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The Abstract of article is "Metastasis or the progression of malignancy poses a major challenge in cancer therapy and is the principal reason for increased mortality. The epithelial-Mesenchymal transition (EMT) of the Basement Membrane (BM) allows cells of epithelial phenotype to transform into a mesenchymal-like (quasi-mesenchymal) phenotype and metastasize via the lymphovascular system through a metastatic cascade by intravasation and extravasation. This helps in the progression of carcinoma from the primary site to distant organs. Collagen, laminin, and integrin are the prime components of BM and help in tumor cell metastasis, which makes them ideal cancer drug targets. Further, recent studies have shown that collagen, laminin, and integrin can be used as a biomarker for metastatic cells. In this review, we have summarized the current knowledge of such therapeutics, which are either currently in preclinical or clinical stages and could be promising cancer therapeutics".

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Multiple roles for basement membrane proteins in cancer progression and EMT

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ABSTRACT

Metastasis or the progression of malignancy poses a major challenge in cancer therapy and is the principal reason for increased mortality. The epithelial-Mesenchymal transition (EMT) of the Basement Membrane (BM) allows cells of epithelial phenotype to transform into a mesenchymal-like (quasi-mesenchymal) phenotype and metastasize via the lymphovascular system through a metastatic cascade by intravasation and extravasation. This helps in the progression of carcinoma from the primary site to distant organs. Collagen, laminin, and integrin are the prime components of BM and help in tumor cell metastasis, which makes them ideal cancer drug targets. Further, recent studies have shown that collagen, laminin, and integrin can be used as a biomarker for metastatic cells. In this review, we have summarized the current knowledge of such therapeutics, which are either currently in preclinical or clinical stages and could be promising cancer therapeutics.
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1. Introduction

The basement membrane (BM) is a thin layer of extracellular matrix situated underneath endothelial and epithelial tissues. Cells need to invade through basement membranes to undergo metastasis (Chang and Chaudhuri, 2019). Metastasis is the propagation of malignant cells to distant sites from a primary tumor. It occurs in a series of steps, favorably modeled into a 'metastatic cascade'. Some of the underlying cellular and molecular mechanisms are Epithelial-Mesenchymal Transition (EMT), anoikis, or programmed cell death that happens as a result of detachment from the matrix, invasion, angiogenesis, transport through vessels, and outgrowth of secondary tumors (Geiger and Peeper, 1796). The stiffness of BM is dominant over the pore size of the membrane for metastases and is determined by the ratio of netrin-4 (Net-4) to laminin molecules. The greater the ratio, thesofter the BM, hence downregulating cancer cell invasion activity (Reuten, et at, 2021). Cancers originating in the epithelium, known as carcinomas, constitute the majority of cancers. Losing epithelial characteristics is the primary step for carcinoma progression (Nakaya and Sheng, 2013). The epithelial-to-mesenchymal transition (EMT) allows cells of epithelial phenotype to be mobile and change to a mesenchymal phenotype which further explains why EMT-related pathways have been described in tissue fibrosis and cancer metastasis. EMT can promote tumor cell intravasation of surrounding blood vessels and emigration into a new organ. Matrix metalloproteinases (MMPs) cleave components of basement membranes and are known to play a role in EMT-related processes (Horejs, 2016). Several external and internal cues are thought to induce EMT in a subset of metastatic cancer stem cells (MCSCs), gaining the ability to spread throughout the body (Singh et al., 2018). The basic characteristic pathways and mechanisms of cancer metastasis via the lymphovascular system form the basis of rational therapy against cancer. The EMT pathway can also contribute to therapy resistance and hence can be targeted to eradicate metastatic cells in advanced stages or to prevent tumor cell dissemination in early-stage patients.

2. Basement membrane (BM) proteins

BM mainly composed of collagen IV and laminin is a sheet of extracellular matrix lining the basal side of epithelia and this basal restriction of BM proteins is essential for establishing and maintaining the polarity of epithelial cells. The loss of stratum, a homolog of the mammalian guanine nucleotide exchange factor (GEF), the mammalian suppressor of Sec4 (Mss4) results in missecretion of BM proteins at the apical side of the cells(Devergne et al., 2017; Chang, 2019). The principal BM proteins other than collagen IV and laminin are heparan sulfate proteoglycans, BM-40, and nidogen (Timpl, 1989). Laminins are heterotrimeric; the network nodes are formed by the three short arms of the cross-shaped laminin molecule with requirements for an α, a β, and γ arm. They bind to cellular receptors with the help of the globular domain present at the end of the long arm. Another network is formed by the interaction of type IV collagen with the laminin network via heparan sulfate chains of agrin and perlecan and extra linkage by nidogen (Hohnester and Yurchenco, 2013). Collagen IV protein is crucial for maintaining the structure and function of BMs under circumstances of upregulating mechanical demands but is replaceable for deposition and initial assembly of components. Laminin is sufficient for basement membrane-like matrices at early stages, but at later stages, collagen IV is responsible for stability, integrity, and functionality(Pöschl et al., 2004).

Integrins help in adhesion, which is essential for regulating various biological functions of cancer cells and act as receptors of ECM, thereby mediating the interactions between cells-cells and cells-ECM. Recent studies have revealed that integrins present on tumor cells or tumor-associated cells in the stroma are involved in the remodeling of ECM and are further essential in establishing crosstalk with other membrane proteins. As mechanotransducers, the integrins are also responsible for sensing changes in the biophysical properties of the ECM (Su et al., 2020; Thomas et al., 2019). Laminin-5 (LN5) supports cell adhesion and migration via interacting with integrins on the basal plasma membrane. Upon interaction of soluble LN5 with integrins α6β1 and α3β1 on the apical cell surface and stimulating cell migration, the integrin signals generates synergistically from the apical and basal surface regulates cell motility and cytoskeletal organization in pathological conditions like tumor invasion and wound healing (Kariya and Miyazaki, 2004).

Nidogen is a key contributor to the genesis of a delicate microenvironment that is essential for stem cell lineage-specific differentiation (Zhou et al., 2021). Heparan sulfate (HS) can be described as complex, unbranched carbohydrate chains that are modified by sulfate and exist either as free, unconjugated chains or as conjugated to proteins. Heparan sulfate proteoglycans (HSPGs) are proteins that are covalently bound with HS chains. HS and HSPGs act as co-receptors for various cell surface receptors by binding to different growth factors (Nagarajan et al., 2018).

3. Role of basement membrane proteins in Cancer and Metastasis

It is well known that in epithelial cancers, cells invade through basement membranes to metastasize. This invasion was previously thought to require protease degradation due to the larger size of cells (≈10μ), but recent studies reveal that protease-independent BM invasion is facilitated by physical forces generated by cancer cells (Chang and Chaudhuri, 2019). In a matrix metalloproteinase-independent manner, cancer-associated fibroblasts (CAFs) promote cancer cell invasion via BM (Fig. 1) (Glentis et al., 2017). CAFs primarily contribute to the stiffness and degradation of the extracellular matrix. Stiffness and degradation of the extracellular matrix are brought about by hypoxia-induced by CAFs and cross-talks between CAFs with macrophage type2 cells and cancer cells. The stiffness contributes to a bridge in the basement membrane (Fig. 1) due to a transforming growth factor-β (TGF-β) related pathway; the degradation in a matrix metalloproteinase (MMP)-related pathway makes a path in the tumor microenvironment, both of which leads to cancer cell invasion (Najafi et al., 2019).

In tumor microenvironments, CAF is the major cell type and promotes cancer progression by interacting with tumor-infiltrating immune cells, secreting hydrogen peroxide, cytokines, different growth factors, chemokines, and by promoting extratumoral oxidative stress (Liao et al., 2019).

Despite extensive ongoing research in the direction of the CAF phenotype, very little is known about the collagens that the CAF phenotype can produce. These collagens are extremely important in cancer and are known to be responsible for various significant steps in tumorigenesis, namely, proliferation, apoptosis, angiogenesis, invasion, and metastasis (Fig. 2) (Nissen et al., 2019). Collagen IV is known to be the major component of the basement membrane (Tyagi and Kalluri, 2006). They are essential for maintaining the BM structure and function. Col IV α chains synthesize α1α1α2, α3α4α5 and α5α5α6 promoters that lead to further formation of collagen networks. Their genes are arranged in a head-to-head manner and paired on three different chromosomes. The α5(IV) gene (COL4A5) and the α6(IV) gene (COL4A6) are regulated by a bidirectional promoter and are present on chromosome Xq22. In the early stage of cancer invasion, loss of the α5(IV)/α6(IV) chains in the BM take place. The minor Col IV α5(IV) chain assists the progression of lung cancer via the non-integrin collagen receptor, discoidin domain receptor-1(DDR1) (Xiao et al., 2015; Ikeda et al., 2006). While a lot is known about the role of type IV collagen in tumorigenesis, the details on the effects of collagens residing in the stroma remain obscure. Hence, the following Table 1 provides an overview of collagen type I, II, III, V, VI, XXIV, and XXVII and their contribution to tumorigenesis.

Laminin is the primary non-collagenous glycoprotein found in the BM and its various isoforms are included in the dissemination of cancer. Its effects are mediated by laminin receptors that belong to two groups:

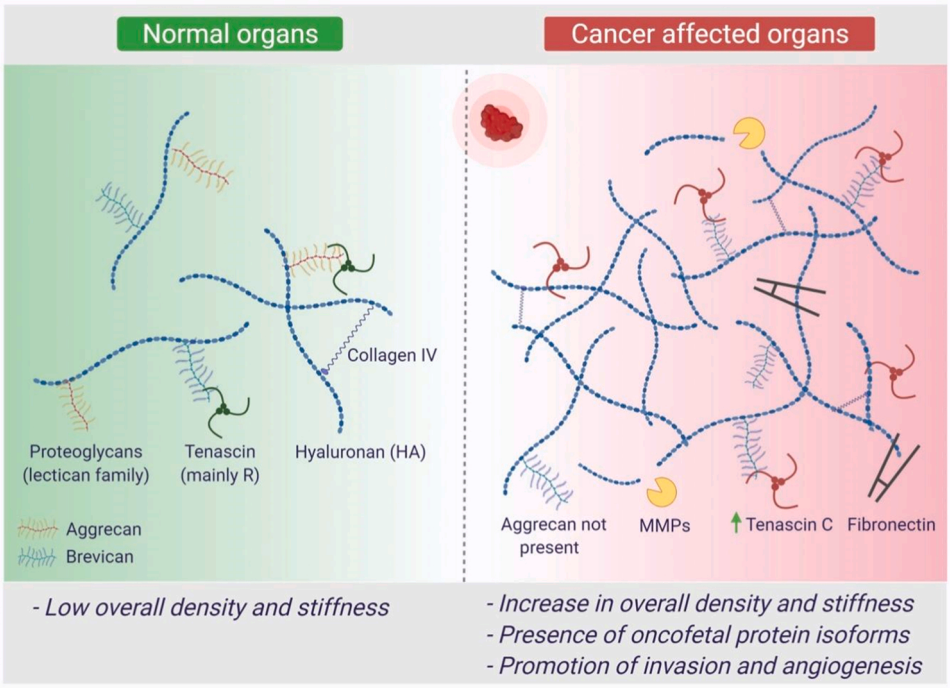

Fig. 1. Differential expression and function of the basement membrane.The differential expression of proteins in normal and cancer tissues. The primary difference of basement membranes in normal organs and pathophysiologies such as cancer is the expression of different proteins and their densities.

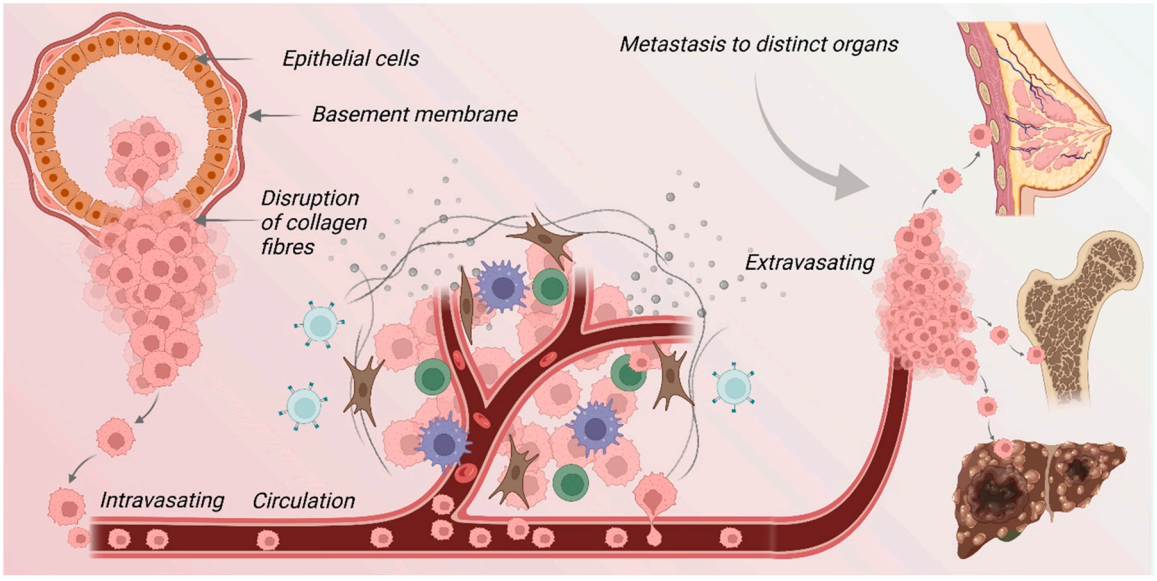

Fig. 2. Role of basement membrane proteins in cancer cell migration and metastasis. The cancer cells are released into the blood flow and migrate via blood vessels to the target sites. The primary transition of normal epithelial cells results in carcinoma in situ. With declined adhesiveness and increased migratory behavior, tumor cells advance to an invasive stage. Succeeding the degradation of the basement membrane, cells invade the surrounding stroma and migrate into blood circulation. Surviving cells arrest in the capillaries of a distant organ. Alternatively, the tumor cells may vent into the circulation and lead to the formation of secondary tumors after proliferation, induction of angiogenesis, and microenvironment initiation.

integrin and non-integrin receptors. Laminin signals via multiple signal transduction pathways including mitogen-activated protein kinases, intracellular calcium, G-proteins, phospholipase D, cytoskeleton components, focal adhesion kinase, and small GTPases of the Rho family (Givant-Horwitz et al., 2005). Laminin-5 consists of α3-, β3- and γ2-chains, hemidesmosomes and anchoring fibrils. LN-5 plays an important role in the induction of cell migration and such enhanced activity is observed when it is in its truncated form, after the proteolytic shedding of the N-terminal fragments of γ2 chains. In epithelial carcinomas, the epithelial cells tend to adhere to the BM, rich with LN-5 with the help of specific integrins as receptors (Katayama and Sekiguchi, 2004; Miyazaki, 2006). The expression of Laminin 332(LN-332) is perturbed in cancer-associated fibroblasts, tumor cells, and the tumor microenvironment (Rousselle and Scoazec, 2020). Laminin-111 increases tumor growth and proliferation of certain cancer cells. It also inhibits the EMT transition of cancer cells and enhances resistance to apoptosis. Laminin-411 and Laminin-421 enhance the motility of cancer cells and Laminin-511 facilitates cell-cell adhesion, thereby affecting the efficacy

Table 1
An overview of different collagen types and their contribution to tumorigenesis.

Collagen Type	Distribution	Tumor Promoting Effects	References
I	Present abundantly in the body; a major component of the bone and is also present in the cornea, blood vessels, sclera, tendon, skin, and ligaments	Has major impacts on bone cancer, and metastasis takes place from bone to other solid tumors; mentioned in lung, breast, pancreas, ovarian, and colorectal cancer	Bager et al. (2015); Willumsen et al. (2014); Kehlet et al. (2016); Kanematsu et al. (2004); Zhao et al. (2011); Cloos et al. (2003); Hall et al. (2006); Ferreira et al. (2016); Zou et al. (2013); Armstrong et al. (2004); Menke et al. (2001); Cheng and Leung (2011); Gao et al. (2016); Barcus et al. (2017)
II	Mostly in cartilage	Cell death and survival	Gelse et al. (2003); Hayashi et al. (2011);Sipilä et al. (2014); Wang et al. (2010)
III	Found in skin, lung, vascular system, liver, and intestine	Plays a role in invasion, metastasis, migration, and proliferation	Gelse et al. (2003); Chintala et al. (1996); Hirai et al. (1991); Menke et al. (2001)
V	Same as collagen type I and III	Helps in growth of tumor	Gelse et al. (2003); Fichard et al. (1995); Huang et al. (2017)
VI	Present in dermis, skin, cornea, adipose, cartilage, lung, tendon, and skeletal muscle	Associated with drug resistance, apoptosis, inflammation, metastasis, invasion, and proliferation	Cescon et al. (2015); Chen et al. (2013); Park and Scherer (2012); Schnoor et al. (2008); Wright et al. (2008); Park et al. (2013); Sok et al., 2013
XI	Found in low levels in trabecular bone, skeletal muscle, trachea, tendons, articular cartilage, brain, lungs, pancreas, and testis	Regulates invasion, metastasis, and proliferation	Ellsworth et al. (2009); Zhao et al. (2009); García-Pravia et al. (2013); Chong et al., 2006; Vecchi et al., 2007; Badea et al. (2008); Wu et al. (2013); Teng et al., 2014; Cheon et al., 2014
XXIV	Found in muscle, bone, liver, kidney, spleen, ovaries, and testis	Plays a role in cell differentiation	Ricard-Blum and Ruggiero (2005); Wang et al., 2012; Misawa et al., 2014
XXVII	Distributed in the developing ears, eyes, heart, lungs, and arteries	n/a	Pace et al. (2003); Plumb et al. (2007); Hjorten et al., 2007

of cell-cell interactions (Maltseva and Rodin, 2018).

Distant metastases are the most common cause of cancer-related death. To break loose from primary cancer, cells de-escalate the cell-to-cell adhesion molecules (CAMs) responsible for keeping them attached to neighboring cancer cells and upregulate other types of CAMs that allow them to attach to the endothelium in the organ. For these adhesion purposes, integrins and their molecular ligands are necessary for the transmigration of cancer cells(Sökeland and Schumacher, 2019). Integrins, as the main receptors for cell adhesion, have multifaceted roles as signaling molecules. In tumors, altered expressions of integrin can be frequently detected. Studies revealed that integrins have roles in supporting oncogenic growth factor receptor (GFR) signaling and GFR-dependent cancer cell migration and invasion (Hamidi and Ivaska, 2018). To understand the impact of epidermal growth factor receptor on adhesion, TGT (tension gauge tether) probes have been used to display the integrin ligand cRGDfK(an αvβ3 integrin selective cyclic peptide) with quantified integrin tension. Exposure to EGF significantly up-regulated the cell circularity and spread area and integrated integrin tension, radial organization, mechanical rupture density, and size of focal adhesions in Cos-7 cells on the surface of TGT probes. These experimental findings suggest that EGFR is responsible for the regulation of integrins and the spatial organizations of focal adhesions (Rao et al., 2020). Cross-talk mechanisms between integrins and GFRs thereby play a significant role in adhesion, cell motility, and growth. This is due to the linkage of integrins with resistance to tyrosine kinase inhibitors (TKIs) of EGFRs. In this case, integrins have two different functions: they can act as a collaborator with the growth factor receptor signaling and can contribute to EMT as a basic mechanism, which in turn affects the response to chemotherapy(Javadi et al., 2020). Integrins drive various stem cell functions including initiation of tumors, metastatic reactivation, epithelial plasticity, and resistance to oncogene-and immune-targeted therapies. Changes in tumor suppressor genes and oncogenes result in deregulation of integrin signaling in cancer. Protumorigenic integrins and oncogenic receptor tyrosine kinases activate the FAK-SFK (focal adhesion kinase-SRC family kinase) signaling pathway collaboratively. Mutations in MARK1, LKB1, and DIXDC1 remove the inhibitory constraint; mutations in PTEN have the same output via activation of FAK as well as Rac. Activation of Rho is reinforced and hence Rac, FAK activates PAK and suppresses NF2. DLC1 inhibits the activation of Rho. These pathways enable specific integrins to either promote or suppress tumorigenesis(Cooper and Giancotti, 2019).

Nidogen 1 (NID1) and nidogen 2 (NID2) are two known nidogen proteins that are known in mammals. In human cancer samples and cell lines, CpG islands of NID1 and NID2 genes are aberrantly methylated. Nidogens are important for cell adhesion by establishing contacts with various cellular integrins and they help in stabilizing the BM structure by maintaining a network with laminin and collagen IV (Ulazzi et al., 2007).

3.1. Human tumors

1. ***Oral cancer:*** *In-vitro* 3D models of early neoplastic, normal, and neoplastic human oral mucosa that closely resembles the in vivo human oral cancer progression were developed on type I collagen biomatrices, by growing dysplastic human oral keratinocytes (DOK cell line), primary normal human oral keratinocytes and neoplastic human oral keratinocytes (PE/CA-PJ15 cell line), with or without the presence of primary fibroblasts from normal human oral mucosa. These tissues were then assessed immunohistochemically for the expression of major BM proteins such as type IV collagen, laminin-332, and fibronectin, whose expressions were gradually more expressed in neoplastic models and were further upregulated by the presence of fibroblasts, except laminin-332. The extracellular matrix deposition of fibronectin as well as the deposition of type IV collagen at the epithelium-biomatrix interface took place only in the presence of fibroblasts. These findings led to the conclusion that during human oral cancer progression, an increased BM protein expression is dependent on the epithelial-mesenchymal environment (Kulasekara et al., 2009; Moharamzadeh et al., 2017; Koontongkaew et al., 2012).

Laminins are autocrine factor produced by cancers and helps in the formation of the tumor. A 32/67 kDa receptor for laminin is found in oral squamous cell carcinoma (OSCC), which helps in the stabilization of the tumor cells by binding themselves to the laminin. After this success fulbinding, the tumor initiates secreting certain enzymeswhich help in the degradation and BM rupturing, following the destruction of Collagen type IV as well as laminin. Laminin-5 performs an important function in oral cancer, such as migration of tumors. They are overexpressed in areas where tumors come in contact with stroma. Laminin-5γ 2 helps in the migration of cancer cells for tumor invasion, and its overexpression

in the oral cancer cells, is an indicator of poor prognosis for a patient. Recent studies have also shown that laminin-5 is present only in squamous cell carcinoma of oral nature but not in dysplastic lesions, which makes laminin-5 a promising target for oral cancer therapy (Rani et al., 2013).

CD147, a transmembrane protein plays a significant role in metastasis and tumorigenesis by enhancing EMT progression in oral squamous cell carcinoma (Min et al., 2020). Anomalous expression of MMP-9 plays a primary role in the remodeling of ECM during the development of oral submucous fibrosis (OSMF), which is regarded as a collagen and collagenase metabolic disorder. It has been experimentally observed that over-expression of MMP-9 results in decreased epithelial lining and collagen-type IV, which further causes degradation of BM added to continuous accumulation of collagen-I upregulated by MMP-9–1562 C>T, R688Q, R279Q, and P574R SNPs, resulting in an early onset of OSMF (Katarkar et al., 2018).

A total of four integrin genes were concluded to be potent biomarkers for oral cancer. Experiments identified higher mRNA expressions of ITGA5, ITGA3, ITGB6, and ITGB1 genes in OSCC (Chang et al., 2018). Recent epidemiological studies revealed significant contributions of periodontal pathogens to a highly aggressive oral cancer phenotype via crosstalk signaling pathways between TLR/MyD88 and integrin/FAK, which can be reversed by the treatment of bacteriocin/nisin(Kamarajan et al., 2020).

2. ***Breast cancer:***Mammographically, the patients with dense breast tissue have a higher chance of developing breast cancer due to more collagen, which leads to increased matrix stiffness and changes in normal cellular responses. The alignment of collagen plays a role in the increased matrix stiffness but does not increase the speed of migrating cells (Fig. 3) (Riching et al., 2014).

   Breast cancer cells recruit CAFs in the surrounding stroma to reveal a new network of stromal collagen, hence favor tumor invasion and metastasis (Wei et al., 2019). The presence of fibrosis and hypoxia within the primary tumor contribute to the metastasis of human breast cancer. Hypoxia-inducible factor 1 activates the transcription of genes that code for collagen prolyl hydroxylases. These are critical for the deposition of collagen by breast cancer cells (Gikes et al., 2013).

   COL1A1(Collagen type I α1) is expressed in all examined breast cancer cells and has been observed to positively regulate metastasis (J. Liu et al., 2018; J. Liu et al., 2018; C.C. Liu et al., 2018). Activation of the collagen I receptor, discoidin domain receptor 2 (DDR2) regulates the stability of SNAIL1 (a family of transcriptional factors responsible for the regulation of EMT during embryonic development) by stimulating the activity of ERK2, in a Src-dependent manner. DDR2 maintains the levels of SNAIL1 in tumor cells that have already undergone EMT, hence promoting tumor cell invasion through collagen-I-rich extracellular matrices. The expression of DDR2 is also correlated with the expression of HIF-1α, a hypoxic marker in clinical samples of breast cancer (Zhang et al., 2013; Ren et al., 2014). Type I collagen facilitates metastasis and cell mobilization via the activation of the TGF-β signaling pathway (Meng et al., 2018). Experiments in knockout mouse models and tissue cultures reveal that collagen XIII, a type II transmembrane protein is involved in cell adhesion and differentiation of various cell types, thereby promoting metastasis and enhancing anoikis resistance (Zhang et al., 2018). Type IV collagen has been observed to be a potential biomarker in metastatic breast cancer cells (Lindgren et al., 2021). It has been noted that breast cancer tissues express significantly higher levels of laminin than normal breast tissue. This overexpression of laminin destroys the BM integrity in breast cancer tissues. Laminin also interacts with various important matrix enzymes, one of them being MMP-2, which results in degradation of the ECM basement membrane (Qiu et al., 2018). Four peptides identified in laminin-111 have been observed to be active in tumor malignancy studies, namely IKVAV, AG73, YIGSR, and C16. IKVAV and AG73 are found on the α1 chain, YIGSR on the β1 chain, and C16 on the γ1 chain, out of which IKVAV, AG73, and C16 strongly promote tumor growth. Hence, we can conclude about the potential effects of laminin-111 on malignant cells (Kikkawa et al., 2013). LM-332 in breast cancer cells is associated with decreased survival (Carpenter et al., 2018). LM332 plays a significant role in the migration of MCF-7 breast carcinoma cells and has also been found to be a component of lung tissue that can induce motility in the breast carcinoma cells, hence proving its role in the pulmonary metastases of breast carcinoma (Carpenter et al., 2017).

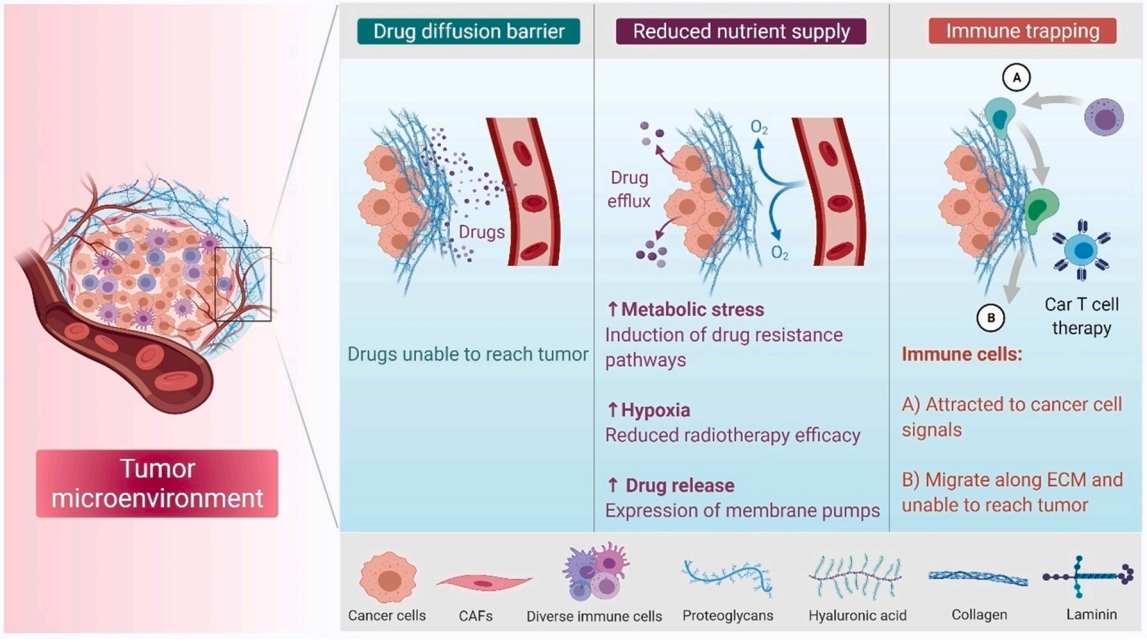

Fig. 3. Extracellular matrix and influence on therapeutic efficiency. ECM orchestrates factors such as drug action via barrier functioning, hypoxia/nutrient supply, and immune cell modulation which essentially dictates the tumor progression.

The expression of Laminin N-terminus α31, an alternative splice isoform derived from the laminin α3 gene enhances by 56% in invasive ductal carcinoma specimens compared to normal tissue, which further increases in nodal metastasis, thus directly contributing to tumor invasiveness(Troughton et al., 2020). LAMA2, the gene encoding laminin subunit αβ 2 was present in lower quantities in tumors of the breast tissue and is associated with overall survival in luminal A subtype cancer patients (Mamoor, 2021).

Functions and associations between integrins β1 and β3 are necessary for breast cancer. Inactivation of β1 integrin draws out the compensatory expression of β3 integrin in breast cancer; however, inhibition of β1 integrin failed to induce similar β3 integrin expression in normal mammary epithelial cells. Hence, the expression of compensatory integrin β3 is necessary for the growth and metastasis of tumors. Previous experiments revealed that simultaneous down-regulated expressions of β1 and β3 integrin reduced survival of cancer cells, which suggests that overexpression of β3 integrin is needed when β1 integrin is inactivated to maintain the survival and characteristics of cancer cells(A. Pan et al., 2018; B. Pan et al., 2018). Circular RNA circSKA3, highly expressed in breast cancer cells and human breast cancer tissues promotes the progression of tumors by complexing with integrin β1 and Tks5, inducing the formation of invadopodium (William et al., 2020). Integrin α11 + +, a positive subset of CAF displays tumor-promoting characteristics in breast cancer via the PDGRFβ/JNK signaling axis(Primac et al., 2019).

Various experiments revealed anescalated expression of NID1 in early to advanced lung metastasis. Because the lungs are one of the most commonly reported sites of distant metastasis in breast cancer, it rendersNID1 a promising biomarkerowing to their pro-metastatic role.(Urooj et al., 2020)

3. ***Lung cancer:*** Lung cancer is one of the most devastating types of malignant tumors and its progression depends on the interactions with the cellular and extracellular matrix environment. The motility of the lung cancer cell is influenced by the stiffness of the matrix related to enhanced collagen crosslinking (Götte and Kovalszky, 2018). ECM remodeling is a characteristic of fibrosis and cancer. Levels of tumstatin, an MMP-9 generated matrikine of collagen IV α3 chain is considerably higher in patients with non-small lung cancer compared to those with idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease and healthy controls (Nielsen et al., 2018). A poorly characterized collagen, type XIX associated with type XVIII and XV in the BM zone can be used as a potential biomarker. Type XIX collagen is enhanced in several types of cancer and can separate non-small cell lung cancer and healthy controls (Thorlacius-Ussing et al., 2020). Collagen XVII (Col XVII) has been proved essential for the maintenance of EMT phenotypes and metastasis in lung cancer stem-like cells. Col XVII activated FAK/AKT/GSK3β pathway by stabilizing laminin-5 and therefore suppressing Snail ubiquitination-degradation. Patients undergoing surgical resection for lung cancer showed overexpression of Col XVII and laminin-5 and had the worst prognosis of all expression types (J. Liu et al., 2018; J. Liu et al., 2018; C.C. Liu et al., 2018). P3H or collagen prolyl hydroxylases are required for the biosynthesis of proper collagen. Hence, the expression of P3H3 was analyzed in a panel of lung cancer cell lines and primary lung tumors and it was observed that ectopically expressed P3H3 inhibited proliferation of cells, formation of a colony of cells, migration, and invasion, promoted apoptosis and cell cycle arrest in the G2/M phase, enhanced p21 and caspase 3/7 activities and decreased cyclin A1 levels. It was concluded that P3H3 can act as a novel tumor suppressor and its protein expression is inversely related to metastasis of the lymph node and tumor differentiation in lung cancer (Li et al., 2018). In lung cancer, cancer stem cells can be represented by CD133 + cells. These can sustain metastatic dissemination and tumor growth. Experiments suggested that collagen glycosylation can play an important role in modulating the creation of a niche that is favorable for the generation and selection/survival of lung cancer stem cells (Gardelli et al., 2021).

Laminin being a primary structural component of the BM is a strong promoter of cell adhesion, migration, differentiation, and proliferation through integrins and other cell receptors lying on the surface. Studies support the importance of serum levels of laminin as a diagnostic marker in lung cancer patients (Tas et al., 2016). Laminin γ 2 (Ln-γ2) is a distinctive subunit of heterotrimeric laminin-332 and its levels were found to be enhanced in patients with non-small cell lung cancer. Ln-γ2 has been significantly associated with poor prognosis in non-small cell lung cancer, especially for early-stage cases (Teng et al., 2016).

Experiments were performed where a lung cancer tissue microarray was constructed and sections of integrin β4 subunit expression were stained using immunohistochemistry. Using cBioPortal(an open-access resource for exploring large-scale cancer genomics data sets), a network map was generated which demonstrated the 50 most highly altered genes flanking ITGB4 in lung squamous cell carcinoma. These included collagens, laminins, CD151, genes in the PI3K and EGFR pathways, and other known signaling partners. Hence, this conclusion was derived that the expression of integrin β4, a laminin receptor promotes the progression of carcinoma, facilitating invasion and metastasis. Integrin β4 also acts as an adverse prognostic marker for non-small cell lung cancer, where it is overexpressed (Stewart et al., 2016).

4. ***Esophageal Cancer:*** The ECM plays a significant role in esophageal cancer and the increased stiffness is capable of transferring alteration in ECM mechanics into cytoplasmic biochemical signals. Abundant collagen isoforms and enzymes such as lysyl oxidase (LOX) and MMPs play a significant role in this turnover. MMPs are involved in ECM stiffness, ECM homeostasis, and ECM remodeling. A variety of glycoproteins and proteoglycans such as fibronectin, laminin, hyaluronic acid, galectin, tenascin C and dermatan sulfate exert significant effects in esophageal cancer due to the activation of oncogenic signaling pathways mainly involved in cytoskeleton alterations during adhesion and migration. The expression of MMP-7 changes in the progression to esophageal adenocarcinoma. It increases at the invasive front in EAC which is partly due to activation of PI 3-kinase and modifies the tumor microenvironment by inducing stromal cell invasion and migration (Garalla et al., 2018). Collagen, the abundant component of ECM plays a significant role in tumor growth and EMT. Expressions of COL1A1, COL10A1, and COL11A1 were found to be enhanced and that of COL4A4, COL6A5, and COL14A1 were significantly down-regulated in esophageal squamous cell carcinoma cells. Hence, several collagen genes can be used as potential biomarkers for esophageal squamous cell carcinoma cells. Gene sets enrichment analysis results revealed that collagen genes are tightly associated with the p53 pathway, PI3K/Akt/mTOR pathway, cell cycle, apoptosis, etc (Li et al., 2019).

The c-type expression of LN-5γ2 is a prognostic factor in superficial esophageal cancer. It is confined to the cytoplasm and is associated with an unfavorable outcome among patients (Ito et al. (2014)

). Integrin β4(CD104, mRNA: ITGβ4) assists in the anchorage of cells to the ECM and contributes to tumor progression. One splice variant, integrin β4E slows esophageal squamous cell migration and other variants allow migration. Integrin β4E regulates esophageal squamous cell tumorigenesis through mutations (Kelly et al. (2020)

). Integrin α6, prevalent in esophageal squamous cell carcinoma cells promotes invasion and metastasis and acts as a potential target of miR-92b for suppressing ESCC motility (Ma et al., 2017). Integrin α5 expression also acts as a prognostic biomarker in esophageal adenocarcinoma(Loeser et al., 2020).

5. ***Adenocarcinoma of the pancreas:*** Pancreatic ductal adenocarcinoma is reported to cause significantly high cancer mortality rates. In a chronic pancreatitis background, collagen around the malignant duct shows an inclined alignment, width, and length and this proves

the importance of collagen as a disease marker of adenocarcinoma of the pancreas (Drifka et al., 2015). Desmoplasia, defined as an aberrant production of the ECM is considered a potential biomarker for the malignancy of pancreatic cancer (Piehler et al., 2020). Collagen V is overly expressed in pancreatic stellate cells and it affects adhesion, migration, viability, and metastasis of the cancer cells (Berchtold et al., 2015). Deletion of collagen I in the myofibroblasts reduces the content of Col1 in the stroma of the pancreatic tumors and increases pancreatic tumor progression (Chen et al., 2021). Type XI collagen is fundamental for understanding the biology of pancreatic ductal adenocarcinoma and PRO-C11-511, an ELISA-based biomarker released from type XI collagen post proteolytic processing at amino acid 511 is an important non-invasive, prognostic biomarker for patients with adenocarcinoma of the pancreas (Nissen et al., 2021). Mild hyperthermia (40°C, 42°C) is known to affect the structure of fibrillary collagen of pancreatic heterotypictumor spheroids (in-vitro 3D pancreatic cancer model), thereby inducing cell death via apoptosis and necrosis (Piehler et al., 2020).

Laminin-332 promotes the differentiation of cancer-associated fibroblasts (CAFs). It was also revealed that the CAFs produce laminin-332, therefore playing a role in its ectopic deposition within the tumor stroma. The differentiation of CAFs is also correlated with an elevated expression of α3β1 integrin, the principal receptor of laminin-332. They also act as potential biomarkers and also play a role in the differentiation and maintenance of the CAF phenotype (Cavaco et al., 2018). The roles of different subunits of LM-332, namely α3, β3, and γ2 have been investigated and all the subunits were upregulated in pancreatic ductal adenocarcinoma. The α3 subunit has a stronger impact on cell invasion, proliferation, and migration, the knockdown of theβ3 subunit shows upregulated levels of E-cadherin and downregulated levels of vimentin and the γ2 subunit is known to mediate invasion, proliferation, migration, and apoptosis (Huang and Chen, 2021). An overexpression of laminin5/LAMC2 and its receptors is observed in cancer cells. LAMC2 promotes invasion and migration of pancreatic cancer cells and activates Akt/NHE1 signaling that in turn initiates the acidic condition of pHe-mediated invasion in PANC-1 cells. Hence, LAMC2 can be a distinctive diagnostic agent in pancreatic cancer metastasis (Wang et al., 2020). EMT is a process that enables metastasis in cancer cells, thus playing an important role in the progression of pancreatic ductal adenocarcinoma(PDAC). Studies were conducted to understand the expression of EMT and MMPs that can digest the basement membrane leading to tumor invasion and it was observed that the E-cadherin/β-catenin complex was upregulated in the experiments revolving around the in-vitro interactions between human PDAC cells and ECM components of the PDAC microenvironment. Collagen exerted a more evident effect and ECM components can have an impact on cell migration and invasive potential differently (Procacci et al., 2018).

KRAS is the most usual mutated gene in pancreatic cancer, however, clinical agents directly targeting KRAS are not available. The approach of targeting MEK1/2 which can inhibit MAPK signaling has not been fruitful either. So, studies were conducted to identify mechanisms of MEK inhibitor resistance in pancreatic cancer. Levels of integrin α subunits 1–6 and β subunits are found to be overexpressed and constitutively active in the pancreatic cancer cell lines. Lumen formation, as well as cell survival in the context of MEK inhibition in pancreatic cancer cells, was significantly downregulated following administration of integrin β1 neutralizing antibody, which suggests that PDAC resistance to MEK is achieved through β1 integrin signaling. B1 integrin also plays a significant role in cell migration and may contribute to lumen formation (Brannon III et al., 2020).

6. ***Colorectal cancer:*** Colorectal cancer is the third most common cancer in women and the second most commonly diagnosed cancer in men. Colorectal cancer involves interactions between cells and the surrounding ECM (Le et al., 2020). The progression of cancer causes an imbalance in the homeostasis of the ECM. Collagen type I, III, and IV act as prognostic biomarkers for colorectal cancer. Experiments unraveled that the levels of these biomarkers may give an insight into the degree of tumor invasiveness and activity (Kehlet et al., 2016). Studies were conducted to compare collagenase and collagen remodeling using immunohistochemistry and Sirius red stain. The experiments revealed an increase in Collagen III and Collagen I in colorectal cancer cells and significantly lesser levels of Collagen IV in tissues with distant metastasis. Besides the remodeling of collagen, the expression of MMP-9, MMP-7, MMP-2, MMP-1, and LOXL2 (lysyl oxidase-like 2) was observed to be enhanced in the stroma, leading to the same (Liang et al., 2020). Immunohistochemical studies of 141 cases of colorectal carcinoma tissue microarray samples revealed the expression of collagen XVII in the colonic mucosa of humans and colorectal carcinoma (Moilanen et al., 2015). The levels of a fragment of type VIII collagen, vastatin were observed to be enhanced in colorectal cancer cell serum, which proves its significance as a biomarker for colorectal cancer (Willumsen et al., 2018). Collagen facilitates metastasis and stemness of colorectal cancer tissue via inducing integrin α2β1, which further activates P13K/AKT signaling. Snail also enhances metastatic capabilities and intensive invasion by acting downstream of PI3K/AKT signaling pathway (Wu et al., 2019).

Laminins which are one of the primary components of ECM interact with their cell surface receptors, thereby regulating various cellular processes. Laminin-332 is a marker of EMT and consists of α3, β3, and γ2 chains that control cell adhesion and migration (Fukazawa et al., 2015). Expression of laminin genes is of prognostic value in colorectal cancer. An increase in permeability of BM due to the high LAMA4/LAMA5 ratio has been detected in patients with poor prognoses (Galatenko et al., 2018). Another study revealed that there is an oversecretion of LAMB1 (laminin β-1)(a glycoprotein not secreted by colorectal cancer cells previously) in E1 cells, the metastatic derivative from the colon adenocarcinoma cell line HCT-116 (Lin et al., 2015). Immunoreactivity of the LAMB3 chain was a poor prognostic factor for stage III cancer patients (Fukazawa et al., 2015). mTORC1- and Wnt-dependent partial dedifferentiation of colorectal cancer cells is brought about by shRNA-mediated knockdown of the α5 laminin chain. Integrin interacts with various ECM components, including laminin-5γ2 which further plays a role in the tumor budding of colorectal cancer cells (Zhou et al., 2020).

7. ***Prostate cancer***: Primary reason for cancer-related deaths in men is metastases of prostate cancer to sites like bone (Fitzgerald et al., 2015). Shreds of evidence involving the bone microstructure of mice femurs were analyzed, with and without inoculation of prostate cancer cells. Additionally, the histological assessment provided evidence of the non-directional bone-forming pattern in the prostate cancer-bearing bone. Alignment of collagen fibrils and biological apatite were impaired, attributable to the disruption of the anisotropic microstructure of bone in multiple phases. It was understood that the metastasis of bone cancer involved the disruption of the collagen/biological apatite alignment in long bones, hence impairing their function mechanically (Sekita et al., 2017). Pathological features of tumors with varying elasticity and the stiffness of human prostate cancer were investigated in a xenograft implantation model using shear wave elastography. Nude male mice injected with human prostate cancer DU-145 cells enumerated that collagen fiber, especially type I plays an important role in the elasticity in human prostate cancer (Wang et al., 2017). Bioinformatic tools were employed in studies exhibiting the role of collagen in prostate cancer. Three Gene Expression Omnibus(GEO) datasets via the GEO2R online tool were used to extract the set of differentially expressed genes and the expression of COL4A6 was further analyzed in databases. Real-time quantitative PCR analysis, Western blot assays, and immunofluorescence staining were utilized to detect the expression of the COL4A6 gene. The studies stated that with the progression of

prostate cancer, the expression of COL4A6 protein is downregulated (Ma et al., 2020). Experiments involving next-generation sequencing and gene expression profiling of prostate cancer tissues identified prolyl hydroxylase P4HA1 as the key enzyme responsible for collagen modification which further results in modification of the ECM in cancer as enhanced in primary prostate cancer and castration-resistant prostate cancer.

Another study involved mass spectrometry and proteomics to analyze the ECM composition in the spheroids that were formed by PC3 or DU145 cancer cells or their cocultures with prostate-derived fibroblasts. PC3 cells were observed to produce laminin chains α3, β3, γ2, HSPG2, and collagen type VI (COL6A1). The primary constituents of the fibronectin and collagen-rich ECM were detected in the fibroblastic spheroids. These were primarily revealed to include two α-chains of the collagen type I (COL1A1 and COL1A2), collagen type XII (COL12A1), collagen type VI (COL6A2 and COL6A3), decorin (DCN), and tenascin (TNC). The fibroblasts also produced MMPs (Ojalill et al., 2020). Studies revealed that fibrillar type I and III collagen initiated a fast cell migration response in PC3 cell lines. Nidogen-1, galectin-3-binding protein, thrombospondin, Laminin 411, and TGF-β-induced protein also showed low induction of migration of the PC3 cells (Caires-dos-Santos et al., 2021). Laminin peptides have a significant role in cancer biology. The laminin-derived peptide C16 enhanced invadopodia of DU145 cell lines via stimulating the expression of ROS, cortactin, Tks4, Tks5, and MMP1. Different expression patterns of integrin receptors and their ligands have been expressed in prostate cancer and they have been recognized as promising targets for inhibiting pathways involved in the progression of prostate cancer(Juan-Rivera and Martínez-Ferrer, 2018). The inhibitor BTT-3033 works by selectively interfering with the connection between integrin α2β1 and its ligand, and its effects were examined using LNcap-FGC and DU-145 prostate cancer cell lines. EMT can be successfully inhibited with the inhibition of integrin α2β1. This further initiates apoptosis via activating ROS, caspase-3 activation, Bax protein upregulation, and depletion of ΔΨm. Hence, integrin α2β1 is revealed to play a critical role in the proliferation of prostate cancer cells (Salemi et al., 2021).

8. ***Ovarian cancer:*** The most perilous gynecological disorder in existence is ovarian cancer. The high mortality in ovarian cancer patients might be due to the emerging drug resistance which can be further amplified by the expression of collagen genes. Studies showed different levels of expression of collagen genes in paclitaxel-(PAC), cisplatin-(CIS), topotecan-(TOP), doxorubicin-(DOX), methotrexate-(MTX), and vincristine-(VIN) resistant ovarian cancer cell lines. COL3A1 gene showed a very upregulated form of expression; COL1A1, COL5A2, COL12A1, and COL17A1 genes exhibited less than 50-fold upregulation, and COL1A2, COL15A1, and COL21A1 showed greater than 50-fold upregulation in expression at the mRNA level. This gave an insight into the role of COL genes and proteins in cytostatic drug resistance in ovarian cancer cells and also suggested that fibrillar collagen expression is involved with PAC and TOP resistance in the ovarian cancer cell lines (Januchowski et al., 2016). A novel collagen biomarker of ovarian cancer associated with cisplatin resistance is COL11A1, which COL11A1 upregulates the expression of oxidation enzymes and fatty acid synthesis by binding to receptors DDR2 and α1β1 integrin and hence activating the Src-Akt-AMPK signal pathway (Nallanthigal et al., 2020). With the ongoing progression of ovarian cancer, the omentum transforms into a thick tougher tissue from a thin lacy organ. Levels of collagen I were increased 5.3 times in the omenta of ovarian cancer patients and TGFβ1 were observed to be responsible for it (Fogg et al., 2020). The expression of COL1A2 was noticeably upregulated in high-grade serous ovarian tumors and is significant in pathways leading to the initiation and progression of ovarian cancer (Mamoor, 2021). Numerous studies determined the role of laminins as a potential prognostic biomarker with the usage of GEO, https://www.ncbi.nlm.nih.gov/geo/ (Gene Expression Omnibus, which is a public functional genomics data repository,containing processed sequence data files), GEPIA, http://gepia.cancer-pku.cn/ (Gene Expresson Profiling Interactive Analysis, which is used for analyzing the RNA sequencing expression data of tumors and samples that mainly fall under large consortium projects like TCGA and GTEx), cBioPortal,https://www.cbioportal.org/, ONCOMINE, https://www.oncomine.com/ (a microarray database specially for cancer and has one of the largest collection of curated cancer genomics data; it is also known to provide a web-based data-mining platform service), TIMER, http://timer.cistrome.org/ (a resource comprehensively built for systematical analysis of immune infiltrates across various types of cancer), Metascape, https://metascape.org/gp/index.html#/main/-step1 (a free resource built for gene annotation and analysis, that helps biologists to make sense of one or multiple gene lists; also provides tools to understand pathways and protein networks and hence analyze and interpret OMICS-based studies), Human Protein Atlas, https://www.proteinatlas.org/ (a unique database mapping all the human proteins in cells, tissues and organs of the human body using systems biology, antibody-based imaging, transcriptomics and mass spectrometry-based proteomics), and Kaplan-Meier Plotter, https://kmplot.com/analysis/ (assesses the correlation between expression of 30k genes and survival in 25k+ samples from 21 different types of tumors, including breast, lung, gastric and ovarian cancers; the sources are mainly GEO and TCGA). Results revealed that the levels of LAMC2, LAMB3, and LAMA5 mRNAs and LAMAC1/C2, LAMB1/B2/B3, and LAMA3 proteins were over expressed in ovarian cancer cell lines. Up-regulation in the levels of LAMA4, LAMB1, and LAMC1 mRNA expression was associated with progression-free survival and overall survival in ovarian cancer. An increase in LAMA2 mRNA levels is associated with progression-free survival and that of LAMC2 mRNA levels is associated with overall survival. Overall, LAMC1 and LAMA5 can be potentially good prognostic factors for ovarian cancer and is especially significant in patients suffering from stage IV ovarian cancer (Diao and Yang, 2021). Laminin-5 consists of three short-chain subunits and one of them, LAM5γ2 has been detected in several malignant tumors Levels of expression of the LAMA3 gene, and its base mutation can alter the level of laminin, having a significant impact on the initiation and prognosis of ovarian cancer (Tang et al., 2019).

Secreted phosphoprotein 1(SPP1) plays a significant role in ovarian cancer, and its expression was noticeably higher in epithelial ovarian cancer tissues than in normal ones. Studies revealed that the growth of ovarian cancer in mice can be prevented by silencing SPP1. Silencing SPP1 blocked Integrin β1/FAK/AKT pathway, while ectopically expressed SPP1 influenced the Integrin β1/FAK/AKT pathway positively (Zeng et al., 2018). Expression of pyruvate dehydrogenase kinase(PDK1), a mitochondrial gatekeeping enzyme, regulates the tumor microenvironment, promotes the metastasis of ovarian cancer cells, and controls lactate production via modulation of integrin α5β1 and JNK/IL-8 signaling (Siu et al., 2020). With the increasing evidence, it has been suggested that the potential use of nidogen-1 and nidogen-2 isa promising ovarian cancer biomarker.

9. ***Skin cancer:*** Skin cancer can broadly be divided into 2 categories, namely melanoma, and non-melanoma skin cancers. Non-melanoma is further classified into 2 main subdivisions, Basal cell carcinoma (BCC) and Squamous Cell Carcinoma (SCC). This category of skin cancer also consists of T-cell lymphomas of cutaneous nature, apocrine carcinoma as well as secondary malignancies that are caused due to metastasis from the primary location. Non-melanomas are the most common type of skin cancer, BCC being more common than SCC in this subdivision. Non-melanomas are the most common cancer in the United States of America. People with lighter complexion have a higher chance of developing SCC or BCC. From current reports, it is evident that the incidence of non-melanoma type of skin cancers is gradually increasing in most of the areas of

the United States. People who have a history of sunburns are more likely to have been exposed to SCC. Research also suggests that sun and UV radiations(whether it is chronic exposure or short exposure with high intensity), are major factors that lead to the development of skin cancer. Radiations given in therapeutic form also expose individuals to a certain level of risk of developing skin cancer. Basement membrane proteins, both collagens, and laminins play an important role in the advancement of both basal cell carcinoma and squamous cell carcinoma. One of these collagens is Collagen XV11, which is abnormally overexpressed in the case of SCC, as in normal epidermal cells, its levels decrease with the upward migration of keratinocytes and their further differentiation (Parikka et al., 2006). At the transcriptional level, overexpression of collagen XVII mRNA was found within the intrusive tumors through reverse-transcriptase polymerase chain reaction (RT-PCR) at the epidermal level and inside epithelial tissues. RT-PCR and northern hybridization affirmed the upgraded expression of collagen XVII in SCC (Stelkovics et al., 2008). The correlation of Collagen XV11 ectodomain shedding is strong with the association of the invasive nature of SCC (Galiger et al., 2018). Blockage of ectodomain shedding of Collagen XV11 can be used as a therapeutic strategy for treating non-melanomas (Galiger et al., 2018). SCC and BCC possess characteristic suppression of PTCH1 tumor suppressor genes, but the mechanism of this carcinogenicity is not particularly evident (Reszko et al., 2011).

Laminin isoform laminin-332, formerly known as laminin-5, is associated with all types of skin cancer. This isoform is associated with different stages of cancer starting from the mutation of normal cells, to cancer cell formation and proliferation, its migration, and angiogenesis (Engbring and Kleinman, 2003). Laminin-332 is up-regulated in certain cases of cancer. In normal cells, hemidesmosomes are the site of laminin-332-α6β4 integrin interaction. They act as an adhesive device thereby inhibiting the movement of the normal cells. However, in cancer cells, this interaction triggers a signaling cascade which leads to cancer cell metastasis and survival. Such a property of laminin-332 makes it an attractive subject for cancer therapeutics. Although, there are certain limitations to its applicability in cancer therapy, such as the treatment should be specifically targeting the cancer cell's laminin-332 and not the laminin-332 of normal cells(the latter would otherwise lead to loss of structural integrity of the tissue) (Tsuruta et. al, 2008). These limitations can be overcome by certain strategies like the development of a specific antagonist which would inhibit laminin-332 of cancer cells without affecting the laminin-332 of normal cells.

This approach was envisioned by Marinkovich, who demonstrated the usage of an antagonist of laminin-332 in the treatment of squamous cell carcinoma (SCC). The G4/5 domain of laminin-332, which is usually absent in normal cells, is almost always expressed in squamous cell carcinoma in human cells. When this set of researchers treated an animal model suffering from SCC, with an antibody acting against the G4/5 domain, remarkable inhibition of tumor proliferation was noticed. It also resulted in an increased rate of tumor cell apoptosis and inhibition of squamous cell carcinoma tumorigenesis. Even though the antibody can recognize both G4/5 and native laminin-332 causing a dramatic rate of inhibition of subcutaneous SCC tumorigenesis, it does so without any disruptive effect on the epithelial integrity of normal cells.

4. Targeting basement membrane protein in Cancer Therapy

4.1. Collagen in cancer cell therapy

Collagen is one of the prime components of the tumor microenvironment and takes part in cancer fibrosis. With developing information on the structure and physiological characteristics of collagen, it has become evident that collagen can be used to create modern helpful procedures in cancer therapeutics. It was earlier believed that Collagen Type I that is produced by Cancer- Associated Fibroblasts (CAFs) enhances various cancer formations, but recent findings in 2021 suggest that it might have roles in protecting certain cells from cancer formation indicating chances of new therapeutic developments.

Collagen is closely related top53 (Xu et al., 2019). p53 is a tumor-suppressing protein that mainly works in decreasing tumor angiogenesis as they produce angiogenesis inhibitors endogenously, one of them being Collagen-derived antiangiogenic factors (CDAFs). These angiogenesis inhibitors inhibit the growth of a network of blood vessels to support the tumor microenvironment(Assadian and Teodoro, 2008). The use of collagen inhibitors with radio or chemotherapy is a basic framework of cancer treatment. The amalgamation of collagenase and trastuzumab when applied with the help of thermosensitive gel resulted in a harmful impact on the cancer cells (A. Pan et al., 2018; B. Pan et al., 2018). Human Epidermal growth factor Receptor 2 (HER2) has been targeted in breast cancer therapy, where a HER2-targeted monoclonal antibody, trastuzumab helps in the inhibition of HER2-positive tumors. A thermosensitive gel, biodegradable in nature, PLGA-PEG-PLGA or poly(dl-lactide-co-glycolide-b-ethylene glycol-b-dl-lactide-co-glycolide) is used for the co-delivery of trastuzumab and collagenase. It further aids in the breakdown of collagen of tumor cells, thereby acting as an anti-tumor drug.

Checkpoint inhibitors when used in a mixture with interleukin-2 delivered proficient outcomes against breast cancer cell lines (Ishihara et al., 2019). Collagen type 1α1 or COL1A1 is related to the elevation of breast carcinoma. Ongoing investigations propose that patients with breast cancer growth with the higher articulation of COL1A1 had a superior acknowledgment to the chemotherapy, which makes COL1A1 a biomarker and an alluring treatment for breast carcinoma (J. Liu et al., 2018; J. Liu et al., 2018; C.C. Liu et al., 2018).

RNA profiling has revealed that lung carcinoma,which is impervious to PD-1/PD-L1 bar exhibited higher collagen content. The cell surface receptor Programmed Death-1 on binding with the ligand Programmed death-ligand 1 (PD-L1), helps in stopping T cell activation. Therefore, PD1/PD-L1 has been regarded as a promising factor in cancer immunotherapy (Jiang et al., 2019). Leukocyte Associated Immunoglobulin Like Receptor 1 (LAIR1) helps in collagen-induced T cell exhaustion. LAIR1 immunosuppression can be achieved by neutralizing the upregulation of LAIR2. This impact joined with SHP-1 restraint inhibition, increases the sensitivity of resistant lung tumors to anti-PD1. Therefore, it can be inferred that LAIR1 is an alluring biomarker for immunotherapy and can be utilized in different cancer therapy (Peng et al., 2020).

In a review intended to recognize therapeutic targets and biomarkers for gastric malignant growth, Gene Expression Omnibus (GEO) was used for getting Differentially Expressed Genes (DEGs) between gastric carcinoma cells and unaffected cells. The core gene expression was checked utilizing Gene Expression Proliferating Interactive Analysis (GEPIA), and UALCAN which is an online portal for facilitating tumor subgroup gene expression and survival analysis (Chandrashekar et al., 2017). Medication reaction investigation was directed by Cancer Therapy Response Portal (CTRP). The previously mentioned study revealed that COL1A1, COL1A2, and different individuals from the collagen families can work as prognostic biomarkers and promising therapeutic targets in gastric malignancy (Chen et al., 2020).

Collagen XI α1 (COL11A1) is found in greater abundance in various cancer cells including breast, thyroid, and pancreatic cancer. It is also related to angiogenesis and resistance to drugs in different cancer types. This indicates that COL11A1 can be used as a target for cancer therapy (Liu et al., 2021). In an experiment performing Enzyme-linked Immunosorbent Assay (ELISA), levels of COL11A1 were measured in 3 different groups of people, one group with breast cancer, another with benign breast diseases, and the third group with healthy individuals. COL11A1 was highest in the group with breast cancer. From this observation, it was inferred that COL11A1 can be used as a biomarker for the early diagnosis of breast cancer (Giussani et al., 2018), (Liu et al., 2021).

Type 1 collagen consists of N-telopeptide (NTX), when present at elevated levels,causes skeletal disease progressions that can be fatal. Therefore, the NTX might be helpful as a biomarker for non-small cell lung adenocarcinoma (NSCLC). From a study of Urinary NTX levels from 30 patients(1 month after chemotherapy), it was concluded that this level can be used in the prediction of response to therapy of NSCLC patients with bone metastasis (Kaira et al., 2010).

In a study conducted by JJ Grzesiak and M Bouvet in 2006 in 8 different pancreatic cell lines, several factors like proliferation, adhesion, migration, integrin expression, etc were estimated. In the majority of the cell lines, type 1 collagen aided in promoting the strongest adhesion, migration as well as proliferation. It was further demonstrated that the cancerous phenotype type 1 collagen is specifically mediated by α2β1 integrin, which makes it an alluring therapeutic target in pancreatic carcinoma treatment (Grzesiak and Bouvet, 2006). Both Squamous cell carcinoma and basal cell carcinomas cells have a marked up-regulation of Col XV11. Collagen XV11 has 2 structural domains, both of which are important in tumor progression. Invasiveness is accelerated by the ectodomain which extends to the extracellular space, and proliferation and survivorship are induced by the endodomain. It is seen in a study that blockage of shedding with the help of monoclonal antibodies of Collagen XV11, results in a decrease of matrix independent growth and invasiveness of SCC cells in organotypic co-cultures. These results imply that the selective inhibition of collagen XV11 can act as a biomarker and can offer a strategy for the non-invasive treatment of skin cancer (Galiger et al., 2018).

4.2. Laminin in cancer cell therapy

Laminin is one of the major proteins of the basement film and is significantly included in tumor arrangement, movement as well as sedate resistance. They moreover take portions in prime events such as angiogenesis of tumor, attack, and metastasis of harmful cells, and particularly the control of Epithelial-Mesenchymal Transition (EMT). There are several documented proofs recommending that laminins can be utilized as a prognostic marker in cancer, and can offer assistance in therapeutics for superior survival of patients (Qin et al., 2017).

67LR, which is a high affinity, non-integrin laminin receptor is a member of the basement membrane proteins, and its interaction with laminin is important in different stages of progression of cancer. The major function of 67LR in a cancer cell is promoting tumor cell adhesion to the basement membrane, which ultimately leads to invasion and metastasis. Therefore, 67LR is expressed in excessive amounts in neoplastic cells. A convenient approach to blocking the cancer progression in such cases is inhibition of the binding of 67LR and laminin (Pesapane et al., 2017). 37 kDa/67 kDa laminin receptor is rightly named as the “Bad boy”, which promotes cancer, neurogenerative diseases, as well as viral and bacterial infections. It is also called the LRP/LR, which contributes to a plethora of cancer types. The specific antibody for Laminin Receptor Precursor (LRP), IgG1-iS18, can block the properties of adhesion and intrusion, which ultimately blocks the metastasis in various types of cancer cells, such as oesophageal, pancreatic, melanoma, or colorectal cancer. W3 (Anti-CD4 antibody), which is a specific antibody for LPR/LR, helps in blocking angiogenesis of Human Umbilical Vein Endothelial Cells (HUVE) (Weiss, 2017).

Tumor Budding (TB) phenomenon in the case of colorectal cancer helps in epithelial-mesenchymal transition (EMT), accompanied by downregulation in the levels of E-cadherin. No such effect is observed in the expression of N-cadherin and vimentin. It was seen that the interaction between laminin-5γ2 (LN-5γ2) and integrin is essential in TB in the case of colorectal cancer. Cucurbitacin B, which is a tetracyclic terpenoid of plant origin, is used to inhibit such interactions, which ultimately leads to the blocking of TB in colorectal cancer due to Yes-associated proteins (YAP) (Zhou et al., 2020).

In Pancreatic Ductal Adenocarcinoma (PDAC), there are 2 prime subunits. These are expressed in PDAC and non-tumor cells in a differential manner. These are LAMA3 or Laminin subunit alpha-3 and LAMC2 or Laminin subunit Gamma-2. A serum consisting of LAMC2 and CA 19–9 together is helped in treating the early stages of Pancreatic Ductal Adenocarcinoma (PDAC) or PDAC operational patients. Therefore, LAMA3 and LAMC2 can be used as biomarkers and act as therapeutic targets in PDAC (Yang et al., 2019). Microarray analysis was employed to study the genes helping in EMT in a single layer or spheroid cultures of Lung cancer stem-like cells (CSCs). It was found that Collagen XVII (ColXVII) is needed for maintaining EMT phenotype along with metastasis ability in lung cancer cells. Col XVII is required to stabilize laminin-5, which thereby activates the FAK/AKT/GSK3β pathway, which surpasses the degradation of Snail ubiquitin. Both were overly expressed in lung cancer patients undergoing surgery, creating a severe condition, and its blockage can decrease the metastatic potential of lung CSCs. From this observation, it can be understood that Col XVII/laminin-5 can be used for the treatment of lung cancer patients, and can also be used as a biomarker (J. Liu et al., 2018; J. Liu et al., 2018; C.C. Liu et al., 2018). In a study to determine the effects of laminin on tamoxifen-sensitive LM05-E breast cancer cell line, it was found that pretreating the cell line with laminin tends to decrease the ability of cancer cells to form mammospheres and secondary mammospheres (Raffo et al., 2013), which further leads to a decrease in Aldehyde Dehydrogenase (ALDH) activity.MAPK/ERK pathway helps in mediating the effects of laminin, which finally induces resistance to tamoxifen in the LM05-E breast cancer cell line (Berardi et al., 2017).

Protocadherins (PCDH) have a significant role in pathogenicity as well as in the spread of cancers like gastric cancer. In a study conducted to explore the function of Protocadherin-8 (PCDH8) in gastric cancer, it was found that higher levels of PCDH-8 are related to poor prognosis in GC, which was correlated with upregulation of LAMC2. So, it can be argued that greater expression of PCDH8 can be used as a marker for poor prognosis in the case of gastric cancer (Lin et al., 2018).

4.3. Integrin in cancer cell therapy

Integrins mediate bidirectional cellular signal transduction and remodeling of stroma in tumors as well as hardening of tumor stroma, which constitutes the principal steps in cancer progression that helps cancer cells in tumor invasion, possessstem cell-like properties as well as helps in acquiring resistance to drugs. Owing to the antagonistic nature of integrin response in the cancer cell and the surrounding tumor microenvironment, integrins, in cancer therapeutics have always been a challenging clinical development (Hamidi and Ivaska, 2018). Adhesion of cells to extracellular matrix is crucial for normal functioning and development in the cell, which is mediated by integrins in normal cells, as well as cells in tumor microenvironment and surroundings. However, in cancer cells, this adhesion is impaired due to the malfunctioning of integrin receptors and ligands of the extracellular matrix, which in turn helps in cancer cell progression, metastasis by extravasation (Valdembri and Serini, 2021). All of this evidence suggests that using integrins for cancer therapeutics is a promising strategy for drug development.

In cancer cells, they promote metastasis and progression and are often associated with poor prognosis in cancer of various types, triple-negative breast cancer in particular. Integrins help in the activation of various pathways as well as crosstalk between various growth factors and their receptors. This crosstalk helps in tumor initiation, growth, and metastasis of tumor cells (Li et. al, 2021). Cellular crosstalk between αvβ6 and Epithelial Growth Regulating Factors, regulates cancer progression. As a therapeutic strategy, blocking integrin αvβ6 or αvβ6 along with Transtuzumab helps in the treatment of breast cancer patients who have developed resistance to Trastuzumab (Schaffner et al., 2013). Considering the varying effects of Integrin αvβ6 in cancer progression, it has extensively been used in tumor imaging and consequent therapy (Niu and Li, 2017).

In OSCC, the smoking, alcohol consumption, and HIV alone are insufficient for disease progression and it was found that oral

periodontal pathogens play a principal role in cancer progression, metastasis, and development of stemness of cancer cells. These pathogens promote cancer by crosstalk between two signaling pathways, Integrin/Focal Adhesion Kinase and TLR/MyD88. This crosstalk can be reversed or inhibited by a bacteriocin called Nicin ZP. In Oral Squamous Cell Carcinoma, cell migration was mediated via the integrin αV which activates the FAK expression, this process is inhibited by Nicin. Along with Nicin, suppressing MyD88 inhibits cellular migration and cancer progression. Therefore, it is evident that Integrin αV can act as a potential biomarker for OSCCs and its crosstalk mechanisms can be inhibited by bacteriocins such as Nicin ZP (Kamarajan and Ateia et al., 2020).

β1 and β3 integrins cell adhesion proteins are involved in various steps of tumor development and cancer progression and it has been proven in preclinical trials that under the influence of antagonists like Arginylglycylaspartic acid (RGD),peptide mimetics of these two integrins significantly inhibit tumor growth. These antagonists mimic the ligands of integrins and bind to them which inhibits the ligand binding of integrins thereby resulting in tumor inhibition. Clinical studies have shown the opposite effects in cells, under different ratios of β1 and β3 integrins, which means that proliferation and cancer metastasis, are two independent incidents and are independently regulated. Further studies are required on the functions of such proteins for better therapeutic approaches (A. Pan et al., 2018; B. Pan et al., 2018).

5. Discussion

Basement membrane proteins play a significant role in cancer formation, cancer cell invasion, and metastasis. Invasion of cells within the matrix is of principal importance for tumor cell division and growth. Basement membrane proteins have a significant effect on the invasive nature of cancer cells of different parts of the body, such as the lung, pancreas, breast, skin, etc. Various studies as mentioned in this review suggest that different Basement membrane proteins can act as an excellent biomarker, which makes it an alluring entity for researchers who aim at developing new therapeutic strategies for different malignancies. With the recent developments in proteomics and gene expression technologies, there has been a significant rise in the discovery of the proteins and receptors associated with membranes. Overexpression of any membrane receptor is usually observed in malignancy, and this feature is used in many cancers cell therapy and early diagnosis. Numerous clinical and preclinical studies have been conducted where certain basement membrane proteins, alone, or integrated with integrins are used as targets for drugs or antibodies. This methodology is with drawbacks such as, in typical cells, hemidesmosomes are the site of laminin-332-α6β4-integrin interlinkage. In disease cells, this link triggers an interrelated course of chemical reactions which prompt malignant cell metastasis and endurance. Such a property of laminin-332 makes it an intriguing subject for malignancy therapeutics. Impediments to its usefulness in malignant growth treatment are, the therapy needs to be explicitly focused on the disease cell's laminin-332 and not the laminin-332 of typical cells, which would prompt loss of integrity of the tissue (Tsuruta et al., 2008). These restrictions can be brought under control by specific techniques like the advancement of explicit antagonists which would restrain laminin-332 of disease cells without affecting the laminin-332 of ordinary unaffected cells.

6. Conclusion

In epithelial cancer, it is a prerequisite for the cells to invade through the basement membrane in the process of metastasis. The cancer cells acquire the ability to breach the basement membrane due to the modification of the cell to matrix adhesion, which is achieved by different proteins such as laminin, collagen, and integrins. BM protein collagen IV is crucial for maintaining the structure and function of BMs. Laminin is sufficient for maintaining the structure of BM at early stages, although Collagen IV is responsible for maintaining the stability and integrity of the membrane as well as different functions at later stages of development. Therefore, abnormal expression of laminin and collagen is a hallmark for a certain types of cancers and therefore can be targeted for developing therapeutics. Basement membrane was earlier thought to be invaded by protease degradation, but with the advancement in science, it can be observed that cancer cells have physical factors that facilitate this invasion. With further understanding of the basement membrane proteins and receptors, new strategies can be developed for safer therapeutic options for cancer, which can be used singly or in combination with pre-existing therapeutics, such as radiotherapy or chemotherapy. Cancer stem cells have a regenerative property and so can form tumors. They also infer resistance to multiple drugs (Prieto-Vila et al., 2017) and help in the metastasis of cancer cells. Diverse cancer stem cell regulators have been identified which makes it easier to develop several drugs and vaccines that target these stem cells. Many such clinical trials are currently in incubation and show promising therapeutic prospects in future cancer cell therapy.

Declaration of Interests

The author declares no conflict of interest.

Data availability

No data was used for the research described in the article.

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