ELSEVIER

Drug discovery in the extracellular matrix

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The extracellular matrix (ECM) is an organised mesh of secreted proteins that provides structure, organisation and orientation to tissues and influences a spectrum of cell behaviours of direct relevance to disease and drug discovery. Many drugs currently in development target components of the ECM, yet most drug discovery teams perceive the ECM as a barrier to efficacious drug action, rather than a therapeutic target. Here we review current therapeutic approaches and consider potentially novel druggable opportunities to target the ECM, taking into account the factors that make it both unique and challenging, including its evolutionary history and innate multi-dimensional complexity.

The extracellular matrix (ECM) is a complex structured network of secreted macromolecules and proteolytic enzymes. The ECM plays a vital role in the structure and development of tissues; it provides mechanical strength, acts as a template for cell growth and influences cell behaviours, such as migration, proliferation, differentiation and adhesion [1]. In addition, ECM molecules directly interact with cell surface receptors to regulate cell activity through key signalling pathways, such as TGF-β [2]. The generic ECM, depicted in Figure 1, is composed of two basic molecular types. Major structural molecules, such as collagens and laminins, form a basic integral network connecting the matrix to the surrounding cells [3,4]. Other glycoproteins endow additional properties to the matrix, for example integrins promote cell adhesion and signalling [3] while elastin and fibronectin-like molecules provide flexibility [5]. Space-filling proteoglycans, through their high water-binding capacity, provide turgor and stabilize the matrix [6]. In addition to enabling tissues to resist compressive forces, proteoglycans organise collagen networks, store growth factors and cytokines and maintain selective filtration [6].

Although the structural components of the ECM do not lend themselves easily to traditional considerations of tractability and drug discovery, the ECM should not be considered as a rigid infrastructure unassailable by small molecules. The ECM is, in fact, a dynamic structure whose processing and turnover is pivotal to providing suitable environments for growth, development and tissue remodelling. Conversely, disruption of these dynamic processes is fundamental to many human diseases. Therefore, the processes of assembly and disassembly of the matrix are clear targets for drug discovery.

The innate dynamism of the ECM may present opportunities for modulation by small molecules. All ECM proteins, and many ECM proteases themselves, are secreted from cells and undergo proteolytic cleavage before they are in their mature state [7]. This mainly involves the cleavage of the signal peptide sequence from the N-terminus, however for proteins that form supramolecular structures (such as collagens and laminins) the process of pro-protein maturation is elaborated. ECM proteases also degrade components of the matrix, enabling cell migration, regulate tissue structure through effects at cell–ECM junctions and, both directly and indirectly, modify signalling pathways [8]. In addition, processing of ECM molecules can reveal cryptic functional fragments not observed in the intact molecule that are implicated in many ECM–cell interactions [9]. So, although most ECM proteins do not contain precedented pharmacophores, knowledge of ECM protease/ECM protein relationships each present opportunities for modulation of processing with small molecule protease inhibitors. In Figure 2 we review known relationships between the major families of ECM components and their processing proteases. The terms used are presented in the 'Glossary'.

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GLOSSARY

A-DOM A domain
ADAM A disintegrin and metallopeptidase domain
ADAMTS A disintegrin-like and metallopeptidase with thrombospondin type 1 motif
ANATO Anaphylatoxin homologous
β-prop integrin β propeller
BMP1 bone morphogenetic protein
C1Q C1Q C-terminal
CC coiled coil
COLF1 C-terminal domain of fibrillar collagen
COLLAGEN collagenous repeat
ECM extracellular matrix
EGF epidermal growth factor
EGFCA calcium binding epidermal growth factor
Endostatin endostatin C-terminal fragment
FACIT fibril associated collagens with interrupted triple helices
FN1 fibronectin 1
FN2 fibronectin 2
FN3 fibronectin 3
FNC fibronectin C-terminal
GPC glypican
HX hemopexin
HYAL hyaluronoglucosaminidase
I-DOM I-domain (β-A domain)
IG immunoglobulin-like
LAMA laminin alpha
LAMB laminin beta
LAMG laminin gamma
LAMN laminin N-terminal
LDLA low-density lipoprotein receptor domain class A
LINK LINK (Hyaluronan binding)
LRR-S leucine rich repeat S
LRR-T leucine rich repeat T
MFAP microfibrillar associated protein
MMP matrix metalloproteinase
PS1 plexin/semaphorin/integrin domain
SDC syndecan domain
SEA sea urchin enterokinase domain
SO somatomedin B like domain
SUSHI SUSHI repeat – complement control protein module
TLL tolloid-like
TSPC thrombospondin C-terminal
TSPN thrombospondin N-terminal
TSPIII thrombospondin type I
TSPNIII thrombospondin type III
VWA von Willebrand factor A
VWC von Willebrand factor C

Many of the diverse interactions between ECM molecules represent druggable opportunities, as the loss of the precise regulation of matrix is known to be implicated in a variety of diseases, including asthma [10], cancer [11], epilepsy [12], hypercholesterolemia [13], inflammatory bowel disease [14], muscular dystrophy [15], osteoarthritis [16], schizophrenia [17], stent restenosis [18], thrombosis [19] and vascular diseases [20,21].

Extracellular matrix drug discovery in an evolutionary context

Extracellular matrix is a key characteristic of all metazoan organisms [22]. The types of matrices formed, however, have been expanded in vertebrates to produce novel tissues, such as bone, tendon and cartilage. Recent analysis has demonstrated that this increase in complexity can be linked to the amplification and diversification of genes involved in the structure, function, signaling and maturation/processing of the ECM during vertebrate evolution [23–26]. By contrast, the mammalian ECM complement has remained relatively stable. There are a few changes exhibited between rodent and primate members of the ADAM and MMP families [25], however such differences are mainly functionally restricted to spermatogenesis, fertilization or expression in the testis [27].

Furthermore, the levels of sequence homology exhibited between ECM families are generally higher compared to most precedented drug targets [28]. For example, cathepsins are a family of cysteine proteases that are important targets for drug discovery, as they play a role in many diseases, such as rheumatoid arthritis and cancer, owing to their broad substrate specificities [29]. An alignment of the seventeen human cathepsins exhibits relatively little conserved sequence across the whole family, even at the active protease domain, when compared to an alignment of a respective ECM family such as the 23 human MMPs (Figures S1 and S2).

The high levels of homology between orthologues in the mammalian ECM have immediate implications for drug discovery and development. First, in terms of their matrices, model organisms are likely to show close correlation with human tissues. Therefore, the understanding of the origin, mechanism and potential treatment of human disease within the ECM is less susceptible to species-specific physiology. Any differences that are exhibited are more likely to be correlated with non-ECM physiology, for example drug metabolism.

Direct study of the evolution of the core domains of ECM proteins can help to inform on their potential druggability. Most ECM proteins exist in multi-gene families where members are highly homologous and generally exhibit similar functions [26]. This form of evolution (known as subfunctionalization) means that the sequences of ECM proteins do not diverge greatly, particularly in the active domains where drug target sites (pharmacophores) are located. Indeed, the tissue specificity may be generated through the evolution of regulatory regions, such as the promoter. Such constrained evolution infers that members of a gene family potentially exhibit promiscuity of drug binding that could result in complex polypharmacology. This could create problems for drug development in some cases, where target specificity is required. For example, attempts to generate cancer therapeutics using broad spectrum MMP inhibitors, such as the second generation MMP inhibitors batimastat, ilomastat and prinomastat, have often failed at clinical trials [30]. Some MMPs repress angiogenesis and inactivate the chemokines that mediate organ-specific metastasis [30,31]. Thus inhibition of these MMPs through broad spectrum MMPs inhibitors can actually be pro-tumorigenic. In such cases a detailed knowledge of family members could be used to aid rational design of specific inhibitors. There may also be opportunities to exploit this conservation to tailor drug polypharmacology to target multiple ECM proteins. It is noteworthy that 10 small molecule drug projects active in 2007 targeted more than one protein from the same ECM gene family by sequence homology alone (e.g. fibrinogen α, β and γ – FGA, FGB and FGG). For example, firategrast, an orally active compound for the treatment

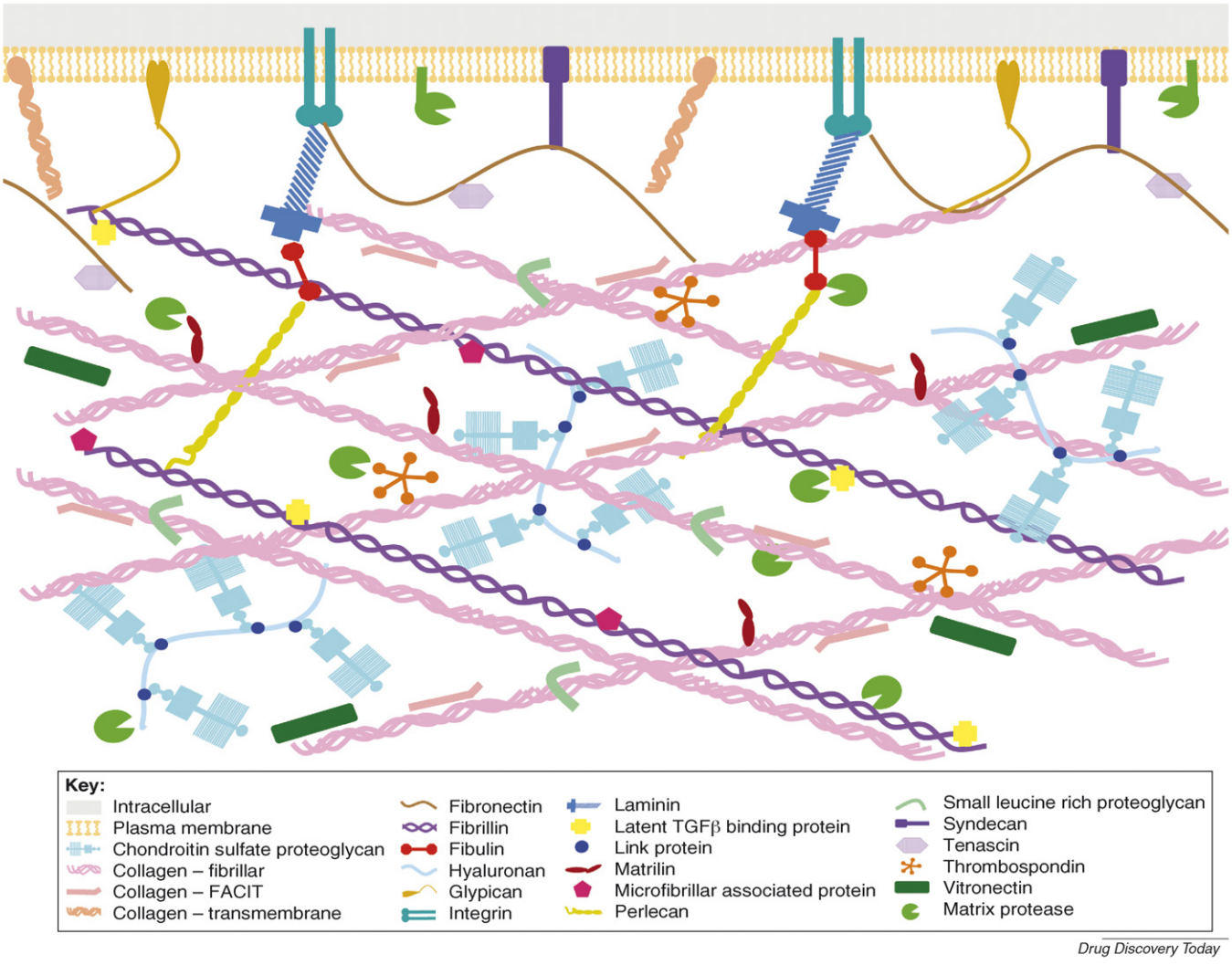


FIGURE 1

The extracellular matrix. Diagrammatic representation of the extracellular matrix depicting major classes of extracellular matrix molecules.

of multiple-sclerosis (Mitsubishi Tanabe Pharmaceuticals), targets both the α4β1 and α4β7 integrin heterodimers owing to the high homology of the two beta proteins (Table S1).

Extracellular matrix druggability

Although several publications have acknowledged the potential significance of the ECM in drug discovery and delivery, most discuss ECM as a barrier to drug delivery rather than a specific target for drug development [32]. By contrast we consider targets in the matrix to be prime opportunities for drug development, possibly leading to highly novel therapeutics.

Biopharmaceutical strategies

As all ECM proteins are secreted, they are all potential targets for therapeutic antibodies (biopharmaceuticals) whether they subsequently partially integrate into the plasma membrane or locate completely within extracellular space. A range of issues would need to be addressed to translate this potential into biopharmaceutical products. On a technical level, development of good antibodies would depend on the antigenicity of the target protein and its degree of extracellular exposure. The subsequent development of a safe biotherapeutic would also depend on the tissue specificity of the target and several other considerations that are not within the scope of this review. Putting these issues aside for a moment, since all components of the ECM are potentially 'biopharmable' this makes the ECM a unique biological system as any individual component or combinations of components could be targeted. Aside from the obvious applications of therapeutic antibodies, this might be equally useful for the development of tools to assist the development of small molecule therapeutics. Despite the apparent biopharmaceutical tractability of the ECM, it is striking to find that biopharmaceuticals are not in the majority of active projects targeting the ECM (Figure 3), reiterating the great potential for development of therapeutic antibodies in this area.

Cell and gene base strategies

To a similar extent, cell and gene based methods of therapeutics are also being used to target the ECM (Figure 3 – annotated as

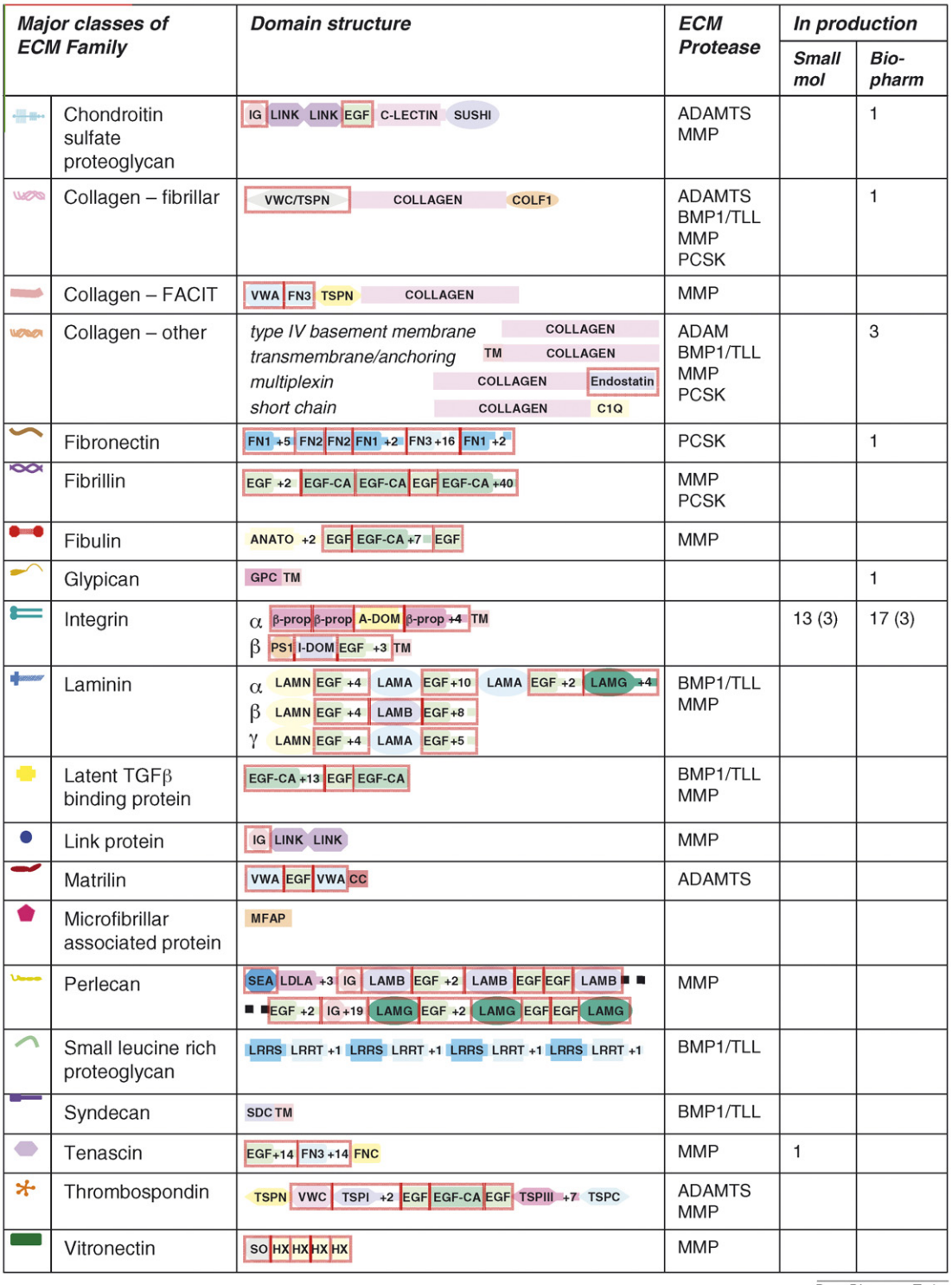


FIGURE 2

Domain structures, protease cleavage and active projects associated with major extracellular matrix protein families. Major extracellular matrix protein families, as depicted in Figure 1, are presented. Extracellular proteases and minor ECM protein families are not included. Information on proteolytic cleavage of proteins obtained from MEROPS [56] and literature [57–61]. Domain structures were obtained from UNIPROT: A-DOM – A domain; ANATO – anaphylatoxin, β-prop – integrin β-propeller; C1Q – C1Q C-terminal domain; CC – coiled coil; COLF1 – C-terminal domain of fibrillar collagen; COLLAGEN – collagenous repeat; EGF – epidermal growth factor; EGFCA – calcium binding epidermal growth factor; endostatin – endostatin C-terminal fragment; FN1 – fibronectin 1; FN2 – fibronectin 2; FN3 – fibronectin 3; FNC – fibronectin C-terminal; GPC – glypican; HX – hemopexin; I-DOM – I-domain (β-A domain); IG – Immunoglobulin-like; LAMA – laminin alpha; LAMB – laminin beta; LAMG – laminin gamma; LAMN – laminin N-terminal; LDLA – low-density lipoprotein receptor domain class A; LINK – LINK Hyaluronan binding; LRR-S – leucine rich repeat S; LRR-T – leucine rich repeat T; MFAP – microfibrillar associated protein; PS1 – plexin/semaphorin/integrin; SDC – Syndecan;

other). In 2007 alone, animal and plant cell based therapies, immunoconjugates, immunotoxins, antisense, gene therapy, RNA interference and recombinant technologies were used in 42 drug discovery projects, of which nearly half (18) were recombinant ECM proteins or recombinant proteins targeting ECM.

Small molecule strategies

Small molecule-based approaches can be used to target many of the ECM proteins by inhibiting the active sites of ECM proteases, blocking the cleavage sites of the ECM protease targets themselves and inhibiting the binding, and subsequent activation, of ECM proteins such as integrins. Indeed, the review of drug discovery projects targeting the ECM (Figure 3) reveals that the majority of studies, in every year analysed, are small molecule-based. This finding confirms that the ECM is substantially druggable and is beginning to be recognised as an important area for drug discovery.

ECM as a mediator of druggability

In addition to targeting the ECM directly, all drug development projects should take the ECM into account. The extracellular microenvironment of the target cell may directly influence the efficacy and result of drug delivery. Not only may drugs bind to ECM proteins themselves, but also the structure of the ECM can often be disrupted in diseases leading to aberrant cell–cell or cell–ECM interactions, cell behaviour and signalling and even response to the therapy itself.

This may be why the perceived notion of ECM is that it is something to circumnavigate rather than target [32]. Degradation of the ECM may be perceived to be a method to increase small molecule delivery to cells, however, in many common diseases such as arthritis and Alzheimer's disease the ECM is already weakened [33,34] and, thus, what may be relatively little damage to a normal ECM could result in an increased breakdown of already compromised tissues. By contrast, dilation of the brain ECM using isotonic buffers has been shown to increase small molecule diffusion by up to 123% [35]. Therefore, ECM can also be positively manipulated to increase the efficacy of small molecule drug delivery.

Matrix metalloproteinases – an evolutionary approach to drug discovery

Matrix metalloproteinases (MMPs) are well established as druggable. MMPs are zinc metalloproteinases that cleave ECM molecules and are involved in the maturation, turnover and healing of the matrix, together with cell proliferation and mobility. Small molecule MMP inhibitors often contain chelating groups, such as carboxylates, hydroxamates and thiols, which tightly bind the catalytic zinc at the active site of the protease domain [21]. We have combined the knowledge gained from understanding both the evolution and druggability of the ECM and drug polypharmacology to expand the potential for drugs that target the MMPs. Phylogenetic analysis of the human protease domain (Figure 4) reveals that the sequences in question are far more similar to each other than previously predicted [25]. Indeed, at the active site of the protease domain, not only are the three histadine residues key for co-ordinating the zinc atom conserved, but a consensus hexapeptide H*EL*GH*AL*G*X*H site can be identified (italics determine the amino acid in the majority of sequences) (Figure S2). Similarity of the MMPs across this hexapeptide region is further reinforced by comparing the ability to binding substrates, revealing MMPs 1, 2, 3, 7 and 9 have significantly similar binding sites ($R^2 > 0.7$) [36] and that conformational changes resulting from the protein binding may generate subsequent substrate specificity.

One example where we can compare compound activities across different MMPs against sequence similarity is CGS-27023A, an orally administered MMP2, MMP8 and MMP9 inhibitor developed by Novartis (Table S1). CGS-27023A is a sulphonamide hydroxamic acid that competitively binds to the zinc ion at the active site of MMPs, inhibiting their activity [37]. Although marketed as an inhibitor for MMP2, MMP8 and MMP9, structures of CGS-27023A complexed with MMP1, MMP3 and MMP13 showing nearly identical binding modes have been reported [38]. The effective concentration of CGS-27023A required for MMP inhibition correlates with the percentage identity to MMP2 or MMP9, where MMPs with more divergent protease domains are less efficiently inhibited by CGS-27023A (Table S3). It is of note that the fibronectin domain sequence present in the protease domains of MMP2 and MMP9 were excluded, as CGS-27023A does not target this site.

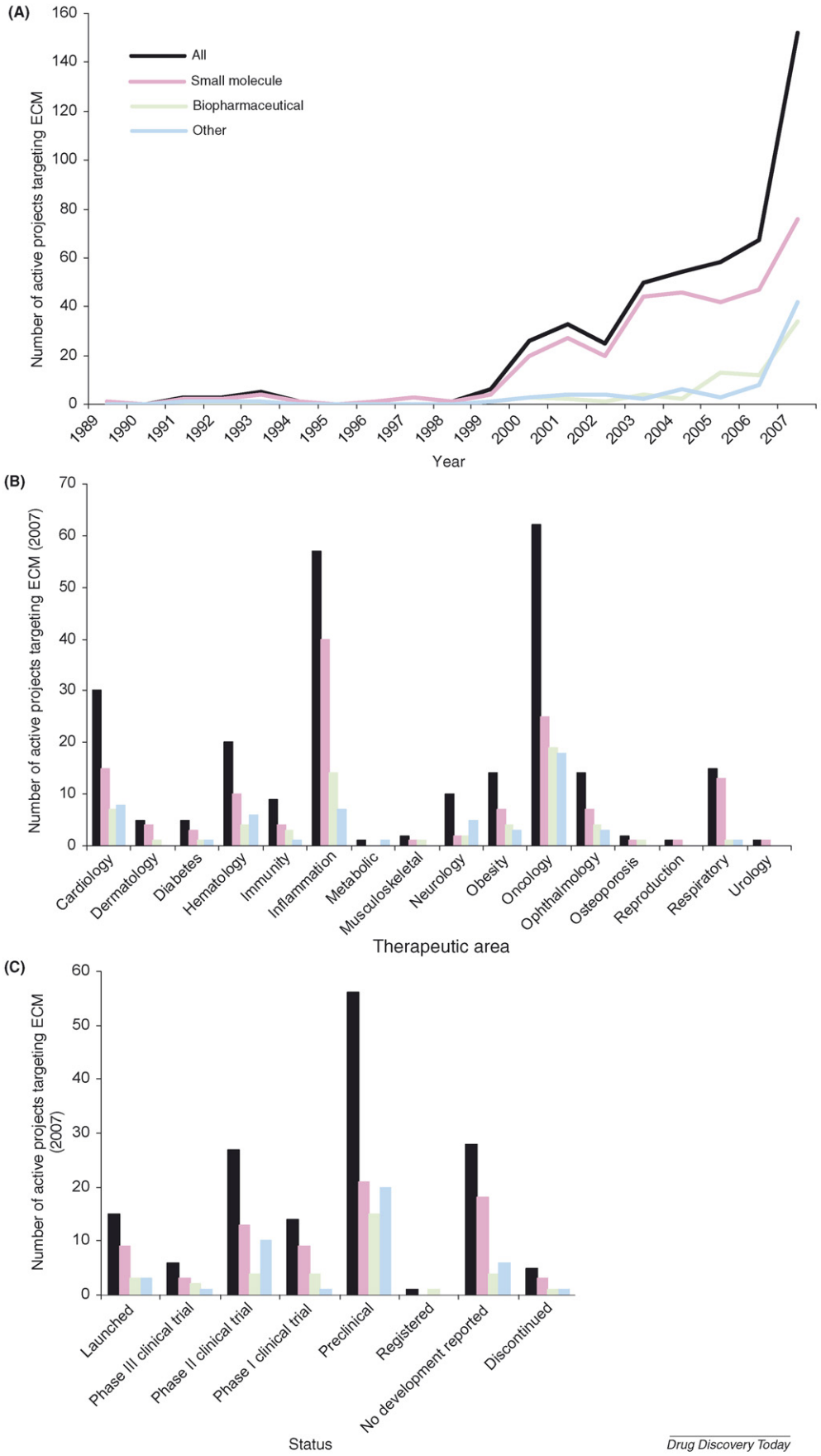
Overlaying annotation of MMPs in drug discovery reveals that members of each of the three clades (Figure 4) have been targeted by small molecule drugs. This finding has important consequences for the interpretation of druggability of the ECM, as small molecules targeting the active sites of MMPs could be more 'polypharmable' than previously considered. Combining mouse knockout phenotypes ([39] and the Mouse Genome Informatics database http://www.informatics.jax.org/) with this analysis provides insight into the spectrum of diseases that could be targeted by MMP inhibition, such as inflammatory diseases, osteoarthritis, cancer and obesity (Figure 4). In addition, biopharmaceutical technology is also being used on MMPs: for example MMP14 is in preclinical studies as a cancer therapeutic (Dyax DX-2400).

A new classification of druggability

By its most general definition, druggability is indicated by the presence of a protein fold that favours interactions with small molecules that satisfy Lipinski's rule of five [40]. Previous analyses have estimated that ~3000 genes meet these criteria – the so called 'druggable genome' [41]. However, for a protein to be considered as a validated drug target it must either play a direct role in disease, or otherwise influence pathways involved in disease. Around 10% of the human genome is believed to be involved in disease onset or progression [28], but these do not substantially overlap with the ~3000 genes that are considered druggable. A recent analysis by Sakharkar [42] analysed these two datasets to generate a curated list of 523 druggable disease genes. When this dataset was compared against the 341 ECM genes, 66 were disease related and 21 druggable.

As demonstrated from the review of active drug projects above, however, we find that much more of the ECM is druggable. Indeed, in 2007 alone, 76 small molecule drug discovery projects targeting

SEA – sea urchin enterokinase; SO – somatomedin B like; SUSHI – SUSHI repeat complement control protein module; TSPC – thrombospondin C-terminal; TSPN – thrombospondin N-terminal; TSPI – thrombospondin type I; TSPNIII – thrombospondin type III; VWA – von Willebrand factor A; VWC – von Willebrand factor C. Annotation of potentially druggable domains was obtained from [62]. Annotation on active small molecule and biopharmaceutical drug projects is located in Supplementary material.


(A)
Number of active projects targeting ECM
All
Small molecule
Biopharmaceutical
Other
Year
(B)
Number of active projects targeting ECM (2007)
Cardiology
Dermatology
Diabetes
Hematology
Immunity
Inflammation
Metabolic
Musculoskeletal
Neurology
Obesity
Oncology
Ophthalmology
Osteoporosis
Reproduction
Respiratory
Urology
Therapeutic area
(C)
Number of active projects targeting ECM (2007)
Launched
Phase III clinical trial
Phase II clinical trial
Phase I clinical trial
Preclinical
Registered
No development reported
Discontinued
Status
Drug Discovery Today

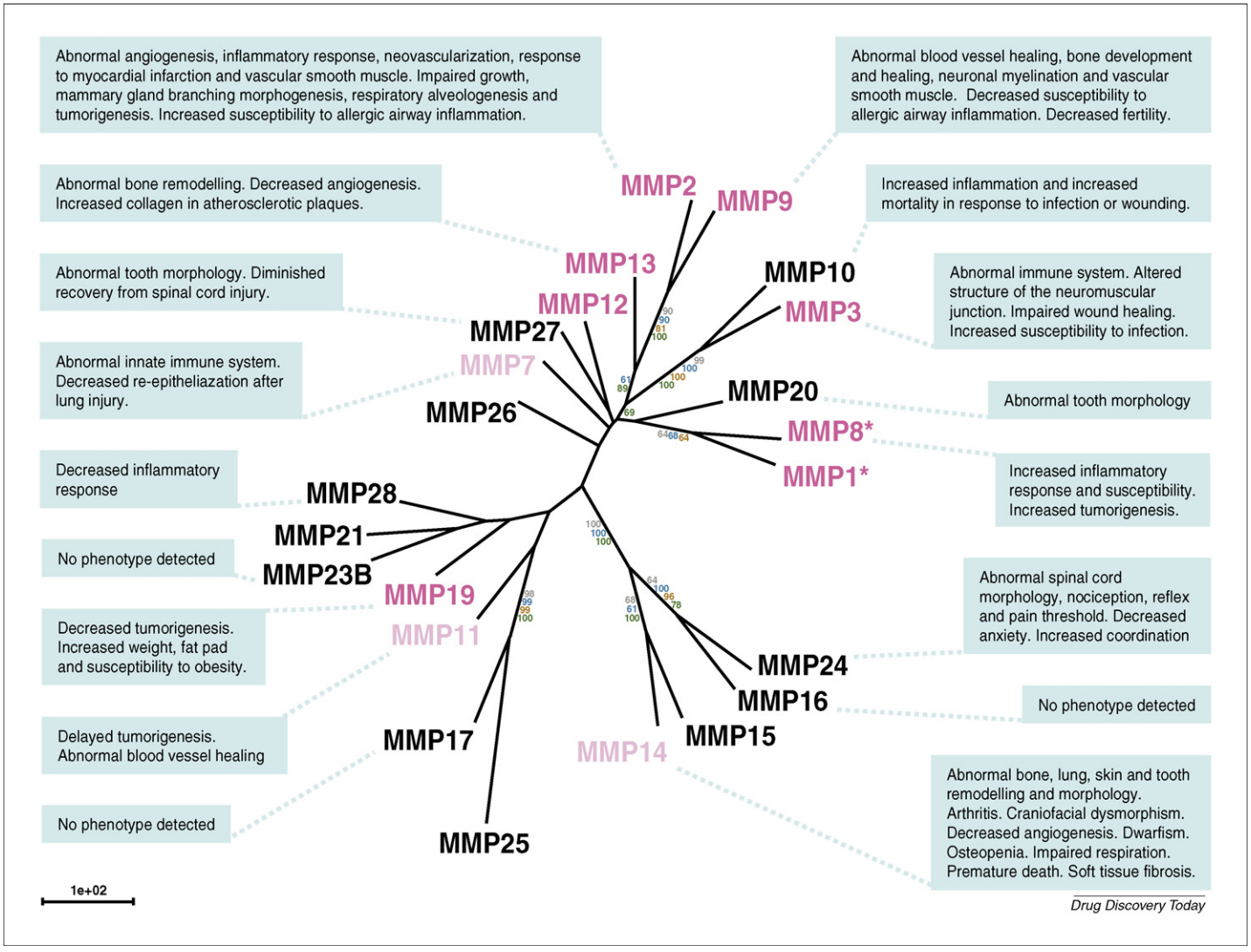


FIGURE 4

Matrix metalloproteinase evolution and druggability. Phylogenetic relationships of the human MMP protease domain (active site) sequences (Zinc Metalloproteinase Domain defined by EMBL Simple Modular Architecture Research Tool). Phylogenetic analysis was performed based upon previously published methods [26]. The tree shown was generated by inferring Maximum Likelihood from a gap-stripped multiple sequence alignment generated in CLUSTALX [63]. Neighbor joining, maximum parsimony and maximum likelihood trees (each 1000 bootstrap replicates) were generated using PHYLIP [64]. Bayesian tree inference values were produced from MRBAYES [65]. The scale bar corresponds to 1e + 02 amino acid replacements per site (horizontal axis). Knockout phenotypes were obtained from Jackson laboratories and literature [39]. MMPs are highlighted based on small molecule drug project targeting: active 2007 – bright pink; pre-2007 – light pink; * – drug launched.

57 ECM molecules were reported in pharmaceutical R&D pipelines, of which nine were launched (Tables S1 and S2). By extension, family members related to known ECM targets associated with active small molecules should also be annotated as druggable. We have annotated these genes using a tiered system, where ECM molecules associated with launched drug projects were annotated as tier 1 and those linked to projects active in 2007 were annotated as tier 2 (Table S2). Additional members of ECM gene families with tier 1 or 2 members, based upon ECM phylogenies [23–26], were annotated as tier 3 with evolutionary and paralogy relationships indicated by percentage identity values to tier 1 and 2 genes (Table S2). For example, out of the 23 MMPs, two are tier 1 (MMP1 and MMP8), six are tier 2 (MMP2, MMP3, MMP9. MMP12, MMP13 and MMP18), and the remaining 15 MMPs are annotated as tier 3 with percentage identity to tier 1 and 2 MMPs. This annotation provides a direct indication of targets that are

FIGURE 3

Drug discovery in the extracellular matrix. **(A)** Drug discovery projects targeting ECM proteins per year. **(B)** Drug discovery projects targeting ECM proteins in 2007 by status. **(C)** Active drug discovery projects targeting extracellular matrix proteins in 2007 by therapeutic area. Colouring depicts the types of drug discovery projects in progress that target extracellular matrix (ECM): small molecule drug discovery – pink; biopharmaceutical (antibody) – green; other (animal/plant derived, antisense, gene therapy, immunoconjugates, recombinants, RNAi and imaging agents) – blue. Annotation of drug discovery projects was obtained from Pharmaprojects (PJB Publications Ltd.) and R&D Focus (IMS World Publications Ltd.). It is of note that some projects target multiple therapeutic areas or matrix proteins.

most likely to exhibit drug polypharmacology and heuristically reflects the complex evolutionary relationships seen within this family [25].

It should be noted that if one ignores the evolutionary history of gene families and restricts the percentage identity, based upon the assumption that proteins related to 50% identity are likely to show related pharmacology [43], 65 ECM genes are annotated as tier 3. As demonstrated in the MMP gene family, however, understanding both the sequence homology at the active site and the evolutionary relationship of the gene family itself can provide a far greater insight into potential druggability. Thus, we demonstrate that an evolutionary approach to the analysis of drug targets and their paralogues has revealed more of the untapped potential for drug discovery in the ECM and the genome in general.

Therapeutic indications of the extracellular matrix

ECM molecules are implicated in a wide variety of diseases, many of which result in a disrupted matrix. This is reflected in the distribution of disease indications for drug projects targeting ECM (Table S1, Figure 3). Although many drugs that modulate the function of ECM molecules are therapeutics for cancer, it is not surprising that the majority of ECM-associated drug projects aim to treat inflammatory diseases, such as arthritis and inflammatory bowel disease, where the matrix is often weakened.

As expected, the dominant trend in ECM drug discovery is the targeting of proteases and integrins (Tables S1 and S2). Mutations in integrin chains are associated with rare genetic diseases such as thrombocytopenia [44], myopathy [45] and epidermolysis bullosa [46] and more common disorders, such as arthritis, asthma, cancer, cardiovascular and inflammatory diseases and thrombosis that are targeted by integrin antagonists (Table S1). The second core group of drugs associated with the ECM are mainly metzincin (ADAM, ADAMTS, BMP1/TLL and MMP) inhibitors that target the zinc metalloproteinase active domain conserved within these four gene families. To date these have mainly been targeted for arthritis and cancer (Figure 3 and Table S1). The metzincin proteases that cleave unique substrates are, however, also targets for other therapeutic areas. For example, MMP12 cleaves elastin and is a target for chronic obstructive pulmonary disease and ADAMTS13 cleaves the glycoprotein von Willebrand Factor (VWF) and is a target for clotting and menstruation disorders (Table S1). Non-metzincin ECM proteases are also being exploited. Hyaluronoglucosaminidases are involved in the degradation of hyaluronan and HYAL1 is currently a target for dermatological disease (Table S1). It is of note that HYAL1 is one of several related genes in a region of chromosome 3p21.3 whose loss is correlated with tumor suppression [47].

The type of ECM molecules associated with drug projects is, however, much wider. Osteonectin (SPARC) is a small single chain polypeptide expressed in endothelia in response to tissue injury and is targeted for cancer and cardiovascular disease (Table S1). In addition, the glycoproteins perlecan (HSPG2), tenascin C (TNC), fibrinogen-like 1 (FGL1), fibrinogen and von Willebrand factor (VWF) are currently being targeted for atherosclerosis, vasodilation, cognition, clotting and thrombosis respectively (Table S1). Although structural ECM molecules are generally not considered druggable, owing to the lack of an obvious pharmacophore, inhibition of mucins has been suggested as a potential therapeutic strategy for chronic airway disorders diseases such as asthma, COPD and cystic fibrosis [48]. In addition, mucin 1 is currently targeted by some treatments for immune disorders and cancer (Table S1).

It is of note that BioAlliance's anti-cancer AMEP compound targets both ADAM and integrin genes (ADAM15, ITGAV and ITGB3). Integrin αVβ3, is widely expressed in various cells including endothelia, osteoblasts, osteoclasts, platelets and vascular smooth muscle cells, interacts with many ECM proteins including fibronectin, fibrinogen, osteopontin and vitronectin through their RGD domains [11,49] and is involved in a variety of processes including angiogenesis, where it is required for maturation and subsequent survival of new blood vessels, apoptosis and osteogenesis (bone resorption) [49,50]. Integrin αVβ3 is also expressed in tumors where induced angiogenesis occurs. Aberrant neovascularization is also implicated in a variety of disorders, such as rheumatoid arthritis [51], restenosis [52] and retinopathy [53]. Thus, a drug blocking the activity of the αVβ3 integrin could be a key therapeutic for a variety of areas. Through its disintegrin-like domain, ADAM15 specifically interacts with the integrin beta chain, beta 3 (ITGB3) acting as an adhesion receptor [54] and is, therefore, also implicated in these diseases. If is of note that the AMEP compound may act to inhibit multiple protein-protein interactions and may also affect other proteins associated with this complex.

Not only can drugs targeting ECM be polypharmacological in the extent that they target multiple proteins, multiple-diseases can also potentially be treated by a single therapeutic. A good example of the potential of a single ECM protease inhibitor to target multiple diseases exists in ADAM15. This protease is strongly upregulated in Inflammatory Bowel Disease [55]. In addition, the role of ADAM15 as an adhesion receptor for platelet αVβ3 integrin leads to platelet activation, secretion and promotes thrombus formation. ADAM15 also has a role in mediating the aggregation of T-lymphocytes in epithelia influencing epithelial restitution and production of pro-inflammatory mediators [55]. Altogether, these findings point to ADAM15 being a possible therapeutic target for the prevention of inappropriate T cell activation or for antithrombotic strategies in cardiovascular pathologies.

As well as being a characteristic of many diseases, weakened connective tissue is also a trait in ageing. Thus, ECM molecules may be considered important biomarkers, or even targets, for understanding both the mechanisms of ageing and potential additional factor of predominantly late onset diseases such as osteoarthritis and Alzheimer's disease.

Conclusion

The ECM is important in the maintenance of the structure, function and signalling of tissues. Disruption to the ECM is implicated in a wide range of diseases. All components of the ECM are potential targets for biopharmaceutical strategies. In addition, we have demonstrated that much of the ECM is druggable and is beginning to be targeted by small molecules. Considering the pan-therapeutic potential of matrix modulation, a better understanding of the ECM and drugs that modulate it may be of great importance to the future of drug discovery.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2008.05.005.

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