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Extracellular Matrix Molecules: Potential Targets in Pharmacotherapy

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***Abstract*——The extracellular matrix (ECM) consists of numerous macromolecules classified traditionally into collagens, elastin, and microfibrillar proteins, proteoglycans including hyaluronan, and noncollagenous glycoproteins. In addition to being necessary structural components, ECM molecules exhibit important functional roles in the control of key cellular events such as adhesion, migration, proliferation, differentiation, and survival. Any structural inherited or acquired defect and/or metabolic disturbance in the ECM may cause cellular and tissue alterations that can lead to the development or progression of disease. Consequently, ECM molecules are important targets for pharmacotherapy. Specific agents that prevent theexcess accumulation of ECM molecules in the vascular system, liver, kidney, skin, and lung; alternatively, agents that inhibit the degradation of the ECM in degenerative diseases such as osteoarthritis would be clinically beneficial. Unfortunately, until recently, the ECM in drug discovery has been largely ignored. However, several of today's drugs that act on various primary targets affect the ECM as a byproduct of the drugs' actions, and this activity may in part be beneficial to the drugs' disease-modifying properties. In the future, agents and compounds targeting directly the ECM will significantly advance the treatment of various human diseases, even those for which efficient therapies are not yet available.**

I. Introduction

The extracellular matrix (ECM[1]) is composed of collagens, elastin, proteoglycans (including hyaluronan), and noncollagenous glycoproteins and forms a complex, three-dimensional network among the cells of different tissues in an organ-specific manner. The ECM was initially considered an inert, space-filling material that provided only mechanical strength to tissues and organs. Today we understand that the ECM is a dynamic structure that interacts with cells and generates signals through feedback loops to control the behavior of cells. Thus, ECM macromolecules are bioactive and modulate cellular events such as adhesion, migration, proliferation, differentiation, and survival (Daley et al., 2008). It is important to realize that structurally very different ECM components possess these activities. It is also important to understand that the ECM molecules are strictly organized and that this organization determines the bioactivity of the ECM. Even minor alterations such

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as a single amino acid substitution in a single ECM component can lead not only to altered physicochemical properties of the tissues but also to changes in the cellular phenotype and in cell-matrix interactions. These changes in tissue function ultimately lead to development of a disease. There is presumably no disease without quantitative and/or qualitative changes in the ECM. However, it is necessary to distinguish between ECM changes that cause the disease and ECM changes that result from the disease because therapeutic strategies will differ depending on primary or secondary causation.

II. Extracellular Matrix Molecules, Their Functions and Related Diseases

In general, ECM components are classified as fiber-forming and non–fiber-forming (interfibrillar) molecules. Certain collagen species and elastin are typical fiber-forming ECM molecules, whereas the proteoglycans and glycoproteins are generally considered interfibrillary ECM molecules. Quite recently, the term "matricellular proteins" has been applied to a group of ECM molecules, including thrombospondin-1 and -2, SPARC (secreted protein, acidic and rich in cysteine), tenascin-C, and osteopontin, that do not function as structural elements but modulate cell-matrix interactions and cell functions such as in tissue repair (Bornstein and Sage, 2002; Kyriakides and Bornstein, 2003).

During the last 2 decades, the number of individually characterized ECM molecules has expanded markedly. Today, nearly 30 different collagen types involving more than 40 distinct polypeptide chains (α chains) are known in humans, and more than 20 other proteins contain collagen-like domains (Myllyharju and Kivirikko, 2004; Ricard-Blum and Ruggiero, 2005). There are also more than 30 different proteoglycans, most of which reside in the ECM (Järveläinen and Wight, 2002; Schaefer and Iozzo, 2008). The molecular multiplicity is true for matrix glycoproteins as well. For example, in mammals at least 15 different laminins have been detected (Sasaki et al., 2004; Miner, 2008) and, in the case of fibronectin, alternative splicing of the V-region has been shown to generate up to 20 fibronectin isoforms in humans (White et al., 2008). The individual ECM molecules, their isoforms, and even some of their proteolytic fragments, such as endostatin, a 20 kDa C-terminal cleavage product of collagen type XVIII (O'Reilly et al., 1997) and related polypeptides from other basement membrane associated collagens, mediate specific functional effects to control and regulate cell behaviors including those required for angiogenesis (Ingber and Folkman, 1989). It can be expected that all ECM molecules have some role in the normal functions in cell biology. The ECM molecules must act in concert in a finely regulated manner to maintain proper cellular function within tissues and organs (Lukashev and Werb, 1998). In this respect, it is interesting to note that the synthesis of ECM molecules is controlled by specific growth factors, among which the transforming growth factor-βs (TGF-βs) are the most prominent (Border and Noble, 1994; Verrecchia and Mauviel, 2007). Furthermore, the life of the ECM molecules is determined by proteases, especially matrix metalloproteases (MMPs) (Visse and Nagase, 2003). Thus, growth factor signaling and control of ECM turnover by proteases are potential targets for new pharmacotherapies.

A long list of human diseases exhibit disturbances in the ECM. Changes in the ECM are especially distinct in the monogenic disorders of the connective tissue, such as osteogenesis imperfecta (Glorieux, 2008), Ehlers-Danlos syndrome (Mao and Bristow, 2001; Parapia and Jackson, 2008), Marfan's syndrome (Dietz et al., 1994; Keane and Pyeritz, 2008), and other genetic disorders of the ECM. Changes in the ECM are also prominent in a large variety of more common, acquired human diseases or in combination with polygenic inheritance, such as coronary heart disease, which is the number one cause of death in the Western world (Katsuda et al., 1992; Nakashima et al., 2008; Wight, 2008). Here, components of the ECM bind and trap lipoproteins, causing lipid build-up and atherosclerotic plaque formation (Williams and Tabas, 1995). Maintaining the integrity of the ECM in the vessel wall seems critical to either preventing or treating cardiovascular disease (Wight and Merrilees, 2004). Another common cardiovascular disease, hypertension, is characterized by stiffer blood vessels, and heart failure by altered cardiac muscle microenvironments that do not support cardiomyocyte survival (Tayebjee et al., 2003; Fedak et al., 2005; Berk et al., 2007). Pulmonary diseases such as asthma and chronic obstructive pulmonary disease are characterized by ECM changes that lead to loss of tissue elasticity and compliance and eventually to fibrosis (Postma and Timens, 2006; Merrilees et al., 2008). Furthermore, hepatic diseases, in particular liver cirrhosis, involve progressive accumulation of scarring proteins (fibrosis) in response to subtle or overt inflammatory reactions (Wallace et al., 2008). Inflammatory bowel diseases (IBDs) ulcerative colitis, and Crohn's disease also exhibit marked organ-specific changes in the composition and

[1] Abbreviations: 5HT, 5-hydroxytryptamine; AA-4500, clostridial collagenase; ACE, angiotensin-converting enzyme; ADAMTS, disintegrin and metalloproteinase with thrombospondin motifs; CTGF, connective tissue growth factor; ECM, extracellular matrix; FG-3019, a human CTGF-specific monoclonal antibody; MMP, matrix metalloprotease; PI-88, phosphomannopentose sulfate; SB431542, 4-(5-benzo(1,3)dioxol-5-yl-4-pyridin-2-yl-1*H*-imidazol-2-yl)benzamide; SD-208, 2-(5-chloro-2-fluorophenyl)-4-[(4-pyridyl)amino]pteridine; SM305, an activin-like receptor kinase inhibitor 5 (ALK5); SPARC, secreted protein, acidic and rich in cysteine; TFO, triplex-forming oligonucleotide; TGF, transforming growth factor; TIMP, tissue inhibitors of MMP; TNF, tumor necrosis factor.

TABLE 1
Main ECM molecules, some of their functional roles, and selected genetic and other diseases related to individual molecules

Group	Distribution/Function	Genetic Disease(s)	Other disease(s)
Collagens			
Fibrillar collagens			
I	Structural component of all tissues except cartilage; e.g. bone, dermis (Gelse et al., 2003), vessel wall (Katsuda et al., 1992; Rauterberg et al., 1993), and heart (Marijianowski et al., 1994)	Osteogenesis imperfecta (Bonadio and Byers, 1985); classic type Ehlers-Danlos syndrome (Nuytinck et al., 2000)	Atherosclerosis (Katsuda et al., 1992; Rauterberg et al., 1993); hypertensive heart disease (López et al., 2001; Díez et al., 2005); fibrotic diseases including chronic kidney diseases (Alexakis et al., 2006)
II	Predominant component of cartilage (Bruckner and van der Rest, 1994); mediates interactions with proteoglycans (Mayne, 1989)	Stickler syndrome type I (Maumenee, 1979; Ahmad et al., 1991); spondyloepiphyseal dysplasia (Tiller et al., 1995); achondrogenesis (Eyre et al., 1986); Kniest dysplasia (Winterpacht et al., 1993)	Osteoarthritis (Nelson et al., 1998)
III	Dominant collagen type of granulation tissue, and also, e.g., muscles and artery wall (Katsuda et al., 1992; Linehan et al., 2001); produced by young fibroblasts before type I collagen (Voermans et al., 2008)	Vascular Ehlers-Danlos syndrome (Pope et al., 1975; Pepin et al., 2000)	Atherosclerosis (Katsuda et al., 1992); hypertensive heart disease (Díez et al., 2005); fibrotic diseases, e.g. chronic kidney diseases (Alexakis et al., 2006)
V	Structural component of basement membrane (Graham et al., 2008); interacts with type I collagen (Birk, 2001); inhibits endothelial cell adhesion, proliferation (Fukuda et al., 1988), and adhesion (Hashimoto et al., 1991)	Classic type Ehlers-Danlos syndrome (Nicholls et al., 1996; Richards et al., 1998)	Atherosclerosis (Katsuda et al., 1992); collagenofibrotic glomerulopathy (Morita et al., 2003); bronchiolitis obliterans syndrome (Burlingham et al., 2007)
XI	Structural component of articular cartilage (Mayne, 1989) and ear (Nerlich, 1995); modulates cartilage matrix homeostasis (Eyre, 2004)	Stickler syndrome type II (Richards et al., 1996) and type III (Brunner et al., 1994); Marshall syndrome (Majava et al., 2007b); otospondylomegaepiphyseal dysplasia (Melkoniemi et al., 2000)	Disc herniation (Mio et al., 2007)
Nonfibrillar collagens			
IV	Structural component of basement membrane (LeBleu et al., 2007); e.g., in kidney (Smith et al., 1989); associated with angiogenesis (Xu et al., 2001)	Alport syndrome (Barker et al., 1990); hereditary angiopathy (Breedveld et al., 2006)	Diabetic nephropathy (Cohen et al., 2001); organ or tumor fibrosis (Kalluri, 2003); cancer progression (Tanjore and Kalluri, 2006)
VIII	Structural component of extracellular matrices, e.g. in sclera (Shuttleworth, 1997) and vasculature (Plenz et al., 2003); involved in stabilization of membranes, angiogenesis and interacts with ECM molecules (Sutmuller et al., 1997; Plenz et al., 2003)	Corneal endothelial dystrophy, e.g., Fuchs' endothelial dystrophy (Biswas et al., 2001)	Atherosclerosis (Plenz et al., 2003); tumor progression (Koon et al., 2004)
X	Structural component of hypertrophic cartilage (Gelse et al., 2003); regulates matrix mineralization and compartmentalization of ECM components (Shen, 2005)	Schmid-type metaphyseal chondroplasia (Warman et al., 1993)	Osteochondritis dissecans (Aurich et al., 2006)
Association collagens			
VI	Dominant structural component of connective tissue; e.g., in vessels, liver (von der Mark et al., 1984), and muscle (Engvall et al., 1986)	Muscle disorders, e.g., myosclerosis myopathy (Merlini et al., 2008b)	Atherosclerosis (Katsuda et al., 1992)
VII	Structural component of basement membrane (Sakai et al., 1986); interacts with other ECM components (Keene et al., 1987)	Dystrophic epidermolysis bullosa (Hovnanian et al., 1992)	Epidermolysis bullosa acquisita (Chen et al., 2007)

TABLE 1—*Continued.*

Group	Distribution/Function	Genetic Disease(s)	Other disease(s)
IX	Structural component of cartilage (Olsen, 1997); interacts with collagen type II (Eyre, 2004)	Stickler syndrome (Van Camp et al., 2006); multiple epiphyseal dysplasia (Bönnemann et al., 2000); Scheuermann disease (Karppinen et al., 2003)	
XII	Structural component of connective tissue, e.g., in skin (Wälchli et al., 1994); interacts with other matrix components (Voermans et al., 2008)		Diabetic retinopathy (Ljubimov et al., 1996); keratoconus (Cheng et al., 2001)
XIV	Structural component of connective tissue, e.g., in blood vessels (Castagnola et al., 1992); interacts with other ECM components (Ehnis et al., 1997)		Diabetic retinopathy (Ljubimov et al., 1996)
XIX	Structural component of basement membrane (Myers et al., 1997); associated with muscle cells (Myers et al., 1999)		Rhabdomyosarcomas (Myers et al., 1999); breast cancer (Amenta et al., 2003)
Transmembrane collagens			
XIII	Structural component of, e.g., skin (Peltonen et al., 1999); interacts with other ECM components, e.g., proteoglycans (Michelacci, 2003)		Tumor development (Väisänen et al., 2005); thyroid-associated ophthalmopathy (Yamada et al., 2000)
XVII	Structural component of cutaneous basement membrane (Uitto and Pulkkinen, 1996); involved in cell-matrix adhesion (Van den Bergh and Giudice, 2003)	Non-Herlitz junctional epidermolysis bullosa (Bauer and Lanschuetzer, 2003)	
Multiplexins			
XV	Structural component of basement membrane (Myers et al., 1996); acts as structural organizer of ECM (Amenta et al., 2005)		Tumorigenesis (Amenta et al., 2003, Fukushige et al., 2005)
XVIII	Structural component of basement membrane (Saarela et al., 1998); inhibition angiogenesis and tumor growth (Myllyharju and Kivirikko, 2001)	Knobloch syndrome (Suzuki et al., 2002)	Fibrotic diseases, e.g., liver fibrosis (Musso et al., 1998)
Elastin and microfibrillar proteins			
Elastin	Structural component of elastic fibers (Rosenbloom et al., 1993); provides elasticity to different tissues, e.g., lungs, large blood vessels, and dermis (Ross, 1973)	Supravalvular aortic stenosis (Ewart et al., 1993); cutis laxa (Tassabehji et al., 1998); Williams-Beuren syndrome (Milewicz et al., 2000)	Hypertension (Martyn and Greenwald, 1997); pulmonary emphysema (Snider et al., 1991); arterial aneurysms (Alberto et al., 2008)
Fibrillin 1	Major structural component of microfibrils together with fibrillin-2 (Ramirez and Pereira, 1999); involved in tissue homeostasis (Zhang et al., 1995)	Marfan's syndrome (Robinson and Booms, 2001); Shprintzen-Goldberg syndrome (Sood et al., 1996); Weill-Marchesani syndrome (Faivre et al., 2003)	Atherosclerosis (Seyama and Wachi, 2004); pulmonary emphysema (Robbesom et al., 2008)
Fibrillin 2	Major structural component of microfibrils together with fibrillin-1 (Ramirez and Pereira, 1999)	Congenital contractural arachnodactyly (Beals and Hecht, 1971)	
Fibulin 1	Structural component of basement membranes (Pan et al., 1993a); interacts with other ECM molecules, e.g., laminins (Timpl and Brown, 1994); modulates platelet adhesion (Godyna et al., 1996)	Synpolydactyly (Debeer et al., 2002); autosomal recessively inherited vitreoretinal dystrophy (Weigell-Weber et al., 2003)	Prostate cancer (Wlazlinski et al., 2007); gastric cancer (Cheng et al., 2008)

TABLE 1—*Continued.*

Group	Distribution/Function	Genetic Disease(s)	Other disease(s)
Fibulin 2	Structural component of basement membranes (Pan et al., 1993b); involved in vasculogenesis and angiogenesis (Tsuda et al., 2001)		Breast cancer progression (Yi et al., 2007)
Fibulin 3	Structural component of blood vessels (Giltay et al., 1999)	Macular degenerative disease (Klenotic et al., 2004)	
Fibulin 4	Structural component of blood vessels (Giltay et al., 1999)	Cutis laxa (Hucthagowder et al., 2006)	Colon tumorigenesis (Gallagher et al., 2001); prostate cancer (Wlazlinski et al., 2007)
Fibulin 5	Organizer of elastic fibers (Yanagisawa et al., 2002); regulator of angiogenesis (Kowal et al., 1999); associated with suppression of tumorigenesis (Albig and Schiemann, 2005)	Cutis laxa (Loeys et al., 2002); age-related macular degeneration (Stone et al., 2004)	Prostate cancer (Wlazlinski et al., 2007)
Fibulin 6	Organizer in cell-cell and cell-matrix interactions (Vogel and Hedgecock, 2001)	Macular degeneration (Schultz et al., 2003)	
Fibulin 7	Cell adhesion molecule, associated with, e.g., dentin formation (de Vega et al., 2007)		
Emilin 1	Microfibril-associated protein (Mongiat et al., 2000); involved in vascular cell morphology and elastogenesis (Zanetti et al., 2004)		Hypertension (Raman and Cobb, 2006)
Proteoglycans and glycosaminoglycans			
Hyaluronan	Major structural carbohydrate component of the ECM (Chen and Abatangelo, 1999); involved in angiogenesis, cell motility, wound healing and cell adhesion (Stuhlmeier, 2006)		Tumorigenesis (Auvinen et al., 2000; Hiltunen et al., 2002; Toole, 2002; Heldin et al., 2008); atherosclerosis and restenosis (Wight, 2008); inflammatory bowel disease (de La Motte et al., 1999; de la Motte et al., 2003)
Hyalectans			
Aggrecan	Structural component of articular cartilage (Dudhia, 2005); interacts with hyaluronan (Kiani et al., 2002)	Intervertebral disc degeneration (Solovieva et al., 2007); spondyloepiphyseal dysplasia (Gleghorn et al., 2005)	Osteoarthritis (Fosang and Little, 2008)
Brevican	Abundant proteoglycan in adult brain (Yamaguchi, 1996)		Tumor progression (Hu et al., 2008)
Neurocan	Structural component of the ECM of brain (Grumet et al., 1996); interacts with other ECM molecules and cell surface receptors (Rauch et al., 2001)		
Versican	Structural component of the ECM, e.g., in blood vessels (Kenagy et al., 2006); mediates cell adhesion and migration (Ang et al., 1999)	Erosive vitreoretinopathy and Wagner disease (Mukhopadhyay et al., 2006)	Atherosclerosis and restenosis (Wight and Merrilees, 2004); tumorigenesis (Nara et al., 1997; Suwiwat et al., 2004) and metastasis (Kim et al., 2009)
Small leucine-rich proteoglycans (SLRPs)			
Asporin	Structural component of articular cartilage (Lorenzo et al., 2001)	Osteoarthritis (Kizawa et al., 2005)	Bone and joint diseases (Ikegawa, 2008)
Biglycan	Structural component of, e.g., vascular wall (Williams, 2001); binds growth factors such as TGF-β and regulates its activity (Hildebrand et al., 1994)		Abdominal aortic aneurysms (Tamarina et al., 1998)

TABLE 1—*Continued.*

Group	Distribution/Function	Genetic Disease(s)	Other disease(s)
Decorin	Structural component of, e.g., skin (Reed and Iozzo, 2002) and vascular wall (Williams, 2001); regulates collagen fibrillogenesis (Zhang et al., 2006); binds growth factors such as TGF-β and neutralizes its activity (Yamaguchi et al., 1990); involved in angiogenesis (Järveläinen et al., 1992 and 2006)	Congenital stromal dystrophy (Bredrup et al., 2005)	Tumorigenesis (Grant et al., 2002; Goldoni et al., 2008; Salomäki et al., 2008); osteoarthritis (Melrose et al., 2008); renal disease (Schaefer et al., 1998 and 2001)
Fibromodulin	Binds to specific collagen types (Hedbom and Heinegård, 1989) and regulates their fibril formation (Svensson et al., 1999); binds growth factors such as TGF-β and regulates its activity (Hildebrand et al., 1994)	Myopia (Majava et al., 2007a)	Osteoarthritis (Melrose et al., 2008)
Keratocan	Structural component of e.g. cornea (Kao and Liu, 2002)	Cornea plana (Pellegata et al., 2000)	Osteoarthritis (Melrose et al., 2008)
Lumican	Structural component of e.g. cornea (Kao and Liu, 2002)	Myopia (Wang et al., 2006; Majava et al., 2007a)	Fibrosis and tumor growth (Naito, 2005); atherosclerosis (Onda et al., 2002)
Osteoadherin	Promotes αv/β3-integrin mediated cell binding (Wendel et al., 1998); regulation of complement activation (Sjöberg et al., 2009)		
PRELP	Anchors basement membranes to the underlying connective tissue (Bengtsson et al., 2002)	Myopia (Majava et al., 2007a)	
Epiphycan	Involved in chondrogenesis (Knudson and Knudson, 2001)		
Opticin	Component of the vitreous humour of the eye (Reardon et al., 2000) and cartilage (Monfort et al., 2008)	Myopia (Majava et al., 2007a); primary open angle glaucoma (Acharya et al., 2007)	
Osteoglycin/Mimecan	Component of the vascular wall (Shanahan et al., 1997); regulation of collagen fibrillogenesis (Tasheva et al., 2002)		
Chondroadherin	Component of the cornea, brain, and skeletal muscle, retina and lens (Tasheva et al., 2004); regulates chondrocyte growth and proliferation (Shen et al., 1998)		
Nyctalopin	Essential for retinal synaptic transmission (Bahadori et al., 2006)	Congenital stationary night blindness (Bech-Hansen et al., 2000; Pusch et al., 2000)	
Tsukushi	Bone morphogenic protein antagonist (Ohta et al., 2004)		
Podocan	Component of glomeruli (Ross et al., 2003)		Glomerulosclerosis (Ross et al., 2003)
Podocan like protein 1	Facilitates nephrin signaling (Huber et al., 2001)		
Basement membrane proteoglycans			
Agrin	Modulator of synaptogenesis (Bezakova and Ruegg, 2003; Williams et al., 2008)		Cirrhosis and hepatocellular carcinoma (Tátrai et al., 2006); Alzheimer's disease (Berzin et al., 2000)
Bamacan	Structural component of basement membrane (Couchman et al., 1996)		Diabetic retinopathy (Ljubimov et al., 1996)

TABLE 1—*Continued.*

Group	Distribution/Function	Genetic Disease(s)	Other disease(s)
Perlecan	Structural component of basement membrane (Iozzo, 1994); regulates, e.g., cell migration and proliferation (Whitelock et al., 2008); involved in angiogenesis (Bix and Iozzo, 2008)	Dyssegmental dysplasia (Silverman-Handmaker type) (Arikawa-Hirasawa et al., 2001); Schwartz-Jampel syndrome (Arikawa-Hirasawa et al., 2002)	Diabetic retinopathy (Ljubimov et al., 1996); tumor growth (Mathiak et al., 1997); Alzheimer's disease (Castillo et al., 1997)
Other extracellular proteoglycans			
PG-100	Proteoglycan form of colony-stimulating factor-1 (Partenheimer et al., 1995)		Hepatitis and liver fibrosis (Högemann et al., 1997)
Testican-1, -2, and -3	Inhibition of different proteases (Nakada et al., 2003; Edgell et al., 2004)		Testican-3: T-cell leukemia (Kamioka et al., 2009)
Noncollagenous ECM glycoproteins			
Fibronectins (>20 different isoforms)	Involved in cellular adhesion (Akiyama et al., 1981), fibril (Kadler et al., 2008) and ECM assembly (Couchman et al., 1990), tissue injury and inflammation (Satoi et al., 1999; Okamura et al., 2001); regulation of vascular morphogenesis including angiogenesis (Astrof and Hynes, 2009)	Glomerulopathy (Castelletti et al., 2008)	Idiopathic pulmonary fibrosis (Kuhn and McDonald, 1991); cancer (Korc, 2007; Astrof and Hynes, 2009); tendinopathy (Riley, 2007)
Laminins	Involved in cell adhesion, migration and differentiation (Colognato and Yurchenco, 2000; Patarroyo et al., 2002)	Congenital muscular dystrophy (Hall et al., 2007); epidermolysis bullosa (Uitto et al., 1994); Pierson syndrome (Zenker et al., 2004)	Tumor progression (Ziober et al., 1996; Ono et al., 1999, Rabinovitz et al., 2001; Nelson et al., 2008)
SPARC (secreted protein, acidic and rich in cysteine)	Inhibition of cell proliferation (Yan and Sage, 1999) and angiogenesis (Chlenski et al., 2006)		Tumor progression and metastasis (Porter et al., 1995; Watkins et al., 2005; Clark and Sage, 2008; Podhajcer et al., 2008); idiopathic osteoporosis (Delany et al., 2008)
Tenascins (tenascin-C, -R, -X, and -W)	Involved in cell adhesion, migration and growth (Chiquet-Ehrismann and Chiquet, 2003), wound healing, and neovascularization (Hsia and Schwarzbauer, 2005; Trebaul et al., 2007)	Ehlers-Danlos syndrome (Burch et al., 1997; Mao and Bristow, 2001)	Fibrotic diseases, inflammation, tumorigenesis (Chiquet-Ehrismann and Chiquet, 2003)
Thrombospondins (1–5)	Involved in cell migration (Yabkowitz et al., 1993), platelet aggregation, inflammatory response, and wound healing (Adams and Lawler, 2004)	Thrombospondin-5; pseudoachondroplasia and multiple epiphyseal dysplasia (Posey et al., 2008)	Tumor progression (Lawler and Detmar, 2004; Kazerounian et al., 2008); atherosclerosis (Roth et al., 1998; Takahashi et al., 2008)
Nidogen/entactin (nidogen 1 and nidogen 2)	Involved in cell adhesion (Yi et al., 1998; Grimpe et al., 1999), wound healing (Sephel et al., 1996) and basement membrane stabilization (Ho et al., 2008)		Osteoarthritis (Kruegel et al., 2008); cancer and tumor progression (Oivula et al., 1999; Ulazzi et al., 2007; Douglas et al., 2008)

organization of the ECM. An interesting link between the ECM and IBDs and inflammation is highlighted by a series of studies that show that hyaluronan accumulates in IBDs and promotes the adhesion and activation of inflammatory cells such as monocytes (de La Motte et al., 1999, 2003). Chronic kidney diseases, including glomerulosclerosis and tubulointerstitial fibrosis, mainly manifest as abnormal build-up of ECM components leading to loss of function (Liu, 2006). Rheumatoid arthritis and osteoarthritis are manifested by breakdown of the joint ECM components (Roach et al., 2007; Melrose et al., 2008). In neurodegenerative diseases such as Alzheimer's disease, heparan sulfate proteoglycans, especially perlecan, are involved in the formation and stabilization of amyloid fibrils (Castillo et al., 1997). Furthermore, in malignancies, alterations of ECM composition have occasionally been claimed to be the main promoter of carcinogenesis (Marastoni et al., 2008). For example, hyaluronan and versican are increased in a number of human tumors and are believed to contribute to a permissive microenvironment for the growth and metastasis of the tumor cells (Toole, 2002; Theocharis, 2008; Ricciardelli et al., 2009). In a recent study, versican was identified as a factor promoting metastasis in a Lewis lung carcinoma model (Kim et al., 2009). In addition, there is a striking difference in the expression of a small proteoglycan decorin between human malignant and benign vascular tumors. Within Kaposi's sarcoma and angiosarcoma, the expression of decorin lacks completely, whereas within hemangiomas, decorin is expressed in abundant amounts (Salomäki et al., 2008). Such results suggest that decorin is likely to possess a suppressive effect on human tumor angiogenesis. Similar results have been obtained using experimental models (Grant et al., 2002). In addition to its role in disease, the ECM can variously function as a mediator for innate and acquired drug resistance (Vincent and Mechti, 2005; Bonacci et al., 2006). Also the side-effects of drugs and diagnostic agents are often due to alterations in the ECM. For example, a recently discovered side effect of the use of gadolinium-based contrast agents leads to scleroderma-like fibrotic lesions in the kidneys (Grobner, 2006).

A summary of the main ECM molecules, some of their known functions, and examples of genetic and other diseases related to them are presented in Table 1. Although the table is not comprehensive, it illustrates the vast molecular multiplicity and functional complexity of the ECM as well as the diversity of diseases related to ECM molecules.

In the next parts of this review, we discuss the effects of current drugs on the ECM and thereafter focus on the potential future ECM-targeted pharmacotherapies and the challenges that ECM-targeted agents place to drug discovery and development processes.

III. Do Currently Used Drugs Target the Extracellular Matrix?

To date, only limited progress has been taken place in the specific targeting of ECM components. Perhaps the best known examples are the drugs that target the major cellular receptors for ECM components, the integrins. These drugs include abciximab (used to treat acute coronary syndrome), efalizumab (used to treat psoriasis), and natalizumab (used to treat multiple sclerosis and Crohn's disease) (Rosove, 2004; Baker, 2007; Schön, 2008). Except for the above protein drugs, practically no others are primarily targeted at the ECM. Nevertheless, several of today's drugs have been shown to influence ECM metabolism and subsequently modulate the composition and organization of the ECM. Table 2 lists examples of currently available drugs affecting the ECM beyond their primary targets. The effects of these drugs on the ECM are often, albeit not always, beneficial in the treatment of various human diseases.

A. Current Anti-Inflammatory and Immunomodulatory Drugs with Beneficial Disease-Modifying Properties on the Extracellular Matrix

Evidence is available indicating that many of the current drugs exert their beneficial disease-modifying properties, at least in part, via their pleiotropic effects on the ECM. This is true for glucocorticoids and certain other anti-inflammatory and immunomodulatory drugs, such as infliximab, a chimeric monoclonal antibody that blocks the action of tumor necrosis factor-α (TNF-α). Such drugs have been shown to effectively modulate the ECM when used in the treatment of specific fibrotic diseases exhibiting overt inflammation, such as Riedel's thyroiditis and Crohn's disease (Moulik et al., 2004; Sorrentino et al., 2007). The effect of glucocorticoids on the ECM dates back almost 20 years, when it was shown that the inhibitory effect of these drugs was not related to their anti-inflammatory activity (Cutroneo et al., 1990). Glucocorticoids are now known to decrease the synthesis of type I collagen and prevent scarring by decreasing the binding of the TGF-β activator protein complex to TGF-β element in the distal promoter of the *proα1* type I collagen gene (Cutroneo and Sterling Jr, 2004). Glucocorticoids may also affect collagen synthesis by reducing prolyl hydroxylase activity (Oikarinen and Hannuksela, 1980), an important rate-limiting enzyme of collagen synthesis (Kivirikko and Risteli, 1976; Myllyharju, 2008). Furthermore, glucocorticoids have been shown to repress collagen synthesis by increasing the degradation of collagen mRNAs (Nuutinen et al., 2001). As summarized in Table 2, besides collagens, several other ECM molecules are also targeted by glucocorticoids. These include elastin (Del Monaco et al., 1997); proteoglycans decorin and biglycan (Kähäri et al., 1995); hyaluronan (Saarni and Hopsu-Havu, 1978); noncollagenous glycoproteins, particularly fibronectin, laminin,

TABLE 2
Examples of currently available drugs modulating ECM metabolism beyond primary target

Drug	Primary Mechanism of Action	Effect on ECM metabolism
Anti-inflammatory and immunomodulatory drugs		
Corticosteroids		
e.g., hydrocortisone, prednisone, dexamethasone	Various genomic and nongenomic mechanisms of action (Stahn et al., 2007)	Modulation of the expression of various types of collagen (Oikarinen et al., 1987; Russell et al., 1989; Oishi et al., 2002), elastin (Del Monaco et al., 1997), proteoglycans decorin and biglycan (Kähäri et al., 1995), HA (Saarni and Hopsu-Havu, 1978), and various noncollagenous matrix glycoproteins such as fibronectin, laminin, and tenascin (Dean et al., 1988; Simo et al., 1992; Ekblom et al., 1993); suppression of MMP synthesis and activity (DiBattista et al., 1991; Sadowski and Steinmeyer, 2001); influence on TIMP expression and activity (Sadowski and Steinmeyer, 2001)
NSAIDs		
e.g., indomethacin, diclofenac, naproxen, and -coxibs such as celecoxib	Inhibition of cyclooxygenase enzymes -1 and -2 (Gasparini et al., 2003)	Modulation of the synthesis of fibronectin (Ernst et al., 1995), various types of collagen (Ernst et al., 1995; Liu et al., 2007), large chondroitin sulfate proteoglycans (Okada et al., 1994), and HA (Sussmann et al., 2004); suppression of MMP expression, synthesis, and activity (Sadowski and Steinmeyer, 2001; Pavlovic et al., 2006)
Other immunosuppressive drugs		
Cyclosporine A	Calcineurin inhibitor (Ho et al., 1996)	Differential effect on collagen synthesis and fibrosis (Eickelberg et al., 2001; Fornoni et al., 2001; Waller et al., 2004); inhibition of MMP activity (Fornoni et al., 2001; Chiu et al., 2009; Saygili et al., 2009)
Leflunomide	Pyrimidine synthesis inhibitor (Fukushima et al., 2007)	Inhibitory effect on fibrogenesis (Yao et al., 2004; Si et al., 2007)
Methotrexate	Inhibitor of dihydrofolate reductase (Warren et al., 2008)	Reduction of type IV collagen synthesis and ECM expansion (Yozai et al., 2005); influence on MMP and TIMP production (Seitz and Dayer, 2000; Fiedorczyk et al., 2006).
Sirolimus/ rapamycin	Mammalian target of rapamycin (mTOR) inhibitor (Sehgal, 2003; Granville et al., 2006)	Blocking of the synthesis of fibrillin-1 (Schaefer et al., 2007); blocking of HA accumulation (Gouëffic et al., 2007); inhibition of growth factor induced collagen synthesis (Park et al., 2005)
Tacrolimus	Calcineurin inhibitor (Nghiem et al., 2002)	Suppression of cytokine stimulated MMP synthesis (Migita et al., 2005); stimulation of collagen synthesis in vascular smooth muscle cells via TGF-β signaling (Giordano et al., 2008)
Microbial drugs		
Doxycycline	Antimicrobial drug	Inhibition of specific MMPs (Golup et al., 1998; Ahuja, 2003; Clark et al., 2008)
Minocycline	Antimicrobial drug	Inhibition of specific MMPs (Sutton et al., 2005; Machado et al., 2006)
Cytokine modulators		
Etanercept	Inhibition of TNF-α receptor (Moreland, 1999)	Modulation of type II collagen synthesis and degradation (Briot et al., 2008)
Infliximab, adalimumab	Inhibition of TNF-α (Moreland, 1999)	Inhibition of fibrosis (Sorrentino et al., 2007); downregulation of tissue degrading MMPs (Wendling et al, 2008; Di Sabatino et al., 2009)
Thalidomide	Inhibitory action on TNF-α (Moreira et al., 1993)	Attenuation of fibrosis (Chong et al., 2006; Yndestad et al., 2006); influence on endostatin level (Aydoğan et al., 2007)

TABLE 2—*Continued.*

Drug	Primary Mechanism of Action	Effect on ECM metabolism
Other drugs		
ACE-inhibitors		
e.g., Captopril, enalapril and numerous other ones	Blocking of angiotensin converting enzyme (Johnston and Jackson, 1983)	Modulation of collagen and proteoglycan synthesis and fibrosis (Kaneto et al., 1994; Cruz et al., 2000; Wapstra et al., 2001); influence on MMPs (Rizzoni et al., 2004; Aoki et al., 2007; Okada et al., 2008)
ATR-blockers		
e.g., Losartan and numerous other ones	Blocking of angiotensin II receptor (Gavras and Salerno, 1996)	Upregulation of thrombospondin-1 expression (Fischer et al., 2001); downregulation of fibronectin expression (Fischer et al., 2001); inhibition of CTGF and fibrosis (Rupérez et al., 2003); inhibition of specific MMPs and TIMPs (Masutomo et al., 2001; Saygili et al., 2009)
Calcium channel blockers		
e.g., Amlodipine, felodipine, diltiazem, and verapamil	Blocking of the L-type calcium channel (Mason et al., 2003)	Inhibition of collagen expression and accumulation (Roth et al., 1996; Sugiura et al., 2000); modulation of MMP activity (Roth et al., 1996; Wada et al., 2001)
Calcium sensitizing drugs		
e.g., Levosimendan	Calcium-sensitizer (Ng, 2004)	Reduction of MMP-2 (Tziakas et al., 2005)
Endothelin receptor antagonists		
e.g., Bosentan	Endothelin-1 inhibitor (Motte et al., 2006)	Upregulation of MMP-9 (Giannelli et al., 2005); downregulation of fibronectin (Siddiqui et al., 2006)
Statins		
e.g., Simvastatin, atorvastatin, and numerous other ones	Inhibition of HMG-CoA reductase (Vaughan and Gotto, 2004)	Inhibition of collagen and CTGF production (Martin et al., 2005; Rupérez et al., 2007); reduction of HA accumulation (Sakr et al., 2008); reduction of MMP-9 synthesis (Kalyanasundaram et al., 2006)
Tranilast	Histamine H1 receptor antagonist (Namazi and Soma, 2005)	Inhibition of collagen synthesis (Yamada et al., 1994) and accumulation (Isaji et al., 1987)
Tyrosine kinase inhibitors		
e.g., Imatinib	Specific tyrosine kinase inhibitor (Lydon and Druker, 2004)	Blocking of the stimulation of TGF-β induced collagen gene expression (Bhattacharyya et al., 2009)

HA, hyaluronan.

and tenascin (Dean et al., 1988; Simo et al., 1992; Ekblom et al., 1993); and certain ECM-degrading MMPs (DiBattista et al., 1991; Sadowski and Steinmeyer, 2001) as well as their inhibitors [i.e., tissue inhibitors of MMPs (TIMPs)] (Sadowski and Steinmeyer, 2001). The effects of glucocorticoids on these molecules are also likely to play a role in their antifibrotic property (Schoepe et al., 2006), although the mechanisms whereby glucocorticoids regulate these ECM genes are far less understood. However, certain MMPs are regulated by glucocorticoids via interference with the binding of the transcription factor activator protein-1, the major enhancer factor of the collagenase promoter (Jonat et al., 1990). Infliximab and other TNF-α antagonists can also act on the ECM by stimulating MMP activity and, therefore, ECM degradation (Wendling et al., 2008; Di Sabatino et al., 2009).

Nonsteroidal anti-inflammatory drugs, which primarily inhibit cyclooxygenase enzymes and thereby prevent the synthesis of prostanoids, are able to ameliorate fibrotic processes via influencing TGF-β synthesis (Liu et al., 2007). Furthermore, nonsteroidal anti-inflammatory drugs have been shown to affect the ECM through suppression of MMP expression, synthesis, and activity (Sadowski and Steinmeyer, 2001; Pavlovic et al., 2006). This mechanism of action has also been described for antimicrobial tetracycline analogs such as doxycycline (Golup et al., 1998; Ahuja, 2003; Clark et al., 2008) and minocycline (Sutton et al., 2005; Machado et al., 2006) when used in the treatment of abdominal aortic aneurysm and neurodegenerative diseases, respectively (Abdul-Hussien et al., 2009; Kim and Suh, 2009).

It has recently been discovered that cyclosporine A, a widely used immunosuppressant and an inhibitor of the mitochondrial permeability pore, is a curative agent for congenital collagen type VI myopathies (i.e., Ullrich congenital muscular dystrophy and Bethlem myopathy) (Merlini et al., 2008a). That is, cyclosporine A corrects mitochondrial dysfunction and muscle apoptosis that are characteristic features in these patients (Merlini et al., 2008a). This discovery is of great importance, because it demonstrates that an unexpected collagen type VI/ mitochondrial connection forms the basis of the pathogenesis of collagen type VI myopathies (Maraldi et al., 2009). Furthermore, it also represents a proof of the principle that hereditary diseases, including hereditary ECM diseases, can be treated with proper drugs downstream of the genetic lesion, if the pathogenetic mechanism is understood (Olsen, 2008). Besides being a curative agent for Ullrich congenital muscular dystrophy and Bethlem myopathy, cyclosporine A can beneficially contribute to ECM remodelling by regulating the activity of specific MMPs (Chiu et al., 2009; Saygili et al., 2009). These examples highlight the point that the mechanisms driving fibrogenesis are not necessarily the same as those regulating inflammation (Wynn, 2007, 2008; Sivakumar and Das, 2008) and that there is a specific need to develop drugs targeting the ECM besides developing better drugs for various inflammatory diseases.

B. Other Current Drugs with Beneficial Disease-Modifying Properties on the Extracellular Matrix

In addition to anti-inflammatory and immunomodulatory drugs, there are several other drug classes that have been shown to influence the ECM in a beneficial way beyond their primary targets. This is true for antihypertensive agents, particularly angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers, which all possess marked antifibrotic properties via their ability to reduce collagen production (Roth et al., 1996; Sugiura et al., 2000; Tayebjee et al., 2003; Duprez, 2006). ACE inhibitors such as captopril primarily block angiotensin II-converting enzyme (Johnston and Jackson, 1983) and limit ECM expansion in numerous models of acute and chronic renal disease (Taal and Brenner, 2000). Angiotensin receptor blockers, including losartan, inhibit the effects of angiotensin by selectively blocking angiotensin II type 1 receptor (Gavras and Salerno, 1996). As a result, antifibrotic action is also evident. Both of the angiotensin II-blocking drugs act on the ECM by reducing sustained overexpression of TGF-β (Peters et al., 1999). The combination of angiotensin II blockade and straight inhibition of TGF-β with antibodies has proven to be a promising therapeutic strategy to slow down fibrotic diseases (Yu et al., 2002, 2004). Angiotensin II blockade by angiotensin II type 1 receptor blockers in patients with Marfan's syndrome has been found to significantly slow the rate of progressive aortic-root dilation (Brooke et al., 2008). In addition, calcium channel blockers such as nifedipine and amlodipine, which block the L-type calcium channel (Mason et al., 2003), have been proposed to act on the ECM via suppressing TGF-β, thereby resulting in reduced matrix accumulation (Sugiura et al., 2000). However, this finding has been disputed in some published work (Campistol et al., 2001). On the other hand, calcium channel blockers have also been reported to modulate the activity/expression of MMPs and TIMPs, but the mechanisms of action are still unclear (Roth et al., 1996; Wada et al., 2001). Cholesterol-lowering drugs, the statins, can reduce tissue fibrosis (Louneva et al., 2006) by their ability to inhibit angiotensin-induced connective tissue growth factor production (CTGF) (Rupérez et al., 2007). Statins inhibit the conversion of HMG-CoA to mevalonate, which is required for the post-translational modification of Rho family and Ras GTPases (Jackson et al., 1997). Rho family GTPases Rac1 and Cdc42 have been shown to be the principal mediators of the TGF-β-stimulated expression of CTGF in human gingival fibroblasts, and CTGF expression can be reduced significantly with lovastatin (Black and Trackman, 2008). The use of pravastatin has

also been reported to inhibit the Rho/CTGF/ECM cascade in human fibrosis explants (Haydont et al., 2007).

Other examples of current drugs that are able to modulate ECM metabolism in a way that can be regarded beneficial for disease-modifying processes include several newer agents, such as levosimendan, a calcium sensitizer used for patients with decompensated heart failure (Ng, 2004; Tziakas et al., 2005). Levosimendan use reduces the serum level of MMP-2 in these patients (Tziakas et al., 2005). In contrast, bosentan, an endothelin ET_A- and ET_B-receptor antagonist, increases the serum MMP-9 without affecting TIMPs when used in patients with pulmonary arterial hypertension (Giannelli et al., 2005, 2006). Thus, bosentan favors proteolytic imbalance by increasing the turnover of ECM proteins. Sirolimus, an effective antimitotic agent used in stent restenosis therapy, blocks the accumulation of hyaluronan and the adhesion of monocytes to ECM produced by vascular smooth muscle cells (Gouëffic et al., 2007). Of course, numerous other examples of drugs and pharmaceutical agents influencing the ECM in a potentially beneficial way exist. However, the problem with all the mentioned drugs is that their effects on the ECM are rather weak and unspecific.

C. Deleterious Effects of Current Drugs on the Extracellular Matrix

The effects of current drugs on the ECM are not always desired. A classic example is peritoneal fibrosis and a wide variety of skin lesions after the use of the β-adrenergic-blocking drug practolol (Brown et al., 1974), although the mechanism whereby practolol causes peritoneal fibrosis and cutaneous lesions is, unfortunately, not known. Methysergide, a receptor antagonist for the 5-hydroxytryptamine (5HT) receptor 2C, earlier prescribed for prophylaxis of migraine, has also caused retroperitoneal fibrosis (Utz et al., 1965). It is noteworthy that the antiobesity drugs dexfenfluramine and fenfluramine, which act by releasing 5HT and also partially via conversion to the active metabolite norfenfluramine, directly stimulate $5HT_{2B}$-receptors and have been associated with hyperplastic valvular and endocardial lesions with increased ECM via TGF-β-mediated mechanisms (Gardin et al., 2000; Jian et al., 2002; Rothman and Baumann, 2002). Because of this side effect, these agents were voluntarily withdrawn from the market in 1997. Furthermore, dopamine receptor agonists of the ergot-derivative class used in the treatment of Parkinson's disease and prolactin-producing pituitary gland tumors have caused valvular diseases, possibly via their effects on $5HT_{2B}$-receptors (Antonini and Poewe, 2007). Antineoplastic agents bleomycin and cyclophosphamide represent additional well known drugs with side effects on the ECM that include fibrosis (Lazo and Hoyt, 1990). Bleomycin seems to mediate fibrosis by increasing the expression and synthesis of TGF-β1 (Cutroneo et al., 2007). Methotrexate, a first-line antirheumatic drug by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), primarily inhibits the metabolism of folic acid. Because of its first-pass metabolism in the liver, it may cause liver fibrosis (Salliot and van der Heijde, 2008; Lindsay et al., 2009). The underlying mechanisms for methotrexate-induced liver cell damage are still incompletely understood. However, the activation of complement pathway within the liver tissue has been suggested to play an important role (Belinsky et al., 2007). Gingival enlargement due to an increase in the ECM of the gingival connective tissue has been traditionally recognized as an adverse effect of phenytoin and L-type calcium channel blocker therapies as well as cyclosporin use (Bonnaure-Mallet et al., 1995; Brunet et al., 1996). Evidence is available indicating that in the case of phenytoin, TGF-β1 and also platelet-derived growth factor-BB are closely associated with this aesthetic side effect (i.e., gingival enlargements) (Kuru et al., 2004). The underlying mechanisms whereby L-type calcium channel blockers cause gingival hyperplasia remains to be fully understood. The proposed mechanisms include defective collagenase activity that was due to decreased uptake of folic acid (Brown et al., 1990) as well as up-regulation of TGF-β1 and other factors responsible for the production of a fibrous scaffold in the gingiva (Lafzi et al., 2006).

Recently discovered deleterious effects of drugs on the ECM are tendinopathies associated with the use of statins (Marie et al., 2008) and fluoroquinolones (Conforti et al., 2007). Furthermore, skeletal consequences (particularly increased risk of bone fractures in the appendicular skeleton in women with type 2 diabetes, caused by thiazolidinediones, an antidiabetic drug class) has been noticed (Grey, 2008). Statin and fluoroquinolone-induced tendinopathies have mainly been attributed to the ability of these two drug classes to modulate the activity of specific MMPs in tendon cells (Corps et al., 2002, 2005; Pullatt et al., 2007). The side effects of thiazolidinediones on bones are thought to be mainly due to the proadipocytic and antiosteoblastogenic effects of these drugs on pluripotent mesenchymal stem cells (Lecka-Czernik et al., 2002; Shockley et al., 2009). However, reduction in ECM production via inhibited TGF-β1 or CTGF expression may be of equal importance (Peng et al., 2006; Gao et al., 2007) in defining the efficacy of these drugs. The new biological anti-inflammatory and immunomodulatory drugs, such as tumor necrosis factor inhibitors and the interleukin-1 inhibitor anakinra, may also cause adverse side-effects on the ECM, particularly in the skin (Deng et al., 2006; Regula et al., 2008). In clinical practice, glucocorticoids are probably the most well known drugs that cause marked side-effects via their influence on the ECM. Systemic use of glucocorticoids for a longer period of time in the treatments of chronic inflammatory disease processes is almost inevitably harmful to healthy tissues (McDonough et al., 2008), particularly bones, by causing premature or ex-

aggerated osteoporosis (Ton et al., 2005; Canalis et al., 2007), and skin, by inducing its thinning (Schoepe et al., 2006; Zöller et al., 2008). Recent developments in bone biology have markedly advanced our understanding of how glucocorticoids affect the receptor activator of the nuclear factor-κB–ligand–osteoprotegerin system and the Wnt-catenin signaling pathway (Berris et al., 2007; Canalis et al., 2007) and via these effects favor osteoclastogenesis instead of osteoblastogenesis. Glucocorticoids can also inhibit osteoblast-driven synthesis of type I collagen, the major component of the bone ECM, with a consequent decrease in bone matrix available for mineralization (Canalis, 2005). Additional mechanisms whereby glucocorticoids induce osteoporosis include enhanced expression of selected MMPs by osteoblasts (Delany et al., 1995) and effects on the synthesis or receptor binding of growth factors (Canalis et al., 2007). However, the exact mechanisms of glucocorticoid-induced osteoporosis are still incompletely understood. The molecular mechanisms of glucocorticoid-induced skin atrophy are similarly complicated. Glucocorticoids are known to regulate the gene expression of a number of ECM molecules and other molecules in cutaneous cells via many and diverse genomic and nongenomic mechanisms, including TGF-β signaling pathway as described in section III.A (Cutroneo and Sterling Jr, 2004; Schoepe et al., 2006). To avoid the harmful effects of glucocorticoids on healthy tissues, site-specific targeting using modified glucocorticoids is desired (Joner et al., 2008). Therefore, the involvement of ECM proteins should be more often considered as possible targets in the mechanistic toxicology during drug development when possible side-effects are sought to be avoided.

IV. Potential Future Pharmacotherapies Targeting the Extracellular Matrix

As discussed above, several of the currently available drugs can modulate ECM metabolism and assembly beyond their primary targets. However, their effects on the ECM are often neither potent nor specific enough. Furthermore, several drugs can have deleterious effects on the ECM. Therefore, novel drugs influencing the ECM in a more direct way are still desired. In recent years, the number of drug development projects aiming to primarily target the ECM has increased (Huxley-Jones et al., 2008). In these projects, cell- and gene-based strategies, particularly gene and antisense therapies as well as RNA interference and recombinant technologies, are used (Huxley-Jones et al., 2008). Although these approaches offer fascinating new ways to treat various human diseases (Isner et al., 1996; Ye at al., 2007), they have not yet been put into clinical practice. The multiplicity and functional complexity of the ECM molecules and the diversity of diseases related to the ECM offer significant challenges for future targeting strategies. However, the overwhelming evidence, some of which has been presented in this review, indicates a need to target specific components of the ECM to prevent or treat a variety of diseases. On the other hand, the molecular complexity of diseases suggests that agents targeting not only a single ECM molecule but concomitantly several aspects of the ECM will also have an important position in future drug development. The widespread targeting has already been successfully applied in the development of the second-generation tyrosine kinase inhibitors used for the treatment of cancers (Baselga, 2006). In the following chapters, potential future pharmacotherapies targeting primarily the synthesis, degradation, or signaling of the ECM will be discussed. A summary of these drugs is presented in Table 3. Furthermore, a schematic illustration of the ECM and its outside-in signaling pathways as well as the sites of potential future pharmacotherapeutics targeting the ECM are shown in Fig. 1.

A. Targeting the Synthesis of the Extracellular Matrix

Fibrosis, characterized as a relative increase in the amount of fibrous connective tissue, is a hallmark of numerous human diseases, most of which exhibit an inflammatory component in their pathogenesis. However, as discussed above, current anti-inflammatory and immunomodulatory drugs as well as certain other drugs have only a limited efficacy in preventing fibrotic processes. Much evidence is available indicating that the molecular family of transforming growth factor-βs (here grouped as TGF-β) are essential mediators of fibrosis. Indeed, TGF-β has been implicated in the fibrotic disorders of heart, kidney, liver, lung, skin, and several other organs (Gordon and Blobe, 2008). Therefore, TGF-β is a highly potential target for antifibrotic therapy. Current understanding of the signaling pathways of TGF-β provides three main strategies for blocking pathological TGF-β responses in the treatment of fibrotic processes: 1) blocking the TGF-β ligand by neutralizing antibodies [such as metelimumab (Denton et al., 2007) and lerdelimumab (Cordeiro, 2003)], soluble TGF-β receptors, receptor mimetics, or natural TGF-β-binding proteins such as decorin; 2) blocking TGF-β receptor activation and downstream signaling by orally active small-molecule TGF-β receptor kinase inhibitors such as SB431542 (Mori et al., 2004), SD-208 (Uhl et al., 2004), and SM305 (Ishida et al., 2006); and 3) selective inhibition of intracellular signal transduction by interfering with Smads by physiological endogenous inhibitor Smad7 or with coactivators by aptamers (thioredoxin A-Smad anchor for receptor activation) (Varga and Pasche, 2008). However, because TGF-β blockade has not yet translated into an effective and safe therapy in human patients, additional growth factors or cytokines involved in fibrotic processes have also been explored as potential targets for the treatment of fibrosis. These molecules include interleukin-6, interleukin-13, CC and CXC family of chemokines, bone morphogenetic protein-7 and

TABLE 3
Examples of potential future pharmacotherapies targeting the synthesis, degradation, or signaling of the ECM

Drug	Mechanism of action
Drugs targeting the synthesis of the ECM	
Cytokine inhibitors	
Lerdelimumab (Cordeiro, 2003)	Antibody to TGF-β2
Metelimumab (Denton et al., 2007)	Antibody to TGF-β1
GC-1008 (Grütter et al., 2008)	Antibody to TGF-β1
SB431542 (Mori et al., 2004)	Inhibits TGF-β signaling through selective interference with ALK5-mediated Smad activation
SD-208 (Uhl et al., 2004)	TGF-β receptor I kinase inhibitor
SM305 (Ishida et al., 2006)	Inhibits TGF-β signaling through selective interference with ALK5-mediated Smad activation
FG-3019 (Aikawa et al., 2006)	Antibody to CTGF
Cytokines	Recombinant TGF-β3
Avotermin (Durani et al., 2008)	
Ilodecakin (Marshall, 1999)	Recombinant interleukin-10
Drugs targeting the degradation of the ECM	
Tanomastat (Hirte et al., 2006)	MMP inhibitor
Cipemastat (Trocade) (Ishikawa et al., 2005)	Collagenase and MMP-14 inhibitor
FR255031 (Ishikawa et al., 2005)	Broad-spectrum MMP inhibitor
Balicatib (Desmarais et al., 2008)	Selective cathepsin K inhibitor
Odanacatib (Gauthier et al., 2008)	Selective cathepsin K inhibitor
PI-88 (McKenzie, 2007)	Inhibits heparanase activity
AA-4500 (Occleston et al., 2008)	Collagenase stimulator
Drugs targeting the signaling of the ECM	
Etaracizumab (Delbaldo et al., 2008)	Antibody to αv/β3 integrin
Vedolizumab (MLN0002) (Feagan et al., 2008; Behm and Bickston, 2009)	Antibody to α4/β7 integrin
Volociximab (Ricart et al., 2008)	Antibody to α5/β1 integrin

CTGF (Nguyen and Goldschmeding, 2008; Sivakumar and Das, 2008). For example, FG-3019 (Aikawa et al., 2006) is an IgG1 antibody that can bind specifically to domain 2 of CTGF and block angiotensin II and advanced glycation end product-induced fibronectin production by vascular smooth muscle cells (Occleston et al., 2008). This drug reduces or inhibits fibrosis in lung, liver, and kidney in vivo. As such, it has already been used in phase I/II clinical trials for treatment of idiopathic pulmonary fibrosis, and trials for treatment of focal segmental glomerulosclerosis and other fibrotic diseases are planned (Occleston et al., 2008). On the other hand, TGF-β3, which is present in high levels in developing embryonic skin and thus also in embryonic wounds, is known to be involved in wound healing with no scar. Therefore, recombinant human TGF-β3 called avotermin has been developed and tested for scar formation in adults (Durani et al., 2008; Ferguson et al., 2009). Avotermin has been postulated to promote the regeneration of normal skin and to improve scar appearance by reducing the deposition of ECM components such as collagen and fibronectin and by influencing the organization of the newly deposited ECM in the wounded dermis (Occleston et al., 2008). Ilodecakin, a recombinant interleukin-10 (Marshall, 1999), is another example of a cytokine drug modulating ECM metabolism in a way that creates an environment conducive for degenerative wound healing (Moroguchi et al., 2004; Peranteau et al., 2008). Which of the above agents will finally translate into clinical practice remains to be seen. However, recent results with avotermin are encouraging: in three double-blinded, placebo controlled studies, avotermin administered intradermally to both margins of skin incisions, before wounding and 24 h later, has shown an accelerated and permanent improvement in scarring without any substantial adverse events (Ferguson et al., 2009).

Besides interfering with the activity of profibrotic growth factors and cytokines, the synthesis of ECM molecules can be regulated more directly by targeting their promoters and enhancers. A series of triplex-forming oligonucleotides (TFOs) have been developed for inhibiting the transcription of α1(I) collagen gene (Ye et al., 2005). Furthermore, bioconjugation of oligonucleotides with other molecules such as lipids, sugars, or peptides makes the site-specific delivery of TFOs possible (Ye et al., 2007). This kind of targeted delivery of TFOs provides a whole new area for antifibrotic drugs in pharmacotherapy. On the other hand, it is also possible to influence the synthesis of ECM molecules at the post-translational level. For example, inhibition of type I collagen prolyl-4-hydroxylase generates scurvy-like unstable collagen fibrils and results in reduced collagen production (Rocnik et al., 1998). In contrast, overexpression of the α subunit of type I collagen prolyl-4-hydroxylase is associated with excess collagen production (John et al., 1999). Thus, collagen prolyl-4-hydroxylases, and especially their α subunits, can be regarded as attractive targets for pharmacological inhibition to control excessive collagen accumulation in fibrotic diseases and severe scarring (Myllyharju, 2008). Here, organ-specific targeting is still an unresolved problem. Collagen is the

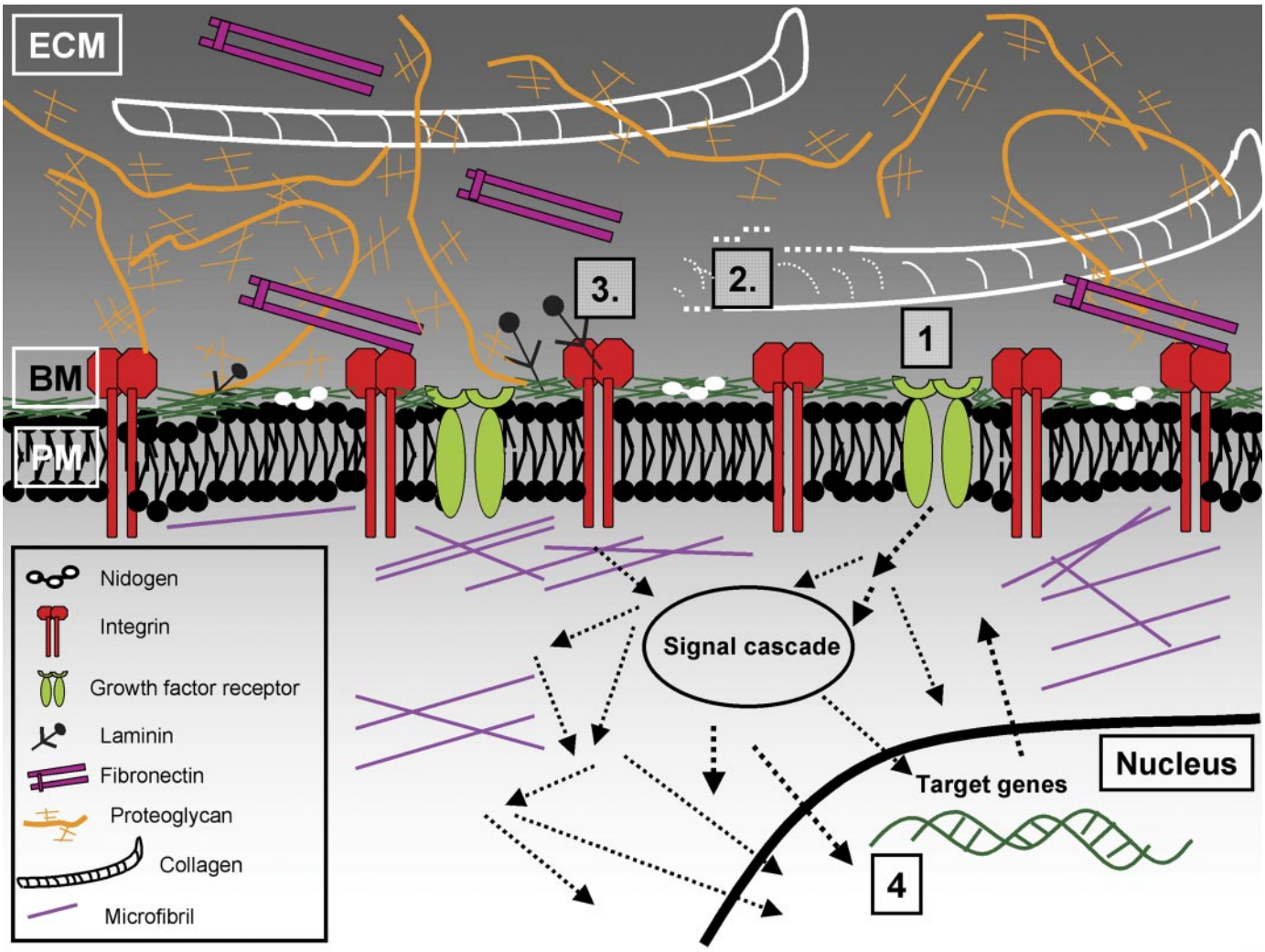

FIG. 1. Schematic illustration of the ECM and potential targets in pharmacotherapy in the future. 1, targeting the synthesis of the ECM by blocking of specific growth factors such as TGF-β, their receptor molecules, or intracellular signal transduction. 2, controlling of the degradation of ECM by interfering with enzymes involved in ECM remodelling (e.g., MMPs, ADAMTS, cathepsins) and/or their inhibitors. 3, interfering with the ECM signaling pathways (e.g., via integrins) either by blocking the ECM and integrin interactions or subsequent signal transduction. 4, influencing the transcription of specific ECM molecules (e.g., by TFOs). BM, basement membrane; PM, plasma membrane.

main component of all fibrous connective tissues from skin to bone or tubular organs. When type I collagen synthesis is targeted, side effects are expected to be noted in all organs synthesizing collagen.

Although the inhibition of ECM synthesis is desired in the treatment of fibrotic diseases, there are also numerous situations in which drugs capable of increasing ECM production are useful. These situations include degenerative diseases of intervertebral disc and articular cartilage, impaired wound healing, and nerve basement membrane regeneration (Wang et al., 2004; Roughley et al., 2006; Armstrong et al., 2007). Nutraceuticals, in particular glucosamine, have been used as a treatment option in degenerative diseases of cartilage. It has been proposed that glucosamine leads to an increased glycosaminoglycan production by chondrocytes, because it is the basic building block of glycosaminoglycan molecules. However, the results have been controversial (Bassleer et al., 1998; Mroz and Silbert, 2004). Nevertheless, glucosamine, when used in combination with chondroitin sulfate, has been claimed to be effective in the subgroup of arthrotic patients with moderate-to-severe knee pain (Clegg et al., 2006). A plausible explanation as to why these agents reduce pain is that they possess anti-inflammatory activities rather than anabolic properties to replace joint fluid (Sakai et al., 2006). However, approaches to develop nutraceuticals for the treatment of degenerative cartilage diseases may still be worthwhile, even though targeted delivery of TFOs, as well as growth factors stimulating ECM production or molecules inhibiting matrix degradation, is likely to provide a more practical and potent remedy for various degenerative diseases including those of the cartilage.

B. Targeting the Degradation of the Extracellular Matrix

Proteolytic degradation of ECM components is a pathognomic feature, not only of well known degenera-

tive diseases such as osteoarthritis (Smith, 1999; Kobayashi et al., 2005) but also in cardiovascular pathologies (Raffetto and Khalil, 2008), malignancies (Ingber, 2008), and several other diseases. Numerous enzymes are able to degrade individual ECM components. However, ECM degradation is primarily under the control of specific MMPs and their inhibitors (i.e., TIMPs) (Visse and Nagase, 2003), disintegrin and metalloproteinase with thrombopondin motifs (ADAMTS) family of proteinases (Tang, 2001), and cysteine protease cathepsins (Chapman et al., 1997). Thus, strategies for the prevention of proteolytic matrix degradation have mainly focused on these enzymes. Synthetic broad-spectrum MMP inhibitors such as batimastat, ilomastat, and marimastat, as well as more selective MMP inhibitors, particularly tanomastat and trocade, have been developed and tested in clinical trials, foremost to treat cancer (Overall and Kleifeld, 2006). Unfortunately, the results from these trials have been disappointing (Coussens et al., 2002; Hirte et al., 2006). The reasons for the failures of the above synthetic MMP inhibitors are not exactly understood, but it has been thought that they cover too wide a spectrum and so more selective MMP inhibitors are still required (Hu et al., 2007). In line with this idea, evidence is available suggesting that efforts to inhibit MMP activity should be directed at therapies exploiting endogenous MMP inhibitors, TIMPs (Ramirez-Correa et al., 2004; Zacchigna et al., 2004), or monoclonal antibodies against individual MMPs (Martens et al., 2007). Experiences from animal studies indicate that ADAMTS inhibitors are likely to have a position as future drugs. For example, inhibition of specific ADAMTS, namely ADAMTS-4 and -5, by a flavonoid called nobiletin, has been found to decrease aggrecan degradation in cartilage and subsequently to prevent cartilage destruction (Imada et al., 2008). The most promising results of the potential utility of targeting matrix degradation in pharmacotherapy come from studies using cathepsin inhibitors, particularly cathepsin K inhibitors. There are two cathepsin K inhibitors, odanacatib (Gauthier et al., 2008) and balicatib (Desmarais et al., 2008), both of which have been demonstrated to inhibit bone resorption and to increase bone mass in patients with osteoporosis (Stoch and Wagner, 2008). It can be expected that cathepsin K inhibitors will be the first targeted agents getting approval to be used for ECM therapy, especially for osteoporosis. Cathepsin K inhibitors also are promising strategies for targeting proteolytic degradation of the ECM for use in pharmacotherapy. It remains to be seen whether in the future there will be specific drugs that inhibit ECM degradation within vascular wall and through this mechanism prevent acute coronary syndromes and other aneurysmatic processes in the vasculature (Kim et al., 2005; Senzaki, 2006; Hu et al., 2007).

In addition to targeting the enzymes that degrade the ECM, a number of other potential candidate enzymes and their inhibitors have to be evaluated for drug discovery. For example, inhibition of hyaluronidases, the enzymes that degrade hyaluronan, provides an attractive pharmacological tool to be used in physiological processes ranging from fertilization to aging and in pathological processes such as malignancies (Girish and Kemparaju, 2007). Furthermore, the finding that heparanase is elevated in a wide variety of tumor types and is subsequently linked to the development of pathological processes has led to an explosion of therapeutic strategies to inhibit its enzyme activity. So far at least one compound, the sulfated oligosaccharide PI-88, which both inhibits heparanase activity and has effects on growth factor binding, has reached clinical trials, where it has shown promising efficacy (McKenzie, 2007). A molecule named AA-4500 that can stimulate collagenase activity has demonstrated efficacy in phase III trial when administered locally to treat Dupuytren's contracture (Occleston et al., 2008). On the other hand, putrescine, inhibitor of tissue transglutaminase (required for crosslinking of collagen with other ECM proteins), has shown no greater efficacy than placebo in phase II trial when evaluated as treatment for hypertrophic scarring (Occleston et al., 2008).

C. Targeting the Signaling of the Extracellular Matrix

The altered assembly of connective tissue, whether it is a result of the synthesis or degradation of the matrix components, can markedly modify cell-matrix interactions by activating various signaling pathways that regulate cell behavior particularly growth, differentiation, motility and viability of the cells (Lukashev and Werb, 1998; Larsen et al., 2006; Grzesiak et al., 2007; Marastoni et al., 2008). The effects of individual matrix molecules on the cells are primarily transmitted through specific cell-surface receptors called integrins that are transmembrane heterodimeric glycoproteins composed of one α and one β subunit (Hynes, 2002). So far, 18 α and 8 β subunits have been identified in mammals, and these subunits can form at least 24 different combinations, each able to specifically bind one or several ECM molecules. Because integrins usually recognize only relatively short peptide motifs in a molecule (Ruoslahti and Pierschbacher, 1987; Hynes, 2002), it is possible to target the integrin recognition peptide motifs of the ECM molecules by using specific blocking antibodies and through this mechanism influence interactions between the remodelled matrix and the integrins. This approach has successfully been used with cytokines such as TNF-α, whose receptor binding and activity can be blocked [e.g., with a monoclonal chimeric antibody infliximab, a fully human monoclonal antibody adalimumab, or a PEGylated Fab′ fragment of a humanized TNF-α inhibitor monoclonal antibody certolizumab (Bourne et al., 2008)]. However, strategies for generating antibodies against ECM molecules and using them for therapies have not gained much favor (Huxley-Jones et al., 2008). Instead, strategies for generating monoclo-

nal antibodies against integrins have been under intensive investigation. As mentioned earlier, there are already a few anti-integrin antibodies in clinical practice used for acute coronary syndrome, psoriasis, multiple sclerosis, and Crohn's disease (Rosove, 2004; Baker, 2007; Schön, 2008). Although the use of these anti-integrin antibodies as drugs has not always been completely safe (Baker, 2007; Schön, 2008; Tamhane and Gurm, 2008), each of them has clearly verified that this approach is very useful in drug discovery. For example, vedolizumab (MLN0002), a humanized antibody targeting the $\alpha4\beta7$ integrin, has exhibited a beneficial effect on active Crohn's disease (Feagan et al., 2008) and ulcerative colitis (Behm and Bickston, 2009) by virtue of its highly selective capacity to block lymphocyte migration to inflamed areas of the gut. Vedolizumab specifically interferes with the interaction between the $\alpha4\beta7$ integrin on lymphocytes and its principal ligand, mucosal addressin cell adhesion molecule-1, on endothelial cells (Berlin et al., 1993). It is noteworthy that $\alpha4\beta7$ integrin can also bind fibronectin (Rüegg et al., 1992), suggesting that, in the future, vedolizumab may have a wide spectrum of application in the treatment of pathological conditions such as atherosclerosis, cardiac hypertrophy, and tumorigenesis (Astrof and Hynes, 2009). Volociximab, a chimeric humanized monoclonal antibody that is a high-affinity function inhibitor of the $\alpha5\beta1$ integrin, has been applied in clinical phase II trials for solid tumors in renal cell carcinoma, metastatic melanoma, and pancreatic cancer (Huveneers et al., 2007). The rationale of using volociximab in cancer therapy can be based on the fact that integrin $\alpha5\beta1$, which binds fibronectin, is expressed mainly on vascular endothelial cells and up-regulated together with fibronectin in tumor vasculature (Astrof and Hynes, 2009). As such, volociximab has a potential to inhibit tumor angiogenesis, without which tumors cannot grow. It remains to be seen whether volociximab might also provide a cure for a large number of nonmalignant human diseases that are dependent on angiogenesis (Folkman, 2007). On the other hand, as mentioned earlier, angiogenesis is also under regulation of a number of other integrins, particularly the αv integrin subfamily, several ECM molecules (including some of their proteolytically released cleavage products such as endostatin), and different soluble factors (i.e., growth factors and cytokines) (Ingber and Folkman, 1989; Hynes, 2007). Therefore, it is likely that in most situations, volociximab alone is not potent enough to repress angiogenesis, and developing antiangiogenic therapies based on the other molecules mentioned above would be vital.

Besides generating anti-integrin antibodies, it is possible to generate specific small-molecule compounds, peptidomimetics, to block integrin signaling pathways that are activated by the remodelled ECM. Indeed, this approach has been recognized to be an important area in drug discovery (Huveneers et al., 2007; Huxley-Jones et al., 2008). Eptifibatide, a synthetic cyclic peptide with a Lys-Gly-ASP (KGD) sequence that antagonizes $\alpha v\beta3$ integrin, is an example of the small-molecule integrin antagonists. Eptifibatide acts at the final common step of the platelet aggregation pathway and has already been in use for years for patients with acute coronary syndrome and/or undergoing percutaneous coronary intervention (Curran and Keating, 2005). A number of other small-molecule integrin antagonists, both peptide and nonpeptide peptidomimetics, inhibiting different integrins have been developed for use in treating various human diseases such as cancer, rheumatoid arthritis, osteoporosis, asthma, and ulcerative colitis (Huveneers et al., 2007; Woodside and Vanderslice, 2008). Targeting nonintegrin ECM receptors may also have therapeutic value. For example, blocking antibodies to CD44, which is the main receptor for hyaluronan but interacts with a number of other ECM components, induces resistance to developing type 1 diabetes in a mouse model (Weiss et al., 2000). Administration of hyaluronan oligosaccharides, which interfere with CD44 polyvalent binding to hyaluronan, are effective inhibitors of several tumor types in vivo, such as mammary and lung carcinomas and melanoma (Zeng et al., 1998; Toole et al., 2008). Similar to other future drugs discussed above, it remains to be seen whether and when these compounds are ready for clinical use. Currently, a major drawback with the above potential future therapies may be the lack of their oral use. In addition, there are huge difficulties in developing therapies that are not only site-specific but also have few side effects.

V. Conclusions

Our aim has been to convince the reader that many, and perhaps most, human diseases have some connection to the remodelling of the ECM and tissue pathology. However, currently available drugs are neither specific nor potent enough to target ECM molecules and prevent tissue destruction due to diseases. The approach that we have reviewed is both complex and complicated. Success has been achieved at targeting the receptors for many of the ECM components. Targeting the cytokines, enzymes, and signaling molecules involved in the synthesis, accumulation, and degradation of the ECM is another approach that is showing encouraging results. Less attention has been given to targeting specific individual ECM components as a means of interfering with specific diseases. However, a growing number of examples show that specific ECM components have a dramatic effect on several disease phenotypes, so this approach may be a fruitful area for drug development in the future. What is certain is that the ECM has been a neglected target for drug pharmacotherapy in the past but promises to be an important target to consider in the future.

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