Review

Prospective of extracellular matrix and drug correlations in disease management

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ABSTRACT

The extracellular matrix (ECM) comprises of many structural molecules that constitute the extracellular environment. ECM molecules are characterized by specific features like diversity, complexity and signaling, which are also results of improvement or development of disease mediated by some physiological changes. Several drugs have also been used to manage diseases and they have been reported to modulate ECM assembly, including physiological changes, beyond their primary targets and ECM metabolism. This review highlights the alteration of ECM environment for diseases and effect of different classes of drugs like nonsteroidal anti-inflammatory drugs, immune suppressant drug, steroids on ECM or its components. Thus, it is summarized from previously conducted researches that diseases can be managed by targeting specific components of ECM which are involved in the pathophysiology of diseases. Moreover, the drug delivery focused on targeting the ECM components also has the potential for the discovery of targeted and site specific release of drugs. Therefore, ECM or its components could be future targets for the development of new drugs for controlling various disease conditions including neurodegenerative diseases and cancers.

1. Introduction

The extracellular matrix (ECM) comprises of diverse structural molecules which are involved in structural support, including cellular signaling. These molecules are classified as proteins, proteoglycans or their components like elastin, collagens, hyaluronan, and noncollagenous proteins with carbohydrates moiety [1] (Fig. 1). The communication through these molecules results in focal adhesion and alteration in cell morphology and movement. Moreover, it has been reported that progression of a disease is the result of any dynamic change in structural components of ECM. The disease could be managed using such therapeutic molecules that help to control these changes of ECM environment. Many scientific reports have explained that ECM could be a bridge for disease progression and management [2,3]. It has been well established that organization of ECM molecules has its own distinct features and responsible for the diverse biological activities [2,3]. Structural changes, even a single amino acid change in ECM peptide sequence can lead to significant
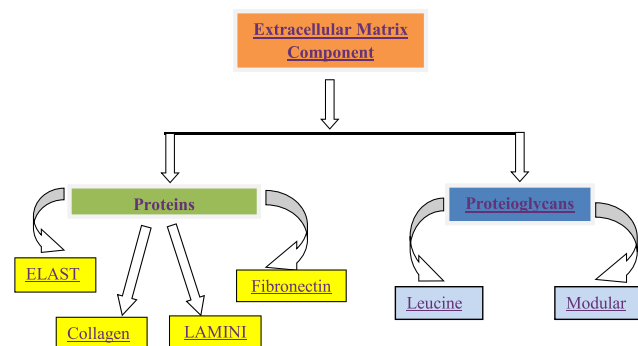

Fig. 1 – Showing different class of ECM and its different components for drug Targeting.
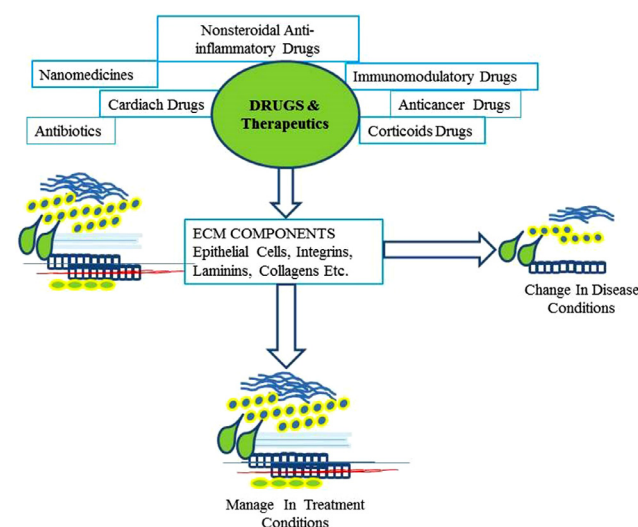

Fig. 2 – Showing ECM and its different component in pathophysiology of diseases and drugs Correlations.

changes in cellular physicochemical properties required for the progression of the disease. Many chemicals or drugs, like anti-inflammatory, anticancers, cardiac, immunomodulatory drugs or biological molecules such as metalloproteinase (MPs), have been tested to inhibit and remodel/degrade the structural components of ECM molecules (Fig. 2). Moreover, the chemical agents or antibiotics have also been reported to cause some specific changes in ECM environments of these molecules even in the organ like brain, liver, vascular system, kidney, lungs and skin or even in resistant microbial cells [4]. The use of modern technologies such as genetic engineering, specifically antisense and gene therapies including RNA interference, have been tested for disease management [5]. These new technologies have shown promising prospectives in the development of effective ways for the treatment of many human diseases [6,7].

The dynamic structural nature of ECM has encouraged scientists worldwide to accelerate the researches in the field of neurobiology and to find out attractive therapeutic targets that could be beneficial to control the diseases. It has been well established that many endopeptidases degraded ECM molecules which are also known as matrixins are characterized as zinc-dependent catalytic proteins.

These matrixins play a significant role in the reproduction, development of embryo, morphogenesis and tissue desorption as well as for remodeling and activation/inhibition. They are secreted in response to oxidative stress, UV radiation and cytokines [8]. The synthesis of ECM has been described through the control of growth factors [9,10], and their life is determined by matrix metalloproteases (MMPs) [11]. The increase in MMPs activity has been observed in various physiological and disease condition. They are characterized by location, substrate specificity and regulation. The significant contribution of these enzymes has been described in photoaging [12], wound healing [13,14], skeletal growth or remodeling, arthritis, inflammation, angiogenesis and cancers [15]. These previously described researches probably stated that progression of any disease is due to qualitative and/or quantitative alteration in the ECM environment. Therefore, it is crucial to elaborate differences between the changes of ECM in diseased conditions. Moreover, it has been reported that pathophysiology of the disease is the result of variability of ECM which can be reversed or regulated by prescribed drugs, to the patient [16]. Thus, the ECM molecule targeted therapeutic strategies will be fruitful to manage diseases, including cancers and neurological disorders.

2. Drugs and ECM

The communication of signaling molecules has resulted in many functions, including focal adhesions and alteration in cell morphology and movement. Moreover, any dynamic change in structural components of ECM molecules (generally by drugs) may lead to either progression of disease or its curing [2]. The changes in ECM environment is thought to be cause of various diseases, and influence of drug on ECM components in treatment of diseases have been well explored here. The various ECM components in many diseases are summarized in Table 1 and effects of particular class of drug on ECM are described in the following sections.

2.1. Nonsteroidal anti-inflammatory drugs and ECM

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins (PGs), and these drugs affect many pathophysiological and physiological processes like inflammation, blood clotting, wound healing, kidney function and cardiovascular disease. It has been well reported that PG synthesis is regulated by the catalytic activity of cyclooxygenase-1 (COX-1) and COX-2 on arachidonic acid. COX-2 has also been reported as a tumor promoter component of ECM and its increased synthesis can lead to a change in the ECM environment which have been observed in many cancers, including oesophagal, colon, lung, gastric, breast and pancreatic cancers. Further, NSAIDs have also been reported to affect the expression of a small leucine-rich proteoglycan (SLRPGs), in prostate cancer. Thus, NSAIDs drugs inhibit COXs, affect ECM components and exert its chemoprotective effects in many cancers [17]. Breast cancer patients diagnosed with postpartum have been reported with poor cancer prognosis and these can play a significant role as a diagnostic marker for breast cancer. In recently conducted studied in rats, the

Table 1 – Representing drug targeting ECM molecules for the management of disease.

Drug/Class of Drug	Effect on ECM	Disease condition	Ref
NSAID	TGF synthesis	Ameliorate fibrotic processes	[22]
	Proteolytic degradation of MMPS		
	MMPs inhibition	Inflamation	[27]
	Regulation of protein tenascin-C in cancerious cell	Inflamation	[27]
Cyclosporin	Increased, MMP-9, TIMP-1 activity	Inflamation	
ISD	Increased in synthesis of type collagen IV, V and fibronectin	MPGN type I, glomerulosclerosis and interstitial fibrosis	[36]
	Increased Collagen, GAG and DNA synthesis	Fibrotic tissue in gingiva and kidney	[37,38]
Everolimus	DecreasingVEGF and release of IL	Prevant migration, adhesion and detachment	[39]
Euclaptol	Decrease in MMP-9 expression and NF-ΚB	Pulmonary inflamation	[41]
Glucocorticoid	GCs inhibit MAPK pathway and activation of FAK	Inflamation	[49]
Bethamethasone	expression of MMP-2 and MMP-9 decreased	Lungs diseases	[49]
	Increased level of T3, COL and m-RNA alkaline phosphatase activity	Cartilage	[49]
Captopril	Reduces ECM expression like TGF-β	Acute and chronic inflammatory diseases	[49]
Nifedipine and Amlodipine	Reduces expression of TGF-β	Cardiac diseases	[70–72]
Lovastatin	Reduces CTGF expression	Fibrotic explants	[73]
Levosimendon	Decreases the MMP-2 serum level	Heart failure	[73]
Bosentan	Increase MMP-9 serum	Pulmonary arterial hypertension	[74,75]
Bleomycin	Inhibitory effect on expression of MMP-9, TIMP-1, INF-γ and TGF-β	Pulmonary fibrosis	[80]
Cyclophosphamide	Inhibitory effect on expression of MMP-9, TIMP-1, INF-γ and TGF-β	Pulmonary fibrosis	[82]
Doxycycline	Decrease in VEGF-C/VEGF receptor 3 signaling, IL-1β, TNF-α and VEGF-C macrophage infiltration and inflammatory cytokine expression	Lymphangiogenesis	[83]
Fluoroquinolon	Effect on MMPs	Fluoroquinolon	[86]
Vancomycin	Expression of specific sequence D-Ala-D-Lac or D-Ala-D-Ser	Resistant bacteria	[86,87]
Taxol, Doxorubicin	Affect exression of integrin, MMPS and cell migration	Cancerious cell	[89]
Thalidomide	Inhibition of epression of VEGF-165 and MMP-2	Lung cancer	[92]
Thiazolidinediones	Inhibition of TGF-1 or CTGF gene expression	Antiosteoblastogenic and proadipocytic	[97,98]
Vedolizumab	Target integrins	Crohn's disease, cardiac hypertrophy, atherosclerosis and tumorigenesis	[110–112]

mammary ECM has been reported with tumor inhibitory properties. In contrast, postpartum mammary gland reported with tumors promotional activity and NSAIDs are reported suppressive in this context by targeting the ECM s with an additional protective effect in the mammary ECM.

The other matrix components like fibronectin, fibrillar collagens, matricellular proteins and hyaluronan have been associated not only in ovulation but also in breast cancers. The regulation of bone physiology or osteology of bone depends on the level of signaling molecules or their receptors, for example an increased expression of transforming growth factor $\beta1$(TGFβ1), but its receptors TGFβ-R1, TGFβ-R2 and TFGβ-R3 expression was not observed. The reduced expressions of bone morphogenetic protein (BMP-7), collagen I (COL-I), Runt-related transcription factor-2, and osterix were reported with the use of NSAIDs [18]. Moreover, other than the release of PGs, MMPs have also been released from macrophages which damage the ECM and causes vascular remodeling. Similarly, the involvement of ECM in wound healing has also been explored which is strictly a sequential process starting with hemostasis, followed by inflammation, formation of ECM, formation or proliferation and remodeling of collagen with vascular regression and finally maturation. These drugs can inhibit COX pathways and disrupt many processes, especially at the proliferation step.

ECM is characterized on the basis of biochemical and structural features, and these features mediate specific signals to particular cells to modulate basic step of signaling that are important in inflammation, including migration of immune cell to targeted tissues and results of sensitization to produce immune cell in response to inflammation. It has been reported that in chronically inflamed tissues, the nature of produced ECM components leads to the activation of immune cell and their survival is due to the exerted required immune responses at the sites of inflammation [19].

Tumor necrosis factors (TNF), steroid drugs and some immunomodulatory therapeutics are the choices of drug to cure the inflammation [20,21]. However, the use of these drugs in the management of inflammation may result in beneficial or non-beneficial effect on ECM. The inflammation is generally mediated by the release of PG in the response of various injuries [20]. It has been reported that these drugs significantly affect the molecular environment of ECM components. PG synthesis inhibitors or NSAIDS generally inhibits COX enzymes to prevent the release of PGs. It has also been reported that they exert their effect on synthesis

of extracellular components like TGF [22] and are able to ameliorate fibrotic processes. Proteolytic degradation of MMPs has also been reported in the inflammation. These anti-inflammatory drugs have also been highlighted to influence not only the activity of MMPs but also the synthesis of cellular enzymes. The effects of ECM in skin tissue by immunomodulatory drugs and the interleukin-1 (IL-1) inhibitor such as anakinra have also been reported [23,24].

Moreover, corticoids have also been reported to be the most favored drug for curing various inflammation which are extensively involved in changing or affecting the ECM components [25]. Adverse effect on bones like premature osteoporosis has been observed by the use of steroidal drugs when they are used to manage the inflammation [26]. The molecular mechanisms of inhibition of MMPs by NS398, selective COX-2 inhibitor and indomethacin have been studied [27]. The authors reported that the synthesis of enzymatic protein and enzymatic activity of MMP-2 in the cancerous cell have been reported elevated, which is due to the binding of specificity protein (Sp) 1 and Sp3 protein constitutively to the consensus sequence. NSAIDs drugs have also been reported to inhibit the phosphorylation, Sp1 DNA binding, and basal and serum-stimulated ERK activity which results in suppressing of the MMP-2 activity. Moreover, the promoter activity and Sp1 phosphorylation of MMP-2 are inhibited by the MEK inhibitor PD98059. They also suggested that over expression of active mitogen-activated protein kinase (MAPKK or MEK) resulted in the antagonizing of NSAIDs activity due to the stimulation of MMP-2 promoter activity and Sp1 phosphorylation [27]. It has also been well reported from *in vivo* and *in vitro* experimentation that anti-angiogenesis and anti-metastasis activities of NSAIDs directly affect the ECM components [28,29]. NSAIDs have also been described to target the ECM components in the cancerous cells of the postpartum mammary gland. In this study, authors reported that the elevated level of extracellular protein tenascin-C, could be regulated by NSAIDs drug [30].

2.2.   *Immunomodulatory and immune suppressant drugs and ECM*

The material and drugs have not only been used to harness the immune system but it also finds applications in drug delivery. Currently, it has been reported that ECM has the ability to modulate the immune responses, which is mediated due to the presence of bioactive motifs in ECM. Moreover, ECM proteins like fibrin, collagen, hyaluronic acid-based materials and synthetic material with immunomodulatory domains like MMP-sensitive peptides, Arg-Gly-Asp (RGD), or leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) ligands have been reported with immunological responses [31].

Moreover, the immunomodulatory, anti-inflammatory and corticosteroids drugs like prednisone hydrocortisone have also been reported to modulate various immunological responses via ECM components. Dexamethasone is the choice of immunomodulatory drug has been prescribed in the management of many diseases. They generally act either by genomic mode or non-genomic mode. However, their physiological behavior towards ECM or its components have

been reported to be distinct like synthesis and modulation of the many kinds of collagen, influence on many proteoglycans decorin and biglycan, suppression of MMP synthesis and activity, and influence on tissue inhibitor of metalloproteases (TIMPs) synthesis and their activities [32]

The immunosuppressive drugs or chemical agents such as proteins, antibodies as monoclonal or polyclonal, intravenous immune globulin and glucocorticoids are the common agents which suppresses the immune response. They reduce the risk of rejection and are a choice of drug for transplantation. These drugs have been tested in cancer chemotherapy, and rheumatoid arthritis and because of their immuno-suppressive nature, they increase the chances of infection. Calcineurin inhibitors (CNI's) like cyclosporine, tacrolimus helps to maintain the normal function of graft tissue. IL inhibitors like sirolimus and everolimus are known to target rampamycin inhibitors, and have been reported to exert their immunosuppressive activity by inhibiting p70S6 kinase and arresting progression of cell cycle resulted in blockade of IL-15 and IL-2 mediated B and T cell proliferation. The influence of TNF-α inhibitors on ECM or its components have also been reported (TNF-α) has been reported to exert beneficial effects on metabolism and glycosaminoglycans (GAGs) and proteoglycans (PGs) tissue in females with rheumatoid arthritis (RA),

Although the immunosuppressive drugs affect collagen and fibrosis synthesis, and inhibit the MMPs activities, the mechanism of action of each class of drug is different [33]. Methotrexate, a dihydrofolate reductase inhibitor inhibits the pyrimidine synthesis and stops fibrogenesis. [34]. Fornoni et al. [35] described that post-transplant bone defect as MC3T3-E1 osteoblasts's association with the cyclosporin A that lead the degradation as well as the synthesis of ECM components. Moreover, when cyclosporin A was administered at 5 mg/ml, an increased MMP-9 activity was observed after 72 h, however, the TIMP-1 and MMP-2 activities remained unaffected while protein accumulation and collagen type I mRNA expression decreased.

The membranoproliferative glomerulonephritis (MPGN) type I associated children when treated with immuno suppresive drugs (ISD) have been observed with increased collagen IV, collagen V and fibronectin in expanded meningeal areas [36]. Heart transplant patients are also treated with cyclosporin and prolong exposure of this drug is always associated with glomerulosclerosis and interstitial fibrosis. Ghiggeri et al. conducted a study using human mesangial cells (hMC) and rat MC (rMC) and concluded that pathogenesis of the disease is associated with an increase in the synthesis of extracellular components like specific collagen III. Cyclosporins have been reported to induce 330% human fibroblast (hFib),110% renal fibroblast (rFib), 170% rMC, 100% hMC, and 130% human tubular epithelia. Moreover, 70-kDa protein has also been observed. However, the synthesis of collagen I and collagen IV has been reported to be unaffected even at high dosage of 5 ng/ml of this class of drugs [37]. Fibrous hyperplasia is another side effect of cyclosporin, which are results of the proliferation of fibroblasts and formation of fibrotic tissue in the gingiva and kidney. A dose-dependent increase in DNA synthesis and reduced glycosarninoglycan(GAG) synthesis was reported

when incubated for 72 h and prolong exposure resulted in increased collagen and GAG synthesis [38].

Everolimus has a significant role in preventing cardiac allograft vasculopathy (CAV), and it is generally prescribed for a heart transplant patient. Everolimus and sirolimus are well-known rapamycin which selectively inhibit mTOR signaling and potentially inhibit the inflammation by decreasing endothelial growth factor (VEGF)($\approx$−65%) and IL-8 release ($\approx$−80%) and inhibits the secretion of receptor antagonist of cytokine IL-1. Moreover, everolimus also has an effect on TNF-α-treated neutrophils and decreases the secretion of IL-8 and VEGF, while contrary stimulating the release of IL-1 receptor antagonist RA. Similar effect has been reported with combination therapy of everolimus and other immunosuppressive drugs. Moreover, everolimus and sirolimus reduce the neutrophil adhesion of human ECM and human endothelial cells β2-integrin/CD18 activation [39].

Attachment and detachment are the two basic processes of inflammation which are mediated by IL-2 but degraded by enzyme neutrophil elastase, which prevent the adherence to laminin, collagen IV and fibronectin. Therefore, to stop inflammation, their migration, adhesion and detachment must be prevented [40]. Eucalyptol has also been known for its anti-inflammatory effect on lung, and its use in cases of pulmonary inflammation has been seen to exert anti-inflammatory actions. It works by decreasing the MMP-9 expression by reducing the level of phosphorylated extracellular signal-regulated kinase protein (NF-ΚB). All these factors described here have been reported to increase in the pulmonary inflammation [41].

2.3. Corticoids drugs and ECM

The mode of action of the glucocorticoid receptor in ECM in mammalian voluntary muscle fiber has been well reported by many workers. Glucocorticoids (GCs) inhibit MAPK pathway in most cells, and they do so either by activating the synthesis of proteins like Glu-induced-leucine zipper, MAPK phosphatase-I and Annexin-I, or by directly activating the components of the MAPK pathway. Studies reported that the receptors through which GC shows their actions in skeletal muscle fibers are located near to the cell surface and the stimulation of these receptors resulted in the activation of focal adhesion kinase (FAK). Moreover, the conformational change brought in laminine facilitated their binding to the integrin α7β1 and destroglycan [42]. Further studies reported that receptors localized in ECM, satellite cells, and area surrounding the mitochondria have been found to play an important role in voluntary muscle differentiation, repair and regeneration [43–45]. The structural changes in the ECM of lungs tissue have also been reported in chronic obstructive pulmonary disease (COPD) and asthma. Corticosteroids alters total ECM and fibroblast deposition in a samples with no serum. The inhaler and beta(2)-agonists, especially long-acting, are the choice of drugs to treat both COPD and asthma diseases [46].

It has been reported that miR-29c is involved in offspring carotid artery remodeling. Recently, it has been observed that there is correlation between synthesis of miR-29c and ECM proteins. A recent study was conducted to demonstrate the effect of under nutritional on offspring carotid arteries remodeling. It has been concluded that the expression of ECM protein components has close relation with miR-29c and any change in miR-29c expression resulted in the change in ECM. To explain this, the study consisted of three groups, and in group-1, 50% were kept on restricted diet started at last half of gestation period, group-2 was maternal under nutrition with metyrapone given from 10 d of gestation, and group-3 was control feed. The observed miR-29c expression was reported differently which was observed at 3 weeks, 3 months and 9 months for groups-1, groups-2 and groups-3 respectively. The maternal under nutrition group has also been described with increased expression for MMP2 and elastin mRNA while increased level of COL4A5 and COL3A1 was reported with group-3. Thus, expression of these with maternal under nutrition group has not seen due to blocking effect of metyrapone on expression [47]. Moreover, a study was conducted to observe the influence of GC on miR-29c and its expected targets in rat aorta smooth muscle cells RAOMCs.

It was found that both Dexamethasone (DEX) and corticosterone (COR) increases the miR-29c synthesis and decreases the synthesis of COL3A1, elastin (ELN), COL4A5 genes and MMP2 in RAOMC, and mifepristone has been reported to block these function. Moreover, miR-29c has also targeted these genes which are confirmed by a decrease in luciferase reporter activity of collagen gene (COL) 4A5 (45%), COL3A1 (35%), (ELN) (17%) and MMP2 (28%) with level of COL3A1 (51% and 16%), COL4A5 (56% and 22%), ELN (53% and 71%) and MMP2 (28% and 53%) and thus it can be confirmed that expression of these proteins can be regulated by the activity of miR-29c. When antimiR-29c was incubated with DEX or COR, it partially attenuated the effect of these hormones on the synthesis of COL3A1(25% and 24%), COL4A5 (26% and 44%), ELN (31% and 55%) and MMP2 (46% and 26%) respectively in RAOMC compared with anti-miR negative control. So on the basis of above, it can be said that in parts, expression of these proteins is regulated by GC through induction of miR-29C [48].

In skin atrophy, the ECM nature changed when it was treated with betamethasone. Recently, it was reported in cases of psoriasis vulgaris, the topical application of betamethasone gel causes skin atrophy by reducing the expression of MMP2, COL1 synthesis and decreases the hyaluronic acid production in human fibroblast and keratinocytes, which causes an epidermal thinning. However, when combined with calcipotriol, it counteracts all ECM changes brought by betamethasone treatment [47].

The exposure to hydrogen sulfide (H$_2$S) leads to a deadly outcome called acute lung injury (ALI) by alleviating the expression of ECM protein, i.e. MMP2 and MMP9. However, DEX has a beneficial role in such cases. To judge, the ALI and A459 cells incubated with NaHS to establish cell model. The biochemical cell reports like lung HE staining, electron microscopy, immunohistochemistry assay and wt/dry ratio demonstrated an increase in ALI, MMP2 and MMP9 expression in both model when both groups were treated with DEX. The symptoms of ALI like alveolar edema, infiltration of inflammatory cells and protein leakage in BAFL ameliorated and the decreased expression of MMP2 and MMP9 were reported both *in vivo* and *in vitro*. The similar effect has

also been reported when these two groups were given glucocorticoid receptor (GR) antagonist mifepristone, and the DEX effects ceased [49].

As it is well known that in cases of most inflammatory diseases, an anti-inflammatory drug, GC is preferred by most of the physicians. However, the post-therapeutic effect has reported that they can induce a lot of unwanted changes in the subjects. The researcher observed the effect of therapeutic entities or physical activity that affected the metabolism of bone on joint cartilage in rats with prednisolone-promoted osteoporosis. The therapeutic role of concurrent use of physical activity with treadmill and vibration platforms training, influenced the ECM components expression and the decreased expression of lubricin and caspase-3 have been confirmed by using western blot and biochemical analysis. Moreover, the expression of lubricin inhibits caspase-3 activity, thereby inhibiting the death of chondrocytes cells in osteoporosis disease [50].

It has been reported that, a loss in bone or cartilage induces difficulty in movements which is a common problem in older person and this problem generally increases as person becomes more older. With the invent of regenerative medicine, it becomes possible to rejuvenate the bone and cartilage. Chondrocytes cells and mesenchymal stem cells are the potential cells for generating bone and cartilage in ossification, and final step is the terminal differentiation and endochondral ossification regulated by two hormones, i.e. T3 and DEX. For this, 3D-alginate cell culture model in which bovine chondrocyte and differentiated mesenchymal stem cell were cultured with T3 and DEX. The cultures were measured for COL and m-RNA expression and the level of alkaline phosphatase was also checked as a marker of terminal differentiation. The studies clearly described that DEX induced terminal differentiation and T3 increased the COL and m-RNA as well as alkaline phosphatase activity. Thus, such study becomes a ray of hope for using immature articular chondrocyte cell in regenerative medicine.

Glioblastoma (GBM) is a progressively degenerative disease with a high ratio of mortality. In such cases, the affected person suffers from two problems of continuous dispersion of tumor cells and high chances of recurrences. These two problems make targeted therapy ineffective and an increase in the intracranial pressure due to fast-growth of GBM cells. In order to improve the survival rate, two therapeutic strategies targeting molecular and cellular processes have shown the potential to control the diseases. The results of clinical trials on such patients described that five factors can affect the dispersion and growth of tumor cells: strong cell to cohesive cell forces [51], adhesion of the cell to ECM [52], motility of cells [53], stiffness of each GBM cell [54] and migration of ECM [55]. Hypothetically, an increased cell to cohesive cell forces and to ECM attachment will result in a decrease in the dispersion of tumor cells. The reduction in dispersal of primary human glioblastoma cells has been reported by DEX activated fibronectin matrix assembly (FNMA). The use of antifibronectin, an antibody complexed with a FITC conjugated secondary antibody, is described with four subtypes of fibronectin expression pattern and each pattern possess different capacity for fibronectin expression and organization.

Clinically, it has been previously reported that Dex treatment increases the capacity for FNMA expression as well as GBM cell aggregates compaction and cohesion. These aggregates incubated with drug (300 μg/ml) also reported an increase in the surface tension from 7.9 ± 0.4 to 20.5 ± 0.9 dunes/cm. The DEX treatment effects can be described by: change in the organization of actin fibers, the appearance of cell tightly attached to the surface, and the translocation of phosphorylated focal adhesion kinase expression from the cytoplasm to cell-substrate site attachment. Better adhesion has been reported with large surface area and it increases as the surface properties like surface area, are increase while shear induces, detachment, decreased cell motility as well as growth rate of the GBM cell. Shannon et al. [56] further stated that the dispersal rate also facilitates the poor prognosis and recurrence of GBM cells. Experimental studies have also described that in GBM cells, both integrin $\alpha5\beta1$ and fibronectin are unregulated. The expression of integrin is involved in either facilitation or inhibition of glioma cell migration. This difference in behavior may be assigned to differences in cell types or by the different ECM composition pattern. In in vitro trials, integrin has been reported to reduced cell migration, when plated onto purified fibronectin, it enhances the invasion and the cells were plated onto matrigel, enriched with ECM protein and fibronectin [57,58].

It is well known that GC has good therapeutic analgesics or anti-inflammatory efficacy in osteoarthritis and inflammatory arthritis. An in vitro study reported that GC reduces proliferation of tendon derived cells, while in vitro and in vivo studies of particular collagen type I synthesis reported that GC has a negative effect on ECM synthesis. The other deleterious effects that can be ascribed to the GC therapy are collagen necrosis, disorganization of collagen, infiltration of inflammatory cells and reduction in the tendons mechanical characteristics. On this basis, it can be said that for treating painful tendinopathy, GC should be the preferred choice. As lifelong treatment of such disease lacks safe therapy report, whenever GC is employed for treatment, the right dosage calibration must be done [59].

A comparative study was made in guinea pigs with chronic allergic inflammation, using Rho-kinase inhibitor and DEX. Pigati et al. [60] described that there was a decrease in mechanical response after antigen exposure, ECM remodeling, oxidative stress and inflammation in the lungs. It was also described that there is a decrease in collagen levels and IFN-γ in bronchial, NF-κB and IL-2,8-iso-PGF2α in distal parenchyma and decrease in number of TIMP-1 positive cells and eosinophils in the alveolar septum in comparison to corticoid treated animals ($P < 0.05$). This combinational treatment approach has shown a good pharmacological prospects towards the treatment of such diseases.

2.4. Cardiac drugs and ECM

Cardiac homeostasis is regulated through the network components of ECM which facilitate force transmission signaling in heart failure. Myocardial stiffness is the result of cardiac ECM expansion and finally leads the diastolic dysfunction. Moreover, ischemic injury is also the result of the dynamic changing in cardiac ECM.

Experimental studies have been done by different workers on the role of antihypertensive agents, especially ACE inhibitors and Ca^{2+} channel blockers, as they also possess antifibrotic properties and it has been reported that they do so by reducing the production of collagen proteins [61–64]. Drugs like captopril which are angiotensin II converting enzyme inhibitor, reduces ECM expression in various models of acute and chronic renal diseases [64,65]. It has been postulated that all these therapeutic molecules act on ECM by lower expression of TGF-β. It has been described that an additive effect of angiotensin II blockade and inhibition of TGF with antibodies has become a promising tool to prevent the progress of fibrotic disorders [66,67]. Drugs like captopril and losartan for patients with fibrotic diseases like Marfan's syndrome have been found to progressively slow down the progress of symptoms like aortic root dilation [68]. In some other works, it can be said that Ca^{2+} channel blockers like nifedipine and amlodipine also reduces the matrix overload by suppressing ECM via TGF expression blockade, which results in low matrix accumulation. However, the observations lack clinical evidence and mechanism of action [62,69–71].

Among various hypolipidemic drugs, the statins have been found to possess antifibrotic properties. And they do so by inhibiting the conversion of 3–hydroxy,3-methyl glutaryl coenzyme-A (HMG Co-A) to mevalonate, that is essential for Rho family and Ras GTPase for the post-translational modification. Diagnostic studies have revealed that Rho family GTPases like Rac1 and Cdc-42 are a key regulator of the TGF-induced synthesis of CTGF in human gingival fibroblast, and experimentally, it has been reportedly observed that HMG Co-A reductase inhibitors like lovastatin can decrease CTGF expression. The other drugs of this category like pravastatin have also been reported to inhibit the same pathway in human fibrotic explants [72].

In an attempt to search drugs which can alter ECM metabolism in a beneficial way for disease modification, a newer agent called levosimendan was described to be significantly effective. This drug is used in patients with uncompensated heart failure, and belongs to the category of Ca sensitizers. In such patients, the drug decreases the MMP-2 serum level. On the other hand, an endothelin subtype A (ETA) and endothelin subtype B (ETB) receptor antagonist, i.e. bosentan, when used in patients with pulmonary arterial hypertension, were reported to increase MMP-9 serum level [73,74]. It was studied that bosentan increases the catabolism of ECM protein. Another antimitotic agent, sirolimus, prescribed in-stent restenosis therapy, inhibits the concentration of hyaluronan protein, and attachment of monocytes to ECM produced by vascular smooth cells. Besides above-stated effects, the effects on ECM are rather nonspecific and less effective [75]. Thus, it is observed that enalapril, captopril like drugs inhibit angiotensin convertase enzyme and thus, are commonly called ACE-inhibitors. The key effects of these enzymes on ECM were reportedly the modulation of proteoglycan, collagen synthesis and fibrosis. The other drugs like losartan or angiotensin receptor-blockers affect ECM including upregulation of thrombospondin-1 expression, down-regulated expression of fibronectin, inhibition of MMPs, TIMPs, CTGF, and fibrosis

2.5.   Antibiotics and ECM

Multicellular communities of bacteria are called biofilm. It works as a mechanical and chemical barrier against many environmental adverse conditions, including antibacterial substances. Moreover, bacterial adherence is also due to the involvement of many ECM molecules [76]. Community onset infection and nosocomial infections are frequently caused by *S.aureus*. It has been established that several virulence factors, such as components of immune evasion, adhesins and toxins, are important to mediate the disease. The microbial cell-attached to the host cell, secreted protein, DNA and polysaccharides, provide protection and survival to the microbial cells. The use of simvastatin against *S. aureus* 29213 to control the infection reported a significant inhibitory effect on ECM components which are involved in biofilm formation or synthesis of ECM components of the cells wall.

The resistance mechanism of microbes against many antibiotics in multidrug resistance (MDR) strain like *S. aureus* has been established due to the expression of many intracellular matrix proteins. Besides the lactamase secretion, resistance against penicillins like beta-lactam antibiotics is due to decrease in drug binding affinity to microbial cell, caused by expression of new protein i.e. penicillin binding-protein 2A [77]. Prevention of collagen degradation in a biofilm is also a way of resistance which has been evaluated using dimethylaminododecyl methacrylate and seems to provide protection to the resin dentin bond and prevents the degradation of biofilm. The effect of concentration of dimethylaminododecyl methacrylate i.e. 0.1%–10% and 5% were reported to inhibit up to 90% MMP-8 and rhMMP-9, respectively [78]. Bleomycin has a stimulatory effect on the synthesis of TIMP-1, INF-γ, MMP9, and TGF-β, which results in pulmonary fibrosis [79]. Recently, it has been described that bone marrow-derived mesenchymal stem cells have an inhibitory effect on the synthesis of MMP9, INF-γ, TIMP-1 and TGF-β and protects the bleomycin-induced pulmonary fibrosis [80]. The cyclophosphamide has also been reported with a similar effect on pulmonary fibrosis by the administration of bleomycin [81].

Lymphangiogenesis results in the further initiation of the pathogenesis process, such as the onset of inflammatory conditions, graft rejection, and cancer metastasis. Lymphangiogenesis has emerged as a novel target to manage the disease and lot of work is being done to inhibit lymphangiogenesis. Doxycycline is a potential therapeutic agent which controls inflammation-induced lymphangiogenesis (ILA) by inhibiting the MMPs activity, resulted in decreased VEGF(vascular endothelial growth factor)-C/VEGF 3 signaling, and also reported to inhibit inflammatory cytokine expression, macrophage infiltration and VEGF-C-induced HDLEC proliferation *in vitro*. Moreover, it has been reported that modulating PI3K/Akt/nuclear factor-kappaB (NF-κB) pathway significantly reduces the synthesis of TNF-α, VEGF-C, IL-1β, and phosphorylation of Akt, NF-κBp65, and eNOS in ILA [82]. Tendinopathies are generally reported with the use of statin and fluoroquinolone, which have been reported to affect the activity of MMPs in tendon cells [83-85]. In vancomycin-resistant strains like *enterococci*, a precursor component was synthesized which also reduced

glycopeptide affinity of the cell to vancomycin. The novel peptides of the PDG wall is characterized by non-cross linked specific sequence D-Ala-D-Lac or D-Ala-D-Ser [86,87]. The glycopeptides do-not have access to bacteria cell wall synthesis sites and wall synthesis is not-inhibited.

2.6. Anticancer drugs and ECM

It is well evaluated that severe structural changes have been associated with the progression and growth of the tumor. ECM plays an important role in various biological processes occurring in tumor cells such as it develops tissue-specific signal mechanism between tumor cells. Recently it has been described that ECM proteins are helpful in controlling the growth and progression of tumor cell [88]. In an earlier reported work, it was pointed out that ECM protein and cell surface receptor proteins, like integrin, play an active role at all steps of tumor cell progression. However, high expression of ECM protein and MMP lowers the chances of prediction in the progression of the tumor, whereas; low expression of another ECM protein laminine is an effective tool for the diagnosis of disease. Such studies have been found to be helpful in clinical approach as targeting ECM protein is a basic tool in the treatment of tumor cell. However, PG on the cell, the ECM protein syndecan and decoran exerts a dual effect on tumor cells. So, this feature makes limiting aspect in antitumor therapy targeting ECM protein. Further evidence in support of the dual role of ECM protein comes from integrin $\beta1$, whose lower amounts have been expressed as breast tumor growth but when highly expressed, enhances metastatic tumor cell dissemination.

The ability of tumor cell to degrade MMPs are evaluated in addition to the expression of integrin. The increased activity of topoisomerase II in osteosarcoma cells of the drugs like doxorubicin affects this activity, and it was found to be similar to the inhibitory effect shown by MMPs inhibitors. Human mammary carcinomas show that ECM composition differs in high and low metastatic capacities. Metastatic with high capacity show much expression of proteins like LTBP3, SNED1, EGLN1 and S100A2. Depending on ECM composition, 8 subtypes of breast and colon tumor have been found. Proteins like EHS-ECM and OSCORT-ECM supports the existence of tumor cells as they cause rapid cell proliferation and its transmission. These proteins are cell cycle-specific in the sense that they help transition from G1 to S phase of the cell cycle. The expression of integrin protein on cell surface and ability of tumor cell to degrade ECM protein by MMPs help in dissemination of tumor cells. A marked correlation between expression of integrin $\beta1$, MMP9, MMP2 and dissemination of tumor cells was established.

Endostar and oroxylon A was found to possess an inhibitory effect on MMP, thereby reducing the migration of tumor cells. Both act against signal mechanism as oroxylon A inhibits extracellular signal-regulated kinase (ERK) that ultimately controls metastasis.

Effective antitumor drug taxol was found to inhibit single-cell migration [89]while another antitumor drug Doxorubicin prevents migration of cluster type cells. Therefore the use of both types of drugs makes an effective treatment of such type of metastasis [88,90].

Recently, a study was carried out using thalidomide analogs 1 and 2 on lung cancer A-549 cells to investigate their inhibitory effect on the migration, proliferation and apoptotic potential. Studies suggested positive results in these concerns. Furthermore, since these analogs cause suppression of expression of VEGF-165 by 42% and 53.2% and those of MMP-2 by 45% and 52%, such targets should to be employed in cancer diagnosis or treatment. Also, only these analogs are active against lung cancer and not thalidomide itself [91]. The acquirement of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors becomes a serious problem in lung cancer treatment. The lungs cancer cells were recently reported to be resistant to EGFR tyrosine kinase inhibitors due to the stromal ECM [92].

2.7. Nanomedicines and ECM

Nanotechnology is an emerging branch in disease regulation and control with promising prospectives for increased efficacy of the drug and its delivery to the targeted sites of infection. Nanotubes and nanoparticles like silver gold, iron, graphene like materials have been tested for the diagnosis and treatment of many diseases. Recently, the safe use of nanotubes with doxycyclin (DOX-encapsulated nanotube-modified adhesive) has been tested for *Streptococcus mutans* and has shown inhibitory activity on MMP-1 [93]. Yücel et al. [94] showed high efficacy of hybrid formulation of nanoparticle and liposomes containing doxycycline with Caco-2 cell monolayers. MMP-2 was potentially inhibited with doxycycline with sodium taurocholate (NaTC). It was proposed that NaCl plays a significant role in enhancing the penetration which is due to inhibition of efflux by interacting with p-glycoproteins, and finally results in the opening of tight junctions. MMPs or collagenases are a cause of Achilles tendon rupture which degrades the matrix and increases MMP-8 activity. Recently it is reported that the administration of doxycycline at clinical dose significantly inhibits the MMPS activity. Moreover, it has also been reported that there is an improved collagen fibril organization, and enhanced biomechanical properties like ultimate tensile strength, stiffness, elastic toughness and maximum load to failure.

The use of bleomycin pulmonary fibrosis and alveolitis could be due to an increased expression of MMP-9 and TIMP-1 in lungs tissue of rat. Rapamycin, also known as sirolimus, is a macrolides agent which inhibits MMP-9 and TIMP-1. Therefore, it is used in the organ transplants, implantation of coronary stents in heart diseases, and also to treat lungs diseases. [95]. Tendinopathiesin tender cells are the desirable effect of fluoroquinolone and statin. It has been described that this is due to the change in the activity of MMPs [83,85,96]. Thiazolidinediones have been tested on pluripotent mesenchymal stem cells for antiosteoblastogenic and pro-adipocytic effect. Inhibition of TGF-1 or CTGF gene expression results in the reduced production of ECM, which might result in pathogenesis of the disease [85,97,98].

2.8.   Therapeutic protein and ECM

It has been established that inflammatory condition is also due to the release or synthesis of TNF-*α*. Macrophages cells are primary producer, but its production in different types of cells like adipose tissue, endothelial cells, lymphoid cells, fibroblasts, neuronal tissue an cardiac myocytes has also been reported in response to lipopolysaccharide. It induces fever, apoptotic cell death, sepsis, cachexia, inflammation, and inhibits viral replication and tumorigenesis.

2.9.   Etanercept, adalimumab, certolizumab and golimumab

It has been previously described that the family of TGF are the primary cause of fibrosis of different organs [99]and can be protected by inhibitors like lerdelimumab [100] and metelimumab [101], and by TGF-receptor kinase inhibitors such as SD-208 [102], SB431542 [103] and SM305 [104]. Avotermin, which is a recombinant, influences newly deposited components and reduces the deposition of collagen and fibronectin, and thus it has been used to regenerate the skin [105]. Moreover approaches like recognition is inhibited through integrity-remodeling matrix interaction have been utilized using monoclonal antibodies in diseases like psoriasis, acute coronary syndrome, Crohn's disease, multiple sclerosis etc. [106,107].

However, generating antibodies to target ECM molecules is little significant [108] because anti-integrin antibodies as drugs have not always been completely safe [109]; for example humanized antibody, vedolizumab (MLN0002), has been generated specifically to target integrins 47 and significantly has been used for Crohn's disease [110], but it block migration of lymphocyte to inflamed areas of the gut which results in the undesirable side effect of ulcerative colitis. Thus, if side effects are managed in the future, vedolizumab could be utilized widely in the treatment of pathological conditions such as cardiac hypertrophy, atherosclerosis and tumorigenesis [111]. Moreover, another example is volociximab whose interaction with integrin 51 and could be utilized to control tumor angiogenesis [112]. It can be concluded that these approaches to block the signaling pathway using peptidomimetics [113]or by integrin inhibitor could be another significant approach to manage the diseases. However, pharmaceuticals significance of integrin antagonists including eptifibatide has also been reported [114].

3.   Drug delivery and ECM components

Accrual and turnover of the ECM is a hallmark of tissue injury, repair and remodeling in human diseases. It has been recently described that absorptions, distribution and efficacy of the administered drug are determined by various ECM components like collagen, microcellular protein, elastin, proteoglycans and fibronectin. Moreover, integrin, some proteases and other ECM biomaterials have also been found to be effective in facilitating the targeted delivery of drugs in the treatment of various diseases including cancers [115,116]
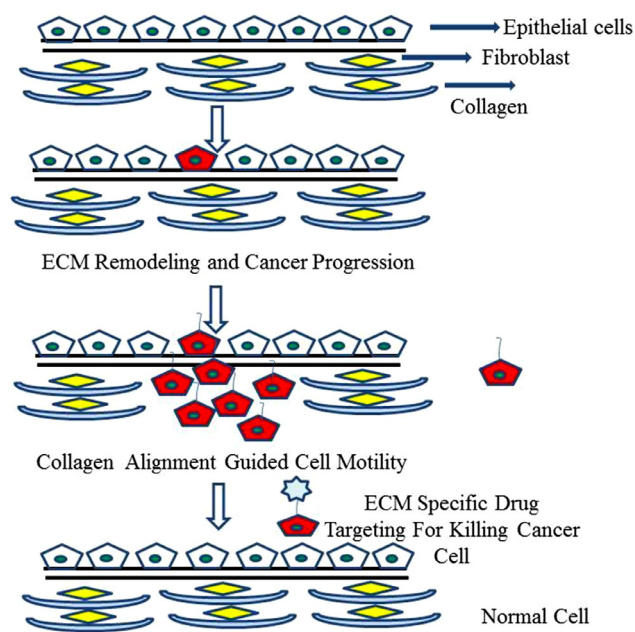

Fig. 3 – Showing change in ECM physiology in cancer progression and manage by ECM targeted drug delivery.
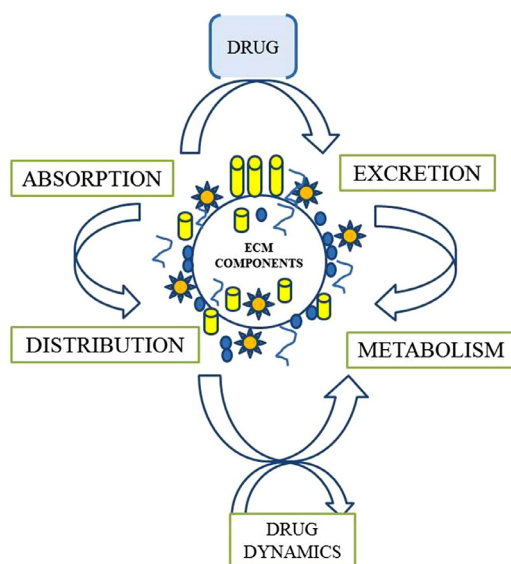

Fig. 4 – Representing ECM components directly involved in management of pharmacokinetics and pharmacodynamics of drug.

(Figs. 3 and 4). Besides the drug loading with integrin, the use of nanoparticles with interin has also been reported for better bio-distribution and uptake of the drug to cancerous cells [117].

Hyaluronan is a main constituent of the ECM and plays a significant adaptable role in repair, tissue injury and management of diseases. The function depends on interactions, location, size and binding partners. The fragmented hyaluronan synthesis by the genes of various
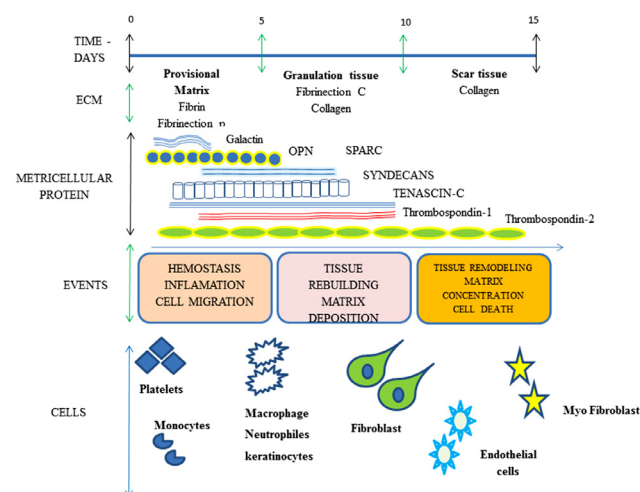
Fig. 5 – Representing ECM dynamic mechanism with time scale involved in management of disease.

types of cell directs tissue repair and inflammatory responses. It interacts with binding proteins to contribute to the pathology of the disease, and these interactions could be a new hope for the design of new therapeutics for inflammatory and fibrosis diseases [118]. Collagen interactions with cell surface receptors and some enzymes like metalloproteinases control various cellular processes. High-resolution structures of triple-helical peptides bond formed with collagen interactions with its natural partner have been studied and tested for liposomal delivery to melanoma cells [119]. Recombinant elastin-like materials, Prepared by recombinant technology or elastin-like recombinamers (ELRs)-based delivery systems has also been tested for drug delivery and showed the complexity of interaction to facilitate the trapped drug at the site of action [120].

4.   ECM dynamics in physiology and pathological conditions

Dynamics of ECM is crucial for the regulation of homeostasis otherwise unregulated or uncontrolled homeostasis of ECM may result in development of pathological or disease conditions including cancers. The homeostasis dynamics is controlled by various cellular biomolecules in time dependent manner (Fig. 5). The time dependent deregulation of MMPs enzymes, epithelial-mesenchymal transition, TGF-β signaling pathways like PI3K/AKT, Wnt, JNK, ERK, Src-FAK have been reported in many disease conditions. The over expressions of enzymes collagen prolyl hydroxylase and precollege lysyl hydroxylase-2 have been reported in the stiffness of breast cancer. The down-regulated expression of enzyme heparanase is linked to the progression of cancer. Thus, lipoprotein-A, vitamins C and heparin-like targeted molecules could be an alternative source of controlling cancer dynamics of ECM. Moreover, the molecules targeting integrins β1 and β3 as well as the cytokines like Src family kinases (SFKs), and focal adhesion kinases FAKs could be effective in the management of the disease conditions [121].

The efforts are accelerated for the designing of therapeutic molecules that target ECM including designing of inhibitors for integrin signaling. Drugs like nilotinib, imatinib and GNF-5 inhibit ABL kinase and impairs the ECM dependent invasion and its degradation. Moreover, molecules those targeting stromal cells, CAFs, Galectin-3 and inhibiting COX-2 enzyme, inhibitors of the β-catenin pathway and TGF-β1 receptor kinase inhibitors are linked to ECM components and can be helpful in the management of various diseases. It has been reported that the expression of hyaluronic acid (HA) depends on the expression of ZEB1 dependent synthesis of HAS2, which results in poor progression of cancer [121,122].

The FRA-1 belongs to AP-1 family of TFs targets ECM components such as promoter of tumor cell proliferation and metastasis includes plasminogen activator, MMP-1, adenosine receptor, Chloride channel accessory2 (Clca2), miR221/222, A2B, and protein ECM1 are involved in angiogenesis, promotes TNBC migration and invasion.

The effect of ECM and its components in therapeutics responses, resistances development including oncogenicity have been well explored. It has been described that the microcellular environment and physical forces are key components of each cellular response and signaling. Every cell has the ability to change a mechanical response into a chemical response. Moreover, the variable mechanical stimuli and ECM dynamics exhibited spatial dissimilarity including isotropy and inhomogeneity of matrix stiffness. The mechanism is explained by the tensegrity principle which is known as a tensional integrity mechanism. Till now, this mechanism has been validated to implement physiologically including mechano-sensing and mechano-transduction at different scales such as integrin cell sensing to the molecule-mechanical interventions or even localized message. The mechanism involves extracellular and intracellular organelles, such as a contribution of ECM and microtubules that work as compression structures while actin filaments have been reported to act as tension structures. The cellular differentiation, proliferation and apoptosis are due to the tensegrity system of the nucleus. The bio-tensegrity mediated by ECM components in pathological progression has been well described and many Tissues and their related ground substances experienced specific forces that mediate biological processes [3,123].

ECM dynamics play a central role in cell differentiation, stem cell niches, rearrangement, angiogenesis, branching, wound repair, bone remodeling as well as remodeling of tissues. Its dynamics have also been reported with uncontrolled or deregulated cell growth, loss of differentiation and failure of cell death which results in the progression of pathological processes. Thus, it is important for designing new therapeutic interferences for the diagnosis and treatment strategies for regenerative medicine and tissue engineering [3]. Many ECM based protein expression like hyaluronic acid receptor CD44, change in fibronectin, and collagen-like ECM molecules have been reported to play a significant role in remodeling and the limb development. The mice studies have shown that deficiency of some MMPs including MMPs-9 and MMPs-13 resulted in the progression of tissue chondrocyte progenitor differentiation as well as architecture. ECM offers several drug delivery material features like structural support,

biochemical support, temporal and spatial control on the delivery of drugs as well as cell molecules. The targeted drug deliveries, synergistic effect with enhanced therapeutic efficacy with specific receptors for ECM have been well explored.

5.   Conclusions

The organization of ECM molecules has its own distinct features and is responsible for diverse biological activity as well as improvement or development of diseases. Moreover, natural or treated ECM molecules cooperate with different proteins, thereby triggering the signaling process that governs proliferation, cell differentiation, adhesion and immigration. Several drugs have been used to manage diseases that can modulate assembly beyond their primary targets and ECM metabolism. The currently used drugs did not show specificity and potentiality on ECM components. However, their effects on the ECM are often neither potent nor specific enough and have shown a harmful or beneficial effect. So, the discovery of novel drugs that possess potentiality and specificity to the ECM in a more direct way is the urgent need of therapy. Recently, the discoveries of new drugs that target the ECM have been accelerated. The uses of modern technologies like genetic engineering, specifically antisense and gene therapies, including RNA interference, have been coupled to make the approach more significant.

Thus, it can be concluded that the ECM involved in the development of disease as well as in the management of diseases uses therapeutics molecules. ECM or its component could be a significant target for the management of the disease. Many techniques offer a great interest to develop effective ways for the treatment of many human diseases and in spite of effective technologies to control many diseases, ECM based gene or targeted drug therapy is not still in clinical practice. Moreover, it is in demand for understanding the functional complexity, diversity of diseases and multiplicity of ECM molecules which offer significant challenges for future targeting strategies. Thus, it is a developing area which can be exploited to develop ECM components as novel therapeutic targets in the treatment of various diseases and also offer a significant implement in tissue absorption and advance drug delivery.

Conflicts of interest

The author declares that they have no conflict of interest.

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Supplementary materials

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