaling at the gene level (15). However, its molecular mechanism of action is still a matter of debate.

An integrative view of the endostatin interaction network, including interactions between endostatin partners, is necessary to provide a clear understanding of how all these molecules work together to regulate angiogenesis, and tumor growth. This global approach places individual proteins into a functional context, and takes into account the fact that a single molecule such as endostatin can affect a wide range of other cell components. Indeed, most proteins and other components carry out their functions within a complex network of interactions and this approach based on protein-protein interaction networks has been developed for several years to give new clues on biological processes (16).

This study was thus designed to identify additional extracellular partners of endostatin in an attempt to obtain new insights into its mechanisms of action, and the biological processes in which it participates. For this purpose, we have developed protein and glycosaminoglycan arrays using an automated surface plasmon resonance (SPR) platform. Proteins and glycosaminoglycans selected for SPR analysis were present in the same tissues or structures, such as basement membranes (17), brain (18), cartilage (19), or they were involved in the same physiopathological processes (angiogenesis, neuro-degenerative diseases) as endostatin, and they were available as full-length molecules. Collagens I and VI, for example, have been selected because the α1 and α2 chains of collagen VI were determined to be potential pan-endothelial markers as was the α1 chain of collagen XVIII containing endostatin (20), and because the genes coding for the α1 and α2 chains of collagen I, and the α3 chain of collagen VI are up-regulated in angiogenic vessels and elevated in tumor endothelium (20). Some proteins and glycosaminoglycans were also included to serve as positive controls for well known interactions with the potential partners of endostatin. We report that endostatin binds to other endogenous angiogenesis inhibitor, the matricellular proteins thrombospondin-1 and SPARC, and to several collagens (I, IV, and VI). Other interacting partners of endostatin are transglutaminase-2, the amyloid peptide Aβ-(1–42), chondroitin, and dermatan sulfate.

**EXPERIMENTAL PROCEDURES**

Source of Proteins and Glycosaminoglycans—Recombinant human endostatin, the trimeric C-terminal domain of collagen XVIII called NC1 and several mutants were produced by
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human embryonic kidney cells expressing Epstein-Barr virus nuclear antigen (293-EBNA cells) according to established protocols (8, 9, 11). Amino acid residues were numbered starting from the first amino acid residue of endostatin (His1, also referred to as His132 when numbering starts from the first amino acid of the entire C-terminal domain NC1 of collagen XVIII). Laminin (L2020) isolated from basement membrane of Engelbreth-Holm-Swarm mouse sarcoma, human collagen I (C5483), human amyloid β protein fragment 1–42 (A9810), chondroitin sulfate from bovine trachea (C8529), heparin (H3393), and dermatan sulfate (C3788) from porcine intestinal mucosa, murine SPARC (S5174), guinea pig transglutaminase (T5398), bovine biglycan (B8041), and human fibronectin (F2006) were purchased from Sigma. Sodium hyaluronate was from Acros Organics (Geel, Belgium). Heparan sulfate from porcine intestinal mucosa was from Celsus (OH). Full-length human α5β1, αvβ3, and αvβ5 integrins were from Chemicon (Millipore, France), and recombinant human thrombospondin-1 was from R&D Systems (Minneapolis, MN). Pepsinized collagens IV and VI from human placenta were a generous gift from Dr. Florence Ruggiero (UMR 5086, CNRS, University Lyon 1, France). Bovine collagen XI was a generous gift from Dr. Marie-Claire Ronzière (UMR 5086, CNRS, University Lyon 1, France).

SPR Arrays—SPR arrays were handled in a Biacore Flexchip system (GE Healthcare), a commercially available high-density array platform that is capable of analyzing one analyte against 400 target spots at a time. Proteins or glycosaminoglycans were printed directly in triplicate at two different concentrations onto the gold surface of a Gold Affinity chip (GE Healthcare) using a non-contact PiezoArray spotter (PerkinElmer Life Sciences). The spotted matrix (15 × 15) comprised 225 spots. Proteins were spotted at concentrations varying from 50 to 200 μg/ml and glycosaminoglycans at 0.5 and 1 mg/ml. Six drops of 330 pl each were delivered to the surface of the chip (total spotted volume, 2.2 nl; spot diameter, 250–300 μm; spotted amount, 100–400 pg/spot). The chips were then dried at room temperature and stored under vacuum at 4 °C until their insertion into the Biacore Flexchip. The regions of interest of the chip were defined when the chip was dry. Each region of interest had four associated reference spots that were used to correct bulk refractive index changes as well as nonspecific binding of the analyte to the chip. The chip was blocked with a buffer containing mammalian proteins (Superblock, Pierce) for 5 times for 5 min. The blocked chip was then equilibrated with phosphate-buffered saline, 0.05% Tween 20 at 500 μl/min for 90 min. The analyte was flowed over the chip surface at 25 °C at a concentration ranging from 50 nM to 5 μM for 25 min at the same flow rate. The dissociation was monitored during injection of phosphate-buffered saline, 0.05% Tween for 40 min. Injected proteins were diluted in phosphate-buffered saline, 0.05% Tween, except full-length integrins, which were diluted in 10 mM Hepes buffer, pH 7.4, containing 150 mM NaCl, 2 mM CaCl2, 2 mM MnCl2, and 50 mM octyl β-D-glucopyranoside. Data collected from reference spots (gold surface) and buffer spots were subtracted from those collected on spotted proteins or glycosaminoglycans to obtain specific binding curves.

RESULTS

We looked for additional partners of endostatin using SPR arrays. This approach was selected because the yeast two-hybrid assay, which is widely used for high throughput discovery of protein interactions, is not the method of choice for studying extracellular interactions. Extracellular proteins are not optimally expressed in the nucleus, they are sticky and this may lead to false positive results. Furthermore, two-hybrid assays are not adapted to identify protein-polysaccharide interactions, which are of major importance for cell-matrix interactions and for the organization of the extracellular matrix. Known interactions were analyzed to validate SPR arrays and the Biacore Flexchip as reliable tools for the investigation of interactions established by endostatin. We confirmed by this technique previously described interactions between heparin/heparan sulfate and several extracellular proteins including endostatin (8, 9, 26), collagens I and V (27, 28), fibronectin, and transglutaminase-2.

Protein-protein interactions between endostatin and laminin (29), endostatin and α5β1 integrin (10, 11), or between tissue transglutaminase and α5β1 integrin (30) were also confirmed, as were interactions between proteins and proteoglycans such as the collagen VI-biglycan interaction (31) (Table 1).

Identification by SPR Arrays of New Partners to Build the Interaction Network of Endostatin—New partners of endostatin, either as a monomer or as a trimer within the NC1 domain of collagen XVIII, were identified (Figs. 1 and 2). They include the amyloid peptide Aβ-(1–42), thrombospondin-1, SPARC, transglutaminase-2, chondroitin sulfate, dermatan sulfate, and collagens I, IV, and VI. Because collagen IV and VI preparations used in this study were solubilized by pepsin treatment, it is likely that endostatin bind to the triple-helical part of these...
### TABLE 1—continued

| Molecule injected in buffer flow (analyte) | Molecule spotted on the array (ligand) |
|------------------------------------------|---------------------------------------|
| Thrombospondin-1                         | Chondroitin sulfate                   |
| Thrombospondin-1                         | Dermatan sulfate                     |
| Thrombospondin-1                         | Heparin                               |
| Thrombospondin-1                         | Endostatin                            |
| Thrombospondin-1                         | NC1(XVIII)                            |
| Thrombospondin-1                         | Transglutaminase-2                   |
| Thrombospondin-1                         | Fibronectin                           |
| Thrombospondin-1                         | Biglycan                              |
| Thrombospondin-1                         | Amloid peptide β-(1–42)               |

**FIGURE 1.** SPR arrays. Injection of collagens I (50 nM), IV (250 nM), and VI (250 nM), thrombospondin-1 (70 nM), heparan sulfate proteoglycan-2 (155 nM), and amyloid peptide (5 μM) over immobilized endostatin spotted onto a Gold Affinity chip.

The interaction network of endostatin and its interaction partners is shown in the figure. The interactions include fibrinectin, collagen molecules, Endostatin did not bind to fibrinectin, collagen XI, or hyaluronan (Table 1).

Direct interactions were also found between transglutaminase-2 and the β-amyloid peptide or transglutaminase-2 and αβ3 integrin. Furthermore, collagen XI was identified as a new ligand of αβ3 integrin, and was shown to bind the amyloid peptide Aβ-(1–42) (Table 1).

**SPR assays were performed with mutants of the NC1 domain to determine the influence of well-characterized mutations on the binding of these new partners to the trimeric NC1 domain.** Mutations of two arginine residues Arg27 and Arg139 in the NC1 domain abolish the binding to heparin (32), whereas individuals homozygous for the D104N polymorphism might have a high risk of occurrence of sporadic breast cancer (33). Mutations of Arg27 and Arg139 decreased binding of the NC1 domain to collagen IV, collagen VI, and the amyloid peptide, suggesting that these two residues participate in these interactions. The D104N mutation, whether in monomeric endostatin or within the NC1 domain, did not significantly alter the ability to bind to heparin, collagens IV and VI, α5β1 integrin, and heparan sulfate proteoglycan 2.

**Analysis of Endostatin Network**—To determine the major structural and functional features of the endostatin interaction network, the network was analyzed using the annotations provided by UniProtKB and InterPro. Annotations were available for the 26 protein partners of endostatin. Endostatin partners lacking annotations (endorepellin, zinc, glycosaminoglycans, and multimolecular complexes) were excluded from the analysis because they are not annotated in UniProtKB.

UniProtKB keywords were found to be present four times on average in the protein partners of endostatin. Only keywords...
used more than four times in the network were thus taken into account for further analysis. We checked that the over-representation of a keyword within the network was not due to an over-representation in UniProtKB human entries. Protein partners of endostatin were frequently and significantly associated to the following keywords “basement membrane,” “extracellular matrix,” and “secreted” for the “cellular component category,” to “calcium” for the “ligand category,” to “cell adhesion” for the “biological process category,” and to “EGF-like domain” for the “domain” category (Table 2).

The procedure described above was applied to InterPro to analyze the domain structure of the protein partners of endostatin (Table 3). InterPro domains were found to be present two times on average in the endostatin network. Only keywords used more than twice in the network were taken into account for further analysis. The most represented domains in the endostatin network were the EGF domain and its variants (EGF calcium-binding, EGF-like, EGF-like calcium-binding, EGF-like region conserved site, EGF-like type 3, and EGF-type aspartate/asparagine hydroxylation conserved site). They were present in 12 proteins over 26 (46%). Although numerous extracellular matrix proteins comprise EGF or EGF-like modules, the number of these modules was increased by at least a factor of 2 in the endostatin network. The network was also enriched in the concanavalin A-like lectin/glucanase domain (found in laminin-1, thrombospondin-1, and perlecan), in collagen triple helix repeats, and in the von Willebrand factor A domain.

**DISCUSSION**

A number of new endostatin partners have been identified by SPR arrays. Of course we cannot rule out the existence of further partners of endostatin as discussed below, but the coverage of interactomes (interaction networks) remains difficult to assess, and is a general concern for existing data sets (34).
Endostatin is a component of basement membrane, and it interacts with collagen IV, a major component of basement membrane, and with collagen VI. Endostatin may link elastic fibers to collagen VI microfibrils in elastic tissues such as the aortic wall where endostatin is present (35). The binding of endostatin to collagen VI is in agreement with the fact that collagen VI is in contact with endothelial basement membranes. Collagen VI might anchor endothelial basement membranes not only by interacting with collagen IV (36), but also by interacting with endostatin.

Endostatin binds to several molecules participating in the control of angiogenesis. Besides integrins and heparan sulfate, it binds to an endogenous inhibitor of angiogenesis, endorepellin, a C-terminal domain of perlecan (37). Heparan sulfate proteoglycan-2 or perlecan, which plays a dual role in angiogenesis (38), also interacts with endostatin. Transglutaminase-2 is a new interacting partner of endostatin that is also involved in angiogenesis. The formation of a complex between this enzyme and VEGFR-2 has been proposed as a mechanism for modulation of endothelial cell response to VEGF (39). We have identified another endogenous inhibitor of angiogenesis, thrombospondin-1, as an interacting partner of endostatin. Thrombospondin-1 and endostatin share several properties. Both are found in platelets, bind to heparin, and are endogenous inhibitors of angiogenesis. Furthermore, the expression of thrombospondin-1 is up-regulated by endostatin (15), and thrombospondin-1 may act as a mediator of anti-angiogenic therapy (40). Endostatin also binds to SPARC, which blocks angiogenesis (41, 42) and is found as well as endostatin in platelets and basement membranes.

Interestingly, SPARC and thrombospondin-1 belong to the matricellular protein family. The term “matricellular” refers to a group of modular, extracellular proteins whose functions are achieved by binding to matrix proteins as well as to cell surface receptors, or to other molecules such as cytokines and proteases that interact, in turn, with the cell surface (43). Members of this protein class serve as biological mediators of cell function by interacting directly with cells or by modulating the activity of growth factors, proteases, and other extracellular matrix proteins (44). Endostatin might regulate cell adhesion not only via integrin signaling, but also in association with thrombospondin-1 and SPARC. Other matricellular proteins, such as members of the tenasin protein family and osteopontin, might also be able to interact with endostatin to control cell adhesion. The participation of the endostatin network to the control of cell adhesion is further supported by the fact that 46% of the protein partners of endostatin are annotated with a Gene Ontology term (45) referring to cell adhesion (data not shown).

| Keyword category (UniProtKB) | Keyword | Number of annotations in endostatin partners (26) | Number of annotations in human proteins (19,398) | Use in endostatin partners | Use in human proteins | Ratio between endostatin partners and human proteins |
|-----------------------------|---------|-----------------------------------------------|-------------------------------------------------|--------------------------|----------------------|-------------------------------------------------|
| Technical term              | Three-dimensional structure | 13 | 3,471 | 50.00 | 17.89 | 2.79 |
| Coding sequence diversity   | Alternative splicing | 10 | 7,307 | 38.86 | 37.67 | 1.02 |
| Cellular component           | Basement membrane | 6 | 35 | 23.08 | 0.18 | 127.90 |
|                              | Extracellular matrix | 13 | 221 | 50.00 | 1.14 | 43.89 |
|                              | Membrane | 7 | 6,427 | 26.92 | 33.13 | 0.81 |
|                              | Secreted | 20 | 1,722 | 76.92 | 8.88 | 8.67 |
| Ligand                      | Calcium | 14 | 800 | 53.85 | 4.12 | 13.06 |
| Biological process           | Cell adhesion | 9 | 425 | 34.62 | 2.19 | 15.80 |
| Disease                     | Disease mutation | 12 | 1,526 | 46.15 | 7.87 | 5.87 |
| Domain                      | EGF-like domain | 9 | 233 | 34.62 | 1.20 | 28.82 |
| Post-translation modification| Glycoprotein | 24 | 4,425 | 92.31 | 22.81 | 4.05 |
|                             | Phosphoprotein | 8 | 6,540 | 30.77 | 33.71 | 0.91 |

| Term                          | Number of occurrence in endostatin partners (26) | Number of occurrence in human proteins (16,774) | Use in endostatin partners | Use in human proteins | Ratio between endostatin partners and human proteins |
|-------------------------------|-------------------------------------------------|-----------------------------------------------|--------------------------|----------------------|-------------------------------------------------|
| Collagen triple helix repeat   | 3 | 82 | 11.54 | 0.49 | 23.60 |
| Concanavalin A-like lectin/glucanase, subgroup | 3 | 76 | 11.54 | 0.45 | 25.47 |
| EGF                           | 7 | 206 | 26.92 | 1.23 | 21.92 |
| EGF calcium binding           | 7 | 74 | 26.92 | 0.44 | 61.03 |
| EGF-like                      | 4 | 146 | 15.38 | 0.87 | 17.68 |
| EGF-like calcium binding      | 7 | 101 | 26.92 | 0.60 | 44.71 |
| EGF-like region, conserved site | 12 | 276 | 46.15 | 1.65 | 28.05 |
| EGF-Like, type 3              | 9 | 232 | 34.62 | 1.38 | 25.03 |
| EGF-type aspartate/asparagine hydroxylation conserved site | 7 | 99 | 26.92 | 0.59 | 45.62 |
| Immunoglobulin I-set          | 3 | 136 | 11.54 | 0.81 | 14.23 |
| Immunoglobulin subtype 2      | 3 | 211 | 11.54 | 1.26 | 9.17 |
| Immunoglobulin-like           | 3 | 709 | 11.54 | 4.23 | 2.73 |
| Immunoglobulin-like fold      | 4 | 706 | 15.38 | 4.21 | 3.66 |
| von Willebrand factor, type A | 3 | 90 | 11.54 | 0.54 | 21.51 |
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We demonstrated that endostatin binds to the amyloid Aβ peptide, which has been previously shown to be co-localized with endostatin in amyloid plaques of patients with Alzheimer disease (18). Several other partners of endostatin are involved in neurodegenerative diseases. They include transglutaminase-2, which catalyzes the cross-linking of the amyloid peptide β (46), fibulin-1 (47), laminin-1 (48), thrombospondin-1 (49), heparan sulfate and heparan sulfate proteoglycans (50), perlecán (51), α5β1 integrin (52), collagen IV (53), and collagen VI, an important component of the neuronal injury response (54). The binding of endostatin to the amyloid peptide could have a protective effect, as suggested for transthyretin (55), and for other extracellular cellular components such as collagens VI (54) and XXV (56). Depending on the trigger event (e.g. increase in VEGF expression), and on the availability of its members in a given tissue at a given time, the endostatin network might be involved either in the control of angiogenesis, and tumor growth, or in neurogenesis and neurodegenerative diseases.

At the molecular level, the major features of the endostatin interaction network are the presence of EGF modules (e.g. in fibulins, nidogens, laminin-1, perlecán, thrombospondin-1, and integrins), and the ability of several partners to bind calcium (e.g. transglutaminase-2). This finding is supported by the fact that 50% of the protein partners of endostatin are annotated with the Gene Ontology term “calcium ion binding” (data not shown). Other extracellular proteins containing EGF modules might be potential partners of endostatin. We are currently studying the structure of EGF domains found in endostatin to identify possible common features, which will be helpful to select EGF domains of multidomain proteins for further interaction studies.

The interaction network will be useful for mimicking gene silencing studies and suppression in silico of glycosaminoglycans, which will be of special interest for glycosaminoglycans, which can be “suppressed” in vivo only by silencing several genes involved in their biosynthesis. It will also be of interest for the set-up of combination therapies, in which drugs targeting different pathways are simultaneously administered. The multifaceted nature of the angiogenic process suggests that the combination of antiangiogenic drugs might be more effective than single-agent therapies (57).

We combined extracellular protein-protein and protein-glycosaminoglycan interactions involving endostatin without discriminating their spatio-temporal expression. The next step will be to switch from a static to a dynamic extracellular interaction network by (i) putting weight on the interactions using kinetic and affinity constants to define the hierarchy of interactions according to their rate of formation and their stability, (ii) determining mutually exclusive interactions from three-dimensional structures and/or docking experiments, and (iii) integrating expression data. The building of a dynamic extracellular interaction network will be of interest to understand how information/signaling is conveyed through the network and to predict the consequences of perturbations due to changes in the expression of pro- and anti-angiogenic factors. The integrated network will be used as a framework to build a mathematical model of endostatin mechanism of action in various physio-pathological processes such as basement membrane assembly, angiogenesis, neurogenesis, and neurodegenerative diseases.

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