The binding of certain growth factors and cytokines to components of the extracellular matrix can regulate their local availability and modulate their biological activities. We show that oncostatin M (OSM), a profibrogenic cytokine and modulator of cancer cell proliferation, specifically binds to collagen types I, III, IV, and VI, immobilized on polystyrene or nitrocellulose. Single collagen chains inhibit these interactions in a dose-dependent manner. Cross-inhibition experiments of collagen-derived peptides point to a limited set of OSM-binding collagenous consensus sequences. Furthermore, this interaction is found for OSM but not for other interleukin-6 type cytokines. OSM binding to collagens is saturable, with dissociation constants around 10^{-8} M and estimated molar ratios of 1–3 molecules of OSM bound to one molecule of triple helical collagen. Furthermore, collagen-bound OSM is biologically active and able to inhibit proliferation of A375 melanoma cells. We conclude that abundant interstitial collagens dictate the spatial pattern of bioavailable OSM. This interaction could be exploited for devising collagenous peptide-antagonists that modulate OSM bioactivity in tumor growth and fibrotic disorders like rheumatoid arthritis and hepatic fibrosis.

Binding of distinct growth factors and cytokines to components of the extracellular matrix (ECM) plays an important role in the modulation of local bioavailability and the activity of these factors, which reciprocally may influence matrix remodeling. To date, several such interactions with matrix components (glycosaminoglycans, glycoproteins, and collagens) have been described. Thus, binding to ECM has been shown for basic fibroblast growth factor (1), platelet-derived growth factor (2), platelet-derivated growth factor (PDGF) (2–4), hepatocyte growth factor (HGF) (5, 6), transforming growth factor β1 (7–11), tumor necrosis factor α (TNF-α), IL-2 (12), and IL-7 (13, 14).

Oncostatin M, a glycoprotein of 28 kDa, is a pleiotropic cytokine and member of the IL-6 type cytokine family. It displays significant similarities in primary and predicted secondary structures with leukemia-inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-11 (15, 16). Members of the IL-6 family share the ability to modulate differentiation of a variety of cell types, which carry gp130 as a common receptor subunit (17) as part of a complex family of hetero- and homodimeric receptors (18). OSM is primarily produced by activated T-cells and monocytes but is detected in other cells, such as endothelial cells and different tumor cell lines derived from meningioma, Kaposi sarcoma, keratoacanthoma, and breast carcinoma (16, 19–22). Depending on the cell type, OSM shows a variety of biological activities on cell growth and differentiation (23). Thus OSM can inhibit the growth of several tumor cell lines, e.g. murine M1 myeloid leukemic cells (24) but stimulates proliferation of fibroblasts (25), endothelial cells (26), and the intermediate cells derived from AIDS-associated Kaposi sarcoma (27). The proinflammatory potential of OSM was demonstrated after subcutaneous injection of OSM in mice, leading to classic morphological signs of inflammation at the site of injection, e.g. extravasation of leukocytes and by its ability to stimulate IL-6 production in endothelial cells in vitro (28, 29). On the other hand, intravenous coinjection of OSM and lipopolysaccharide into BALB/c mice was shown to inhibit lipopolysaccharide-induced production of TNF-α and to reduce lethality (30), pointing to the anti-inflammatory potential of OSM in other scenarios. OSM is a profibrogenic cytokine, as demonstrated by excessive extracellular matrix deposition in a transgenic mouse model of OSM-expressing pancreatic β-islet cells (31) and by enhanced collagen and TIMP-1 expression in hepatic stellate cells (32), fibroblasts, and osteoblasts after addition of OSM (33, 34). Furthermore, OSM was shown to play an important role in liver development and maturation (35, 36).

Here, we describe the specific interaction of OSM with mainly fibrillar collagens I and III, and collagens IV and VI, and their constituent chains, which are not shared by other IL-6 type cytokines, and the biological effect of collagen-bound OSM in cell culture.

EXPERIMENTAL PROCEDURES

Materials

Human recombinant OSM was purchased from IC Chemicals (model ICC-OM-1A, Bad Wildbach, Germany) and BIOMOL (model 51571, Hamburg, Germany), both showing equivalent activities. All other reagents were from Merck or Sigma Chemical Co., Germany, and of the highest purity available. Polystyrene microtiter plates (Immulon 2, Removawells) were from Dynatech (Hamburg, Germany).

Native type I, III, IV, and VI collagens were isolated from human
placenta or skin. Preparation of the pure native collagens and isolation of their respective collagen chains were performed as described before (12).

Methods

Coating of Microtiter Plates with Collagens, Single Collagen Chains, and Collagen Cyanogen Bromide Peptides—Coating of microtiter plates and calculation of coating efficiencies were performed as described (12). Briefly, native collagens and collagen chains were immobilized on polystyrene microtiter wells at concentrations of 2 μg/100 μl/well for binding studies, and at 200 ng/200 μl/well for inhibition experiments. Immobilization was done in 50 mM ammonium bicarbonate, pH 9.6, overnight at 4 °C, followed by three washes with phosphate-buffered saline (PBS), pH 7.4. Unspecific binding sites were blocked with PBS, containing 0.05% Tween 20 (polyoxyethylene sorbitan monolauroate), for 1 h at 4 °C. Coating efficiencies for 2 μg/well native collagens and collagen chains ranged between 21 and 48% (4, 6).

Radiolabeling and OSM Binding Assay—OSM was radiolabeled with the 125I-labeled Bolton-Hunter reagent (PerkinElmer Life Sciences, Boston, MA) according to the manufacturer’s recommendations. 125I-Labeled OSM was separated from free iodine by a Sepharose G-25 column (PD 10, Amersham Biosciences, Inc., Freiburg, Germany) in PBS, containing 0.05% Tween 20 (12). Incorporated radioactivity ranged from 20,000 to 30,000 cpm/μg of OSM. Precipitation with trichloroacetic acid (10% v/v) in the presence of 200 μg of BSA/200 μl, usually yielded 90–96% of protein-bound radioactivity. Purity of radiolabeled OSM was demonstrated by SDS-PAGE and autoradiography (not shown).

For binding studies 1–2 ng of [125I]OSM/100 μl of PBS/0.05% Tween 20 were added to the collagen-coated wells and incubated for 2 h at room temperature, and, finally, after three washes in binding buffer (PBS/0.05% Tween 20) radioactivity bound to the collagen-coated wells was measured in a γ-counter (Berthold, Bad Wildbach, Germany).

Precipitation Assays—Native collagen I was used for fluid-phase binding of radiolabeled OSM. Increasing concentrations (0, 1, 5, 10, and 20 μg/200 μl) of native, solubilized collagen I or BSA were incubated in PBS/0.05% Tween 20, pH 7.4, in 1.5-ml polypropylene tubes (Eppendorf, Hamburg, Germany) at 37 °C for 1.5 h which allowed collagen type I fibrils to form. After fibril formation 1 ng of [125I]OSM was added for an additional 2 h at room temperature. After centrifugation at 10,000 rpm (12,500 × g) for 15 min, the supernatant was removed and the radioactivity in the collagen/BSA/OSM precipitate was determined.

Saturation Binding Experiments—For saturation binding, increasing amounts of unlabeled OSM (0–300 ng) were added to 1 ng (approximately 50,000 cpm) of [125I]OSM in a final volume of 100 μl of binding buffer and incubated for 2 h at room temperature in microtiter wells, which were precoated with 200 ng/100 μl/well native triple-helical collagen or single collagen chains. To exclude different binding affinities of radiolabeled versus unlabeled OSM, binding experiments were also performed by using [125I]OSM up to a concentration of 50 ng per well. The resultant binding curves showed a superimposable pattern (data not shown).

Cross Competition Assay with IL-6 Type Cytokines—To perform inhibition studies with other cytokines binding to the IL-6 receptor subunit gp130, 1–2 ng of [125I]OSM and increasing concentrations (0, 10, 50, 100 ng) of the IL-6 type cytokine LIF (01-176, Upstate Biotechnologies Inc., Lake Placid, NY), IL-6 (01-175, Upstate Biotechnologies Inc.), IL-11 (51561, BIOMOL, Hamburg, Germany), and G-CSF (BDP 36, British Biotechnology, Abingdon, UK) were preincubated with OSM for 1 h, added to microtiter wells precoated with collagen type I, III and VI, followed by washing and counting of collagen-bound OSM as described above.

Dependence of OSM Binding on pH, Osmolarity, and Divalent Cations—To assess the influence of pH, osmolarity, or the presence of divalent cations, collagens were immobilized at 2 μg/100 μl/well and incubated with 1 ng/100 μl [125I]labeled OSM under the following conditions: pH was adjusted between 6.0 and 9.0 by addition of 2 M NaOH or 2 M HCl to PBS/0.05% Tween 20; osmolality was adjusted by using 10 mM Tris-HCl/0.05% Tween 20, pH 7.4, containing increasing amounts of NaCl (50–1,500 mM), resulting in osmolalities between 120 and 3020 mosm; the divalent cations calcium, magnesium, manganese, or EDTA were added from stock solutions to 50 mM Tris-HCl/0.05% Tween 20 to yield final concentrations of 0.24–15 mM, and osmolality was adjusted to 300 mosm with NaCl. Binding of [125I]OSM to precoated collagen types I and VI and the α(1)-chain of collagen type I was performed as described for inhibition experiments.

A375 Cell Proliferation Assay—To determine the biological activity of collagen-bound OSM, a modified OSM bioassay was used (37). Briefly, the human melanoma cell line A375 (ATCC CRL-1872) was cultured in 80-cm2 flasks containing Dulbecco’s modified Eagle’s medium, glutamine (2 mM), and mercaptoethanol (50 μM), supplemented with penicillin (100 units/liter), streptomycin (10 mg/liter), and 5% fetal calf serum (Biochrom, Berlin, Germany) under standardized conditions (37 °C, 8% CO2) in a humidified atmosphere. Collagen I was coated on microtiter wells (Removawells) at a concentration of 2 μg/100 μl/well overnight at 4 °C. Wells were blocked with BSA (1%) in PBS/0.05% Tween 20 for 1 h followed by extensive washing with PBS/Tween. OSM was added at increasing concentrations and incubated for 2 h at room temperature. After 2 h, unbound OSM was removed by washing with PBS/0.05% Tween 20, followed by three washes with PBS. 100 μl of trypsinized A375 cells in the logarithmic growth phase (100,000 cells/ml of medium) was then plated on the collagen-coated wells, which had been preincubated with different concentrations of OSM. In parallel, soluble OSM added to already plated A375 cells served as a positive control. Cells were cultured for 72 h, and the cell number was assessed by a colorimetric cytotoxicity assay (sulforhodamine B-staining) (38).

Statistical Analysis—Binding data are expressed as mean ± S.E. Dissociation constants and the number of binding sites obtained by saturation experiments were analyzed according to the method of Scatchard (12, 39).

RESULTS

OSM Binds to Native Collagens I, III, IV, and VI and Single Collagen Chains—Native triple-helical collagens I, III, IV, and VI or their heat-denatured or reduced and alkylated single chains immobilized on polystyrene microtiter wells bound between 20 and 40% of radiolabeled OSM (1–2 ng) (Fig. 1). Specific binding of radiolabeled OSM to blocked polystyrene wells was around 10%. Native and denatured collagens bound OSM with the order: type III > I > VI > IV. When bound [125I]OSM was eluted from collagen-coated wells by boiling, then reduced with SDS-gel sample buffer and analyzed by SDS-PAGE and autoradiography, only intact OSM was identified (data not shown). Precipitation experiments confirmed the results of the solid phase assays: Fibrils of native collagen I in

![Fig. 1. OSM binds to immobilized native (triple helical) collagens and to single collagen chains.](https://www.jbc.org/content/110/1/3243/F1.large.jpg)
Collagens Sequester Bioactive OSM

Collagens inhibit binding of OSM to immobilized collagens—Binding of OSM to immobilized collagen types I and III and to the monomeric constituent chains of collagen types I, III, and IV was inhibited dose dependently by single collagen chains. Collagen chains were able to block OSM binding to their respective but also to heterotypic immobilized collagens (Fig. 3), demonstrating the potential of collagen chains for cross-inhibition. Single chains of collagens I, III, and VI inhibited binding of OSM to the immobilized native triple helical collagens I and III by up to 30%, whereas these chains inhibited OSM binding to immobilized collagens by up to 80% (Fig. 3). Inhibition varied when different combinations of soluble collagen chains and collagenous substrates were used. Thus, 5 μg/100 μl α1(III) blocked binding of OSM to its immobilized homotypic chain, to immobilized α1(I) and collagen type IV chains by up to 80%, but only by 40% to the immobilized α2(I)-chain. Similar results were obtained when inhibitor and immobilized ligands were reversed. Thus, the α2-chain of collagen type I blocked OSM binding to α1(III) by 50%. When 20 μg/100 μl homotypic inhibitor were used, OSM binding was completely inhibited (Fig. 4).

Saturation Binding Studies and Estimated Affinities of the OSM-Collagen Interaction—When increasing amounts of unlabeled OSM were incubated with a constant amount of [125I]OSM, binding to immobilized collagens was saturable (Fig. 5, A and B, for collagens I and VI, respectively). Saturation was reached between 6 and 10 pmol of OSM/100 μl on 200 ng/well of immobilized collagen type I and between 2 and 4 pmol OSM/100 μl on 200 ng/well of immobilized collagen type VI. Taking into account the coating efficiencies of the respective immobilized collagens (6) and the amount of OSM needed for saturation, Scatchard analysis (12, 39) yielded binding sites of comparable affinity on the tested collagens, with dissociation constants (K_D) of approximately 10^{-8} M. Based on these data, 1 mol of immobilized collagen types I, III, and VI, and 1 mol of the single chains of collagen types I and VI were estimated to bind approximately three (for the native collagens), or 1–1.5 mol (for the α-chains of collagen type I of OSM, respectively) (not shown).

Cross Competition of OSM Binding with IL-6 Type Cytokines—In cross-inhibition experiments with IL-6 type cytokines only G-CSF and IL-6 showed a slight inhibitory effect on the binding of [125I]OSM to collagen types I, III, and VI, whereas unlabeled OSM was by far the best inhibitor (Fig. 6, data for collagens I and VI not shown). The modest inhibitory effect of G-CSF is remarkable, because previous experiments suggested some binding of G-CSF but not of LIF, IL-6, or IL-11 to collagens. This suggests a structural motif on OSM for ECM binding different from the gp130 receptor interactive site.

Role of pH, Osmolality, and Divalent Cations—Binding of OSM to collagen types I, III, IV, and VI and to the α1(I)-chain was not significantly influenced by lowering the pH to 6.0 or increasing it to 9.0, with deviations never exceeding 20% of the amount bound at pH 7.4. Similarly, calcium, magnesium, manganese, or EDTA up to a maximal concentration of 15 mM did not modify the interaction to a significant degree (results not shown). When incubations were performed with increasing concentrations of NaCl, yielding osmolalities between 120 and 3020 mosM, maximal binding of OSM to collagen types I and VI was observed at low osmolalities. Binding was reduced to 50% at approximately 200 mosM, reaching background levels at 2000 mosM, indicating a major contribution of ionic forces to the interaction between OSM and collagens (Fig. 7).

37S Cell Proliferation Assay—Collagen-bound OSM inhibited the growth of the A375 melanoma cell line as assessed by

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2 R. Somasundaram, M. Ruehl, B. Schaefer, M. Schmid, R. Ackermann, E. O. Riecken, M. Zeitz, and D. Schuppan, unpublished data.
Collagens Sequester Bioactive OSM

Fig. 5. Binding of OSM to immobilized collagens follows saturation kinetics. Increasing amounts of unlabeled OSM were added to a constant amount (1 ng) of labeled OSM, followed by incubation for 2 h with immobilized (A) collagen type I and (B) collagen type VI coated at 200 ng/100 μl/well. Bound [125I]OSM was determined as described for Fig. 1, after subtraction of the radioactivity bound to BSA-blocked wells (which ranged between 8 and 17%). The dissociation constants (K_D) of the OSM-collagen interactions were determined graphically by the method of Scatchard (insets), yielding K_D values of around 10^{-8} M. Shown are the results of one (out of three) representative experiments performed in triplicate. K_D values of around 10^{-8} M were also obtained for collagen type III and collagen chains VIα, α1(I), and α2(1) (data not shown).

Fig. 6. Cross competition of OSM binding by IL-6 type cytokines. 1–2 ng of [125I]OSM was preincubated with increasing concentrations (0–100 ng/100 μl) of the soluble IL-6 type cytokines OSM, LIF, G-CSF, IL-6, and IL-11 and then added to collagen type III immobilized at 200 ng/well, for another 2 h, followed by determination of bound radioactivity. Binding is expressed as the percentage of bound radioactivity in the presence of inhibitor relative to the bound radioactivity in the absence of inhibitor. Shown are the results of one out of four representative experiments performed in triplicate. Similar results were obtained with immobilized collagen types I and VI (results not shown).

Fig. 7. Dependence of the OSM-collagen interaction on osmolality. Collagen types I and VI and chain α1(I) were immobilized at 2 μg/well and incubated with 1 ng/100 ml [125I]-labeled OSM under the conditions described under “Methods.” Uncoated wells served as control. After 2-h incubation, bound radioactivity was determined. Shown are the results of one out of three experiments performed in triplicate.

We showed that the pleiotropic and multifunctional cytokine OSM is bound by collagen types I, III, IV, and VI in vitro. Our data from inhibition and cross-inhibition experiments point to common collagenous binding sites, which are saturable and display dissociation constants of 10^{-8–10^{-9}} M. This range is comparable to that found for other protein–protein interactions, e.g. that between plasminogen and fibronectin (40), and is similar to that described for the interaction of the growth factors/cytokines PDGF, HGF, and IL-2 with collagens (4, 6, 12). Furthermore, these affinities are in the range of the interaction of OSM with its low affinity receptor type II (41). This suggests that OSM, PDGF, HGF, and IL-2 (4, 6, 12) harbor identical or overlapping binding sites. Furthermore, these growth factors must contain consensus as well as unique collagen binding sites.

The binding of OSM to the chains of collagens I, III, and IV points to the common collagenous motif (Gly-Pro-Hyp), as binding partner. This is supported by the finding that other proteins of the extracellular matrix such as laminin and fibronectin did not bind OSM significantly and that the synthetic collagen peptide (Gly-Pro-Hyp)_{10} is an inhibitor of the OSM-collagen interaction (data not shown).

We could show that other members of the IL-6 type family, namely LIF, G-CSF, IL-6, and IL-11 did not bind to collagens nor interfered significantly with OSM binding to collagens (Fig. 6). It is notable that, out of the IL-6 type family, OSM is the only stimulator of connective tissue deposition, as shown in an OSM-transgenic mouse model of pancreatic fibrogenesis (31). Preferential binding to (interstitial) collagens, which are the most prominent matrix components in fibrosis, with a resultant reduction in bioactivity, may serve as a (negative) feedback regulation during fibroproliferation. Thus OSM has recently been implicated in the induction of TIMP-1 (32, 33, 42), TIMP-3 (43), and collagen type I in dermal fibroblasts (44). Similarly, OSM up-regulates TIMP-1 in activated hepatic stellate cells (HSC), the major matrix producing cells in human liver fibrosis, whereas low levels of OSM-mRNA are found in fibrotic human liver (32). OSM might act via synergistic mechanisms to enhance fibrosis: 1) inhibition of ECM degradation by increasing the expression of TIMP-1 and hence, inhibition of matrix metalloproteinases, and 2) stimulation of collagen production. OSM enhances collagen synthesis in HSC mainly by...
trypsinized A375 melanoma cells in the logarithmic growth phase by colorimetric assay after trichloroacetic acid fixation and staining with collagen activity.

tive collagenous peptides or their nonpeptidic analogues, are a aptamers are already in development (48, 49). In this regard, OSM antagonists such as blocking antibodies were successfully such as melanoma, glioma, or AIDS-related Kaposi sarcoma. Interaction an interesting target for local plastic potential, as demonstrated in several cell lines (15) but other. Because it was shown that oncostatin M has anti-neoplas-

tissue and the epithelial-mesenchymal equilibrium but may also result in enhanced fibrosis, once matrix remodeling is in the extracellular matrix will lead to reconstitution of fibrous namely PDGF BB and oncostatin M, as profibrogenic factors; serve to store and modulate various growth factors/cytokines, not only the most abundant matrix components but may also in vivo model (47), our finding that collagen-bound in the setting of fibrosis and wound healing, collagens are inhibited melanoma cell proliferation (Fig. 8), makes this interaction an interesting target for local in vivo anti-neoplastic strategies.

In summary, our study demonstrates a specific binding of OSM to interstitial collagens, which may be exploited to modulate the local availability and activity of this cytokine in wound repair and inflammation such as pancreatic and liver fibrosis, and in rheumatoid arthritis, or in neoplastic diseases such as melanoma, glioma, or AIDS-related Kaposi sarcoma. OSM antagonists such as blocking antibodies were successfully tested in murine arthritis models, and OSM-antagonistic RNA aptamers are already in development (48, 49). In this regard, antagonists for extracellular OSM binding sites, e.g. competitive collagenous peptides or their nonpeptidic analogues, are a further promising strategy for modification of OSM biological activity.

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Interstitial Collagens I, III, and VI Sequester and Modulate the Multifunctional Cytokine Oncostatin M

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