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Review Article

Potential Role of Extracellular Matrix and its Components in Cancer Development and Progression

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Abstract: Cancer occurs due to unregulated multiplication of cells. Extracellular matrix (ECM) proteins come in a huge variety, and each one has unique biochemical and biophysical characteristics that affect the phenotype of cells. To ensure tissue homeostasis, the ECM undergoes continuous deposition, remodeling, and degradation from early development until maturity. In order to govern cell behavior and differentiation, the ECM's composition and structure are spatiotemporally controlled. However, when ECM dynamics are dysregulated in any way, illnesses like cancer can arise. Collagen is a major component involved in ECM regulation but after cross linking with each other, it initiates ECM stiffness, loss of cell contacts and cell geometry. Due to which most of the regulators including the Transcriptional coactivator with PDZ-binding motif (TAZ) and Yes-associated protein (YAP) are inhibited and cause extensive cell proliferation and tumor metastasis. Proteases like Metalloproteinases degrades collagen and other proteins that leads to ECM break down and cancer progression. As cancer spreads, the stress and pressure on cells increases which damage arteries and capillaries causing hypoxia. Hypoxia inducible factors take advantage of the situation and enhance invasiveness of cancer cells. This stress generated by tumor cells in their surrounding causes dysregulation of ECM matrix. Finding strategies to study the relationship between mechanical stress in tumors and their destructive behavior is vital for cancer research.

Keywords: Cancer Development and Progression, Tumor Microenvironment, Extracellular Matrix.

1. INTRODUCTION

Cancer refers to the condition in which cells of the specific part of the body proliferate uncontrollably, invade in neighboring cells and organs, and destroy the healthy cells. Sometimes those cells localized in a specific part called benign tumor but sometimes it spread. This spreading of tumor cells from one part to other areas of whole body is known as metastasis or tumor progression [1]. Multiple symptoms indicate tumor progression including lump formation, unexplained bleeding etc. [2]. Cancer became the leading cause of death and almost 90% deaths are due to cancer progression worldwide. This death rate is increasing annually though there are great advances in the treatment of cancer from targeted antibiotic therapy to chemotherapy [3]. Numerous researches are ongoing to explore novel therapeutic components to target cancerous cells either by ceasing their proliferation or by eradicating them [4]. Basically, Tumor microenvironment (TME) is involved in affecting cancer progression that not only consist of tumor but also the non-cancerous cells that include immune cells, endothelial cells, adipocytes, interstitial cell, extracellular matrix etc. TME and especially ECM has proved to be the most advantageous niche for cancer cells enrichment [5]. Extracellular matrix (ECM) is the non-cellular component of tissue and secreted by the cells for the sake of biochemical and structural support. ECM comprises of polysaccharides, proteoglycans, proteins, water and all of these components help in survival, differentiation and functioning of that particular tissue [6]. There are several proteins involved in the formulation of extracellular matrix that are classified into two

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major categories, glycosaminoglycan and fibrous proteins. Collagen, elastin, fibronectin and laminin are included in fibrous proteins while hyaluronic acid, heparin sulfate and chondroitin sulfate are example of glycosaminoglycan. These proteins are evenly distributed in extracellular matrix in the form of crosslinked meshwork [7]. There is a strong relationship between ECM and cancer progression. Cancer cells are responsible for the rigidity of extracellular matrix and in repay the rigid ECM changes the structural characteristic of cancer cells. The connection between these two activates multiple signaling and regulatory pathways. So, it's very important to understand the basic phenomenon that would assist to discover more therapeutic targets for treatment of cancer [8].

1.1. Functioning Mechanism of ECM

All the components of ECM functions in an orderly manner to maintain the physical, structural and biochemical properties of cells and tissues that are crucial to regulate cell behavior. The physical function of ECM is to retain the porosity, rigidity, insolubility of membrane and integrity of tissues [9]. As shown in the Figure 1, ECM provides anchorage site to tissues that helps them in migration from one compartment to other. It also implicates biochemical properties by acting as signal reservoir and initiate signal transduction pathways by interacting the cells with their microenvironment. It can particularly bind to different growth factors and serve as signal co-receptor. It also helps the cell to present signal receptor on their surface and promote cell adhesion. ECM also initiate cell signaling pathways by operating as precursor of signaling fragments. Cells

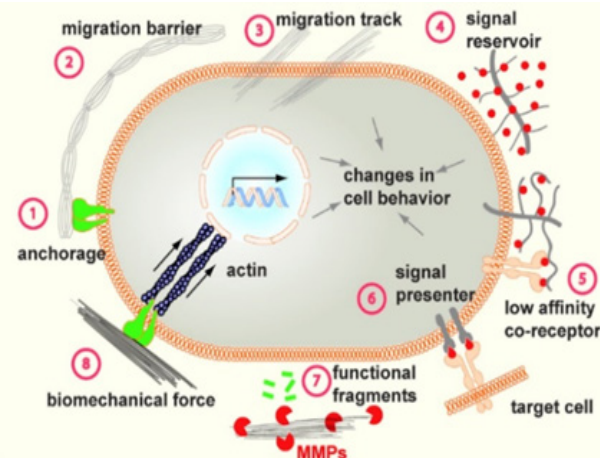

Fig. 1. Functioning mechanism of extracellular matrix.

recognize the biomechanical ability of ECM that is involved in maintaining stiffness of tissues [10].

One of the most interesting features of cell and extracellular matrix is that their relationship is reciprocal. Cells are rearranging various components of ECM to carry out signaling and biosynthetic pathways while ECM regulates and maintain cell's normal behavior and changes in any component of ECM leads to change behavior of other cells which causes different abnormalities or disease like cancer [11].

1.2. Components of ECM

The ECM is made up of a variety of proteins, which result in the varied structures and characteristics that it possesses. Laminin, fibronectin, proteoglycans, and collagen are the ECM's primary building blocks. There are multiple subtypes of these blocks that can further explain their role in the general structure and characteristics of ECM, even among these ECM components (Figure 2). Diverse subtypes of ECM molecules bestow various functions that proved to be crucial for proper operation of entire body since structure determines function**.** Table 1 shows the general components of extracellular matrix and few of those components are comprehensively discussed below:

1.2.1. Collagen

With 28 distinct subtypes identified, collagen is the most important element of the ECM and the most prevalent protein in human tissue. Each kind is made up of right-handed triple helices that are twisted into left-handed helical chains either in form of heterotrimers or homotrimers. The Gly-X-Y motif is present in a wide collection of proteins known as the collagen superfamily, where proline or hydroxyproline are often used for X and Y [13]. The tiny glycine and interchained hydrogen help to stabilise the large proline and right-handed helical shape. Depending on where it is located in the tissue, each collagen fibre is composed of different subtypes of collagen. Kind I collagen, the most prevalent type of fibrillar collagen, is present in connective tissues including skin, bone, tendon, and cornea. Organ development and wound healing are two processes in which collagen I plays a significant role [14].

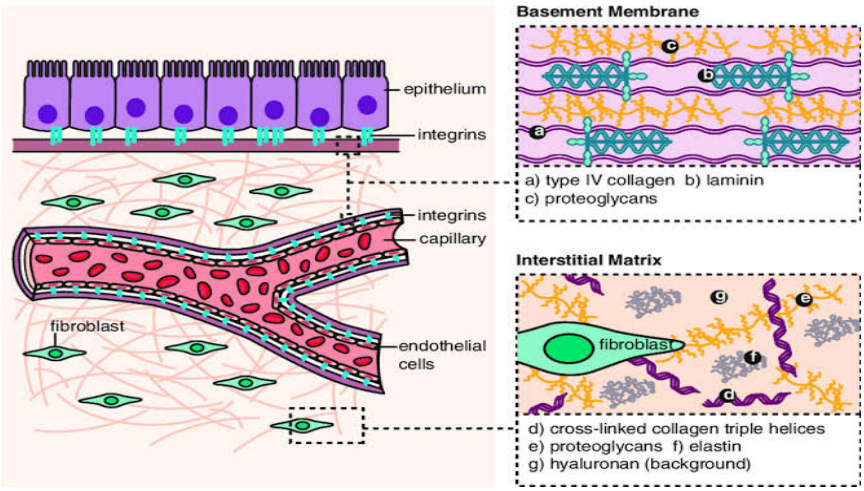

Fig. 2. Arrangement of certain ECM molecules in the basement membrane and interstitial stroma. The distinctive elements of the extracellular matrix are displayed in Panel A (top). The organisation of various proteoglycans, collagens, fibrone [46].

Precursors are created before any fibrillar collagen is generated. The triple helical helix is put together by the chains in (RER)rough endoplasmic reticulum. For initiation of the triple helical helix, lysine and proline are hydroxylated followed by the glycosylation of the molecule. Golgi apparatus is where the procollagen is subsequently processed for cellular export [15]. In the ECM, procollagen is either processed before or after it is secreted.

Specific matrix metalloproteinases (MMPs) break the C terminal propeptide off, and if it is not removed, collagen becomes very soluble and is unable to form fibrils [16, 17]. The N-propeptide in first three collagen types are cut off, but they are left in type V, type XI, and other fibrillar collagens. This doesn't influence fibril production but changes the fibril's shape and diameter. Through steric hindrance and charge interactions, the N-propeptide of type XI and V collagens stick out from the spaces among the collagen molecules to inhibit lateral growth [18]. Currently, it is thought that type XI and type V collagens nucleate and regulate synthesis of collagen fibrils. Despite relatively modest levels in the overall collagen composition of most tissues, it was demonstrated that in case of mice, collagen V deletion results in fibril disassembly. Once produced, the microfibrils may join forces with other microfibrils to expand into bigger fibres. Other ECM proteins mediate this process.

Decorin and biglycan are examples of small leucine rich proteoglycans (SLRPs) that include motifs (collagen binding) that allow to control fibre development, content, shape, and size [20]. Fibril-associated collagens with interrupted helices

Table 1. General components of ECM and their functions [12].

Components of ECM	Functions
Proteoglycans: (Aggrecan. Betaglycan, Decorin, Perlecan Syndecan)	• Facilitate cell movement during tissue morphogenesis and repair; Control the actions of released proteins and play a significant part in cellular chemical communication.
Glycosaminoglycans: (Hyaluronan Chondroitin Sulfate, Dermatan Sulfate, Heparan Sulfate, Keratan Sulfate)	• Co-receptors that work in tandem with traditional cell-surface receptor proteins to bind cells to the ECM and to start their reaction to some extracellular signal proteins; Enables the blood and tissue cells to rapidly diffuse nutrients, metabolites, and hormones; Helps the matrix endure compressive stresses by forming hydrated gels.
Fibrous proteins: (Collagens, Elastin, Fibronectin, Laminin)	• Give the matrix more resilience, and strength; Activate intracellular signalling pathways through influencing cell behaviour and survival, development, shape, and polarity of cells.

(FACIT) don't result in the formation of fibrils and stay connected to collagen microfibrils surface, are another subfamily of collagen. Their main job is to attach to other ECM proteins including proteoglycans and SLRPs and facilitate the creation of higher-order structures. Lysyl oxidase (LOX) further stabilises the supramolecular collagen assembly, which results in improved mechanical qualities all around. Collagen's high tensile strength is a result of the covalent cross-linking of its N and C terminal ends by the enzyme LOX both inside and between microfibres [21].

There are network-forming collagens such type IV, type VIII, and type X besides fibrillar and FACIT collagens. By the help of 7S N-terminal domain, the type Collagen IV assembles into a tetramer. A hexamer is formed by interaction between C-terminal domain of two Collage IV molecules, NC1. The basal lamina and the interstitial stroma are divided by a stable collagen network that is made possible by collagen IV's two domains [22]. The basal lamina contains additional ECM proteins such laminin, nidogen, and perlecan that fortify this barrier and help to preserve the body's cellular order. The role of other ECM proteins including proteoglycans, laminins, and fibronectin cannot be overlooked, even though different forms of collagen are capable of constructing distinct kinds of structures that serve as foundation of ECM construction. They have a significant impact on the extracellular matrix's chemical and physical characteristics through, for example, their chemical properties and binding motifs that bind to growth factor. Moreover, they act as a connection between the cells and the ECM [23].

1.2.2. Proteoglycans

Some proteins that form covalent bonds to glycosaminoglycans (GAGs) are known as proteoglycans. Long chains of repetitions of negatively charged disaccharides, known as GAGs, can be made of chondroitin/dermatan sulphate, heparin sulphate, keratin sulphate or hyaluronan [24]. Proteoglycans are capable of sequestering cations and water by the negative charge of these GAGs, which provides them their space-filling and lubricating properties. Only those proteoglycans that are located in transmembrane, in extracellular and pericellular area will be enclosed in this review [25]. Syndecans makeup four of the thirteen transmembrane proteoglycans. These are proteins that considered to function by way of co-receptors. 3 domains are present in syndecans i.e. ectodomain, transmembrane domain, and an intracellular domain. The ectodomain is found to be linked to the GAGs, which are generally heparan sulphates and can be easily shed by the action of MMPs, [26]. Because syndecans' ectodomains are inherently disordered, there may be an interaction with a wide range of other molecules to execute a variety of natural tasks. Its actions include binding to morphogens and growth factors, assisting exosome absorption, and performing as co-receptor for tyrosine kinases receptor [27].

Perlecan is the most important proteoglycan located in pericellular region of basement membrane. It is basically a heparan sulphate proteoglycan-(HSPG) that consists of a number of domains, each with a unique set of activities and binding sites. These sulphates can attach to a wide range of substances, including collagen, growth factors, and growth factor receptors. The binding of Perlecan connects nidogen, collagen IV and laminin in basement membrane for strengthening of the basement lamina [28, 29].

Hyalectans and SLRPs are two different types of proteoglycans that are present in the extracellular area. Hyalectans have the same structure as lectins, with GAGs linked between the N and C terminal ends of the N terminal, which binds hyaluronic acid, and the C terminal, which binds lectin. Aggrecan, Versican, Neurocan, and Brevican are four different genes that encode hyalectans. While brevican and neurocan are present in CNS, aggrecan can be mostly found in bone cartilage and brain [30].

Versican, on the other hand, is present in practically all organs and tissues' ECM. It might behave as molecular link concerning the extracellular matrix and cell surface. It has been demonstrated that Versican binds to fibronectin and type I collagen, both of which are integrin substrates. Versican sequesters fibronectin from the cells integrins after binding to the RGD motif of fibronectin, which results in a lack of cell adhesion [31]. The 18 different gene products that make up the SLRP family, each of which has several splice variants and processed forms, make up the biggest family of proteoglycans. These proteins feature a leucine-rich repeat-dominated central region and

a relatively small protein core (LRRs). They are expressed in the ECM as different tissue types grow, which suggests that they play a crucial role in controlling organ shape and size throughout homeostasis and embryonic development. Along with other proteoglycans, the SLRPs biglycan and decorin, which include motifs (collagen-binding), control the assembly of collagen fibres [31].

1.2.3. Laminin

The basal lamina or certain mesenchymal compartments frequently contain laminins, which are trimeric glycoproteins made up of γ chains. Although potentially 60 different laminins might be produced by combining the 12 mammalian α, β, and γ chains, thus yet only 16 combinations have been found [12]. The size of the α chains is between 200 and 400 kDa, whereas the size of the β and γ chains is between 120 and 200 kDa. The size of a trimmer can then range from 400 to 800 kDa. Laminins emerge as molecules in cross shape under rotating shadowing-electron microscopy. Its long arm is made up of three chains, which create a -helical coiled coil structure, while each of the three short arms consists of a single chain [32].

Phenotypic maintenance, migration, adhesion, differentiation, and apoptosis resistance of laminins are all cell type-specific. Laminins can establish an active association among the cell and ECM by binding to integrins. To enable the activation of different signalling cascades and intracellular regulation of cytoskeleton, distinct heterotrimeric-laminins will have unique integrin heterodimers-binding companions [33]. Basement membrane is thought to mature when collagen IV is deposited there, which is important for structure stability in development. Laminins bind to collagen IV, although the precise process by which they do so is yet unknown. Initial research suggested that nidogen acts as a bridge between two networks existing in basement membrane by binding to laminin via collagen IV and the LE domains of the γ chain [34, 35]. Nidogen might not be the main link linking laminins and collagen IV, according to recent studies. Heparan sulphates have been found to directly mediate the interaction between laminins and collagen IV. Thought to mediate this function, perlecan was genetically deleted in mice, but this did not cause collagen IV depletion. Agrin, another pericellular HSPG, is now thought to act as a compensatory candidate. According to this concept, the laminin network that contains nidogen as well as the 7S and NC1 domains of collagen IV would all bind to perlecan and agrin [36].

Laminins are essential for assembling the basement membrane and interacting with cells of the ECM. Laminin polymerization appears to be the earliest step in the formation of the basement membrane, according to recent research. Indeed, the failure of basement membrane construction caused by genetic ablation of either γ1 chain or β1 chain evidenced to be lethal. While proteoglycans, collagen and hyaluronic acid make up the majority of ECM's structural elements, laminins are chemicals that allow cells and ECM to interact [37, 38].

1.2.4. Fibronectin

A multi-domain protein called fibronectin connects the cell to the ECM by interacting with the numerous previously mentioned ECM elements. It contains a single gene that encodes it, but due to alternative mRNA splicing in humans, it has 20 isoforms. In the ECM, fibronectin creates a fibrillar network similar to collagen [12]. The two cysteine disulfide linkages that fibronectin normally produce as dimer outside the cell, are essential for it to accumulate in a fibrillar manner. The binding to α5β1 integrins via an RGD binding motif and a synergy site on the fibronectin molecule mediates fibronectin matrix building [39, 40].

The unfolding of soluble secreted fibronectin is done by these integrins, exposing hidden sites for more binding of fibronectin molecules to create the fibrillar network. It has been demonstrated that fibronectin fibril production is inhibited by anti-fibronectin and anti-integrin antibodies. Fibronectin are present at cell surface in high concentrations as a result of integrin clustering that is brought on by fibronectin binding. Through each molecule's N terminal assembly domains, this process increases the contacts between fibronectin and fibronectin [41].

The actin-cytoskeleton causes fibronectin molecules to alter their shape once fibronectin is anchored to surface of cell by help of integrins. As a result, obscure binding sites for, heparan sulphates, fibronectin, collagen, heparin and

supplementary proteins of matrix will become visible in C terminal regions of fibronectin [42]. The network of fibronectin develops and becomes insoluble by robust non-covalent protein-protein connections, however supplementary ECM proteins may promote mature lateral contacts between the fibrils. The comparatively flimsy binding sites are stabilised at certain places by these interactions. The turnover of fibronectin matrix, however, has mostly gone unstudied [43].

Fibronectin has been linked to a number of roles, such as a part in the assembly of collagen type I, because of the numerous binding sites, it possesses for other ECM proteins. It has been demonstrated that collagen fibrils do not accumulate in the absence of fibronectin, pointing to a function for fibronectin in collagen synthesis. However, given that recent research has also suggested that collagen has a function in promoting fibronectin assembly, this interaction may turn out to be reciprocal [44, 45].

2. ECM AND CANCER

2.1. ECM Molecule Dysregulation in the Advancement of Cancer

The significance of ECM in controlling cell proliferation, cell migration and apoptosis has changed how cancer is traditionally viewed. A tissue-specific microenvironment that is crucial to the development of tumor is created by the precise orientation and arrangement of ECM elements microscopically [47]. It is now known that in addition to ongoing active remodelling, the ECM also triggers pharmacological and biophysical signals that affect cell adhesion and migration. Small changes to the homeostasis of the microenvironment can significantly influence the proliferation rate of cancer cells. Collagen, the principal component of the extracellular matrix influences the basic functionality of the matrix. The loss of ECM homeostasis can, in fact, be caused by alterations in the deposition or degradation of collagen [48, 49].

In a dynamic interaction between the microenvironment and resident cells, the surrounding ECM experiences major architectural changes as the tumor cells proliferate. The alterations, including the elevated production of fibronectin and collagens I, III, and IV, indicate that the extracellular matrix and tumor cells must continually engage for the tumor progression. Figure 3 shows the normal regulation of tissue homeostasis which gets disturbed when tumor cells exert pressure on the normal cells, and is more facilitated by the collagen deposition. They form cluster like structure nearby tumor cells and help tumor metastasis [1, 50, 51]. By interrupting with cell polarity and cell-cell adhesion, increased matrix protein deposition accelerates the evolution of tumor by boosting growth factor signalling. The precise part that collagen deposition plays in the development of tumor is complex, though. Recent research has demonstrated that increased collagen cross-linking and deposition promotes the growth of tumor through increasing integrin signalling. However, it is intriguing to note that fibrillar collagens I and III reductions to encourage harmful performance, demonstrating that the biomechanical stresses created by accumulation of collagen is equally advantageous and detrimental consequences on tumor formation [52, 53].

The process of collagen crosslinking is possible by both enzymatic and non-enzymatic ways. Amine oxidase enzymes, LOX family in

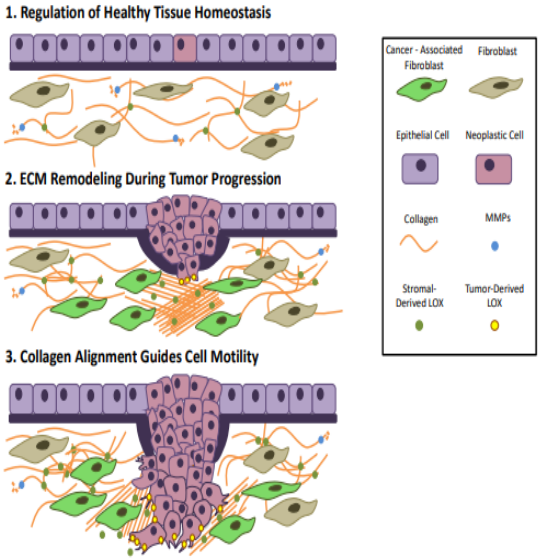

Fig. 3. How the ECM changes when cancer develops and spreads. (1) Rapid proliferation of epithelial neoplastic cells stresses the basement membrane. (2) Because of mechanical stress, the basement membrane swells. Collagen is being deposited more heavily to nearby cancer-related fibroblasts. Collagen is aligned by lysyl oxidase (LOX), which is produced from stromal cells. (3) Neoplastic cells pierce the membrane and move along collagen-aligned fibres [1].

particular, modulates collagen cross-linking in a regulated manner [54]. The production of LOX by the primary tumor cells induces the cross linking of the collagen and elastin, hence enhancing the stiffness of the matrix and the total volume of the adjacent ECM.

Increased ECM stiffness promotes the formation of focal adhesions and cell motility, by stimulating integrins and intensifying cytoskeletal stress induced by Rho. Clinical studies have linked fibrosis, elevated collagen cross-linking and an enhanced probability of cancer metastasis to increased LOX activity. Additionally, increased LOX activity had been observed to promote cell contractility, actin polymerization and migration on the invasive borders of tumors, creating a passageway to follow for succeeding tumor cells [55, 56].

During tumor metastasis, visualisation of the surrounding epithelial tissue has shown localised matrix structure and alignment along the leading edge of invasive tumors. Indeed, it has been shown that local cell invasion of these tumors is directed along collagen fibres that are aligned, which suggests that collagen fibre linearization promotes tumor invasion [57]. It can be said that these closely spaced fibres serve as conduits for spreading cancer cells to leave the tumor. Breast cancer serves as a notable example of collagen alignment during tumor propagation. Despite the fact that epithelial tissues' collagen is often knotted and chaotic frequently, the tissue that surrounds breast tumors becomes thicker, stiffer, and perpendicular to the tumor's border [58]. A recent study indicates that the architecture of the matrix Fibers reduces the protrusions along the collagen fibre, which in turn lessens the distance covered by the migrating cell and boosts the efficiency of tumor migration [59].

In ECM, increased levels of the hyaluronic acid glycosaminoglycan are correlated with greater risk of malignancy and poor prognosis, just as collagen and LOX that are essential in determining the compressive properties of many biological tissues [60, 61]. The ideal biophysical properties for tissue homeostasis result from the interplay between the tensile strength provided by collagen and the compressive compliance conferred by hyaluronic acid. Hyaluronic acid has been identified as both an induction signal and migratory substrate for mesenchymal transition [62]. Hyaluronic acid is frequently utilized as a biomarker for prostate and breast cancer. Increased LOX and collagen levels directly improve stiffness of ECM and physically drive cell proliferation and motility; however, it is yet unknown how hyaluronic acid contributes to cancer spread. However, its dysregulation can act as a vital indicator for cancer invasion and metastasis [63].

2.2. Mechanotransduction is Mediated by Protein Unfolding

ECM signalling is a critical biological mechanism which promotes cell division, cell proliferation, and prevention of apoptosis. In essence, a cell cannot survive if it cannot perceive its mechanical surroundings. Numerous investigations have revealed that via chemical signalling molecules, such as metabolic precursors and growth factors, cells are able to sense their surroundings [64]. It is thought that cells use lamellipodia to physically probe their surroundings and that integrin-based focal adhesions, which feel the mechanical feedback and resistance of their environment and set off an intracellular signalling cascade, sense ECM stiffness. The actin cytoskeleton is thought to be responsible for cells' capacity to explore their surroundings because it prevents polymerization of F-actin from inhibiting cells' ability to generate force, which has biological impact comparable to cells plating on a soft substrate [65]. In particular, contractile actin bundles and their upstream regulators, such Rho-associated protein kinase (ROCK), that are required for cells to involuntarily perceive their surroundings, are what give cells the ability to generate internal forces. While it is evident that mechanical stiffness significantly influences cellular behaviour, the mechanism by which mechanical stress is transduced into gene transcription remains poorly understood [66].

Recent studies have shown how crucial protein unfolding is for transmitting the mechanical force that the ECM exerts. In fact, it has been demonstrated that during force transmission, a major molecule in focal adhesion complexes, talin that connects focal-adhesions to actin cytoskeleton, mechanically unfolds [67]. When condensed to focal-adhesion complexes bound to talin, deletion in liver cancer 1 (DLC1), a negative regulator of cell contractility and RhoA, impacts cell's behaviour. When the talin's R8 domain was mechanically clamped, molecule's mechanical unfolding was

blocked, disrupting DLC1's downstream signalling and, as a result, disrupting cell behaviour [68].

Additionally, every rod subdomain of talin is capable to get unfold over a physiologically significant range of forces (10-40 pN), according to single molecule force microscopy. The mechanical stability of the talin rod bundles might potentially be impacted by a small number of single point mutations, given that the stability range of talin subdomain within the focal adhesion complex is dependent on minute structural changes [69]. These mutations may cause cellular responses to be misinterpreted in response to ECM signals. The performance of cancer cells in tumor microenvironment may be affected by incorrect interpretations of the ECM, which may result in deactivation of DLC1, enhanced cell migration and cell contractility [70].

2.3. TAZ and YAP Mechanotransduction in the Development of Cancer

YAP (Yes-associated protein) and TAZ (Transcriptional coactivator with PDZ-binding motif) are powerful regulators of cell survival and proliferation, and they are essential for controlling differentiation of cells, self-renewal of progenitor cells and development of organs. The YAP/TAZ proteins actively move back and forth between the cytoplasm and nucleus throughout these pathways. YAP/TAZ proteins regulate certain signaling cascades in the cytoplasm, such as the Wnt signaling pathway, in a relatively inactive manner [71]. While, they easily interact with DNA-binding transcription factors in the nucleus, notably those belonging to the TEA domain (TEAD) family, to control the gene expression linked to cell proliferation, a crucial cancer-related characteristic. The accumulation of YAP/TAZ in the cytoplasm following pharmacological inhibition suggests that the major role of YAP/TAZ is the control of gene transcription [72]. Notably, YAP/TAZ activity is suppressed when a cell separates from a substrate, indicating that the F-actin cytoskeleton and mechanical-force may be able to control how quickly YAP/TAZ travels to the nucleus. Furthermore, researchers have observed that the YAP/TAZ nuclear transport and the associated physiological processes are strongly regulated by cell-spreading geometry and matrix elasticity in mammalian systems. All of these findings point to a direct chemical pathway connecting mechanical force with malignant cellular behavior, cell signaling (cytoskeleton mediated) and coupling focal adhesion of mechanical stiffness to the YAP/TAZ pathway to cause tumor invasion and metastasis as described in Figure 4 [73].

There are several putative proteins and routes that might mediate nuclear translocation of YAP/TAZ proteins, even if cytoskeletal stress is sufficient for this to happen. The heparan sulphate proteoglycan agrin, for instance, is well renowned for its specific functioning in the development of neuromuscular junctions during process of embryogenesis [74]. Recent studies have raised the possibility that agrin may potentially behave as ECM sensor, stabilizing focal adhesions and facilitating nuclear translocation of YAP/TAZ protein via the muscle-specific kinase (MuSK) and lipoprotein-related receptor-4 (Lrp4) pathway [75]. The Hippo tumor suppressor pathway is inhibited by the activation of MuSK and Lrp4 by agrin, which eventually results in an increased YAP/TAZ nuclear translocation. It has been demonstrated that agrin depletion stimulates YAP's inhibitory phosphorylation, which forces nuclear YAP to stay in the cytosol. On the other hand, YAP activation was only required for the further delivery of agrin into cells cultivated on flexible matrices. Together with modifications in actomyosin contractility, a number of junctional proteins comprising members of the Angiomotin (AMOT) family of proteins, control protein YAP/TAZ. It has been demonstrated that AMOT proteins directly attach

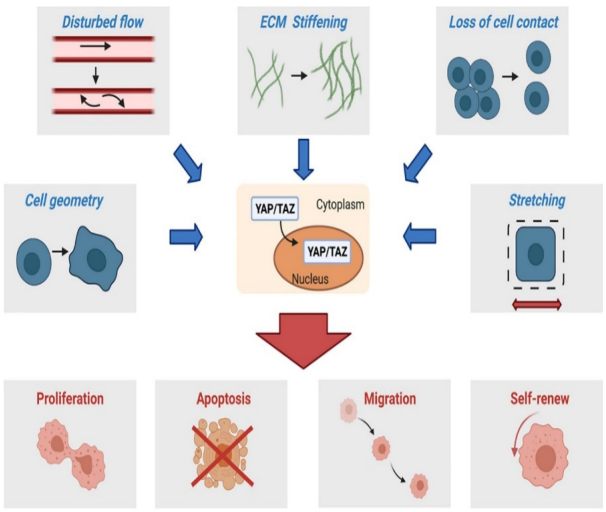

Fig. 4. TAZ and YAP Mechanotransduction in the development of cancer [76].

to YAP, preventing it from functioning. In order to break apart YAP: AMOT complexes and allow YAP to exit its inhibitory state and go into the nucleus, F-actin competes with AMOT for binding [77]. It's interesting to note that depletion of agrin increased YAP: AMOT binding, that eventually caused YAP activity to decline. Recent research further shows that Ras-related GTPase, Rap2 is a crucial intracellular-mediator that affects YAP/TAZ nuclear translocation via transducing ECM rigidity signals [78].

At low stiffness of ECM, Rap2 has been shown to attach and trigger MAP4K7, MAP4K6, MAP4K4 and ARHGAP29, that stimulates LATS1a and LATS2 though blocking nuclear translocation of YAP and TAZ. These results showed that YAP/TAZ activity modulation and ECM sensing are important functions of proteins that are superficially unrelated, such as Rap2 and agrin [79, 80].

2.4. Tumor Initiation and Migration Mediated by the ECM

Their capacity to travel across surrounding tissues and organs, penetrate the neighboring basement membrane is a critical characteristic of carcinoma and other cancer cells. This dense, cross-linked extracellular matrix serves as an anchor for epithelial cells to the surrounding connective tissues and significantly hinders their movement [81]. Nevertheless, as cells must move across the body during the homeostasis of healthy tissues, cancer cells have devised many techniques to circumvent the collagenous barrier [82]. The use of mechanical force is one such approach. The breaking of the basement membrane has increasingly been attributed to mechanical force as a compelling cause. The surrounding basement membrane limits the spread of epithelial cancer cells in terms of space. The proliferation of cancer cells significantly elevates the mechanical stress along the membrane resulting in rupture and permitting cells to escape their environment [83, 84].

Using protruding, F-actin-rich subcellular structures called as invadopodia, anchor cells invade membranes as a different type of membrane navigation. Indeed, leading invasive cells prolong a solitary protrusive arm into basement-membrane, as seen by electron micrographs of invasive tumors. The membrane fissure spreads after the invadopodia's first breach, enabling succeeding cells to cross the collagen border [85, 86]. Elevated quantities of collagen type IV degradation products were also discovered around these breaching locations, suggesting a potential third component of cancer cells migration. The widely held belief that proteases were solely responsible for the breakdown of the basement membrane has given way to an increased concentration of MMPs along the basement membrane [87]. Staining the membrane during invasion demonstrates that laminin and collagen IV are really only partially destroyed by the invadopodia. These findings suggest that rather than facilitating direct invasion, MMPs may contribute to the matrix's softening or to the first rupturing of the basement membrane [84].

2.5. Metalloproteinases (MMPs) in the Development of Tumors

MMPs have a multifaceted function in cancer cells invasion; they not only facilitate the degradation of ECM barriers in the surrounding region but also release active growth factors and promote tumor angiogenesis (Figure 5). The cell surface receptors of integrin family are recognized to be the primary mechanism by which the ECM stimulates cell proliferation [88]. However, it has been shown

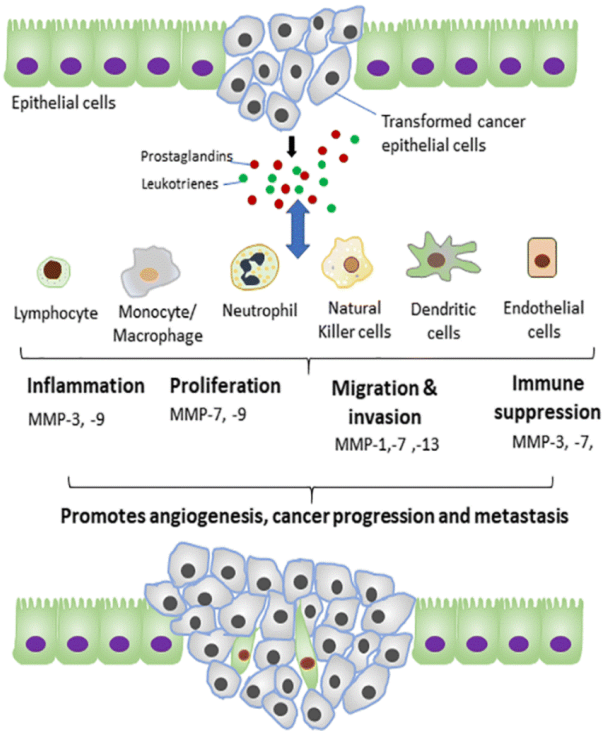

Fig. 5. Various types of Metalloproteinases involved in development of cancer [89].

that some binding sites of ECM obligatory for cell survival and proliferation are "cryptic" or partially concealed within ECM. By destroying and relaxing surrounding collagen, MMPs just reveal these covert binding sites, that enable integrins to communicate with matrix on the cell membrane directly.

MMP-mediated collagen degradation reveals signaling constituents buried within ECM in count to reduce physical barriers and displaying cryptic binding-sites. Different growth factors are inactive when they are embedded in collagen, but they become active when the ECM breaks down, allowing them to interact with their target receptor [88]. For instance, it is known that transforming growth factor β (TGF-β) active form is released during MMP-2 induced ECM breakdown. TGF- β is capable to control cell proliferation, immunological response, and invasion when it is released. In practice, MMPs not just amend the surrounding ECM to promote cell migration physically, but also release growth factors and expose cryptic binding sites, which promote the emergence of a favorable milieu for tumor formation [90].

Despite MMP-induced angiogenesis, the tumor's vascular networks are typically disordered, with inter-capillary distances commonly surpassing the oxygen diffusion limit. As a result, hypoxia (the condition oxygen level in cells decreases) is a characteristic of cancer. Research on the partial pressure of oxygen in tumors indicates a distinct association between weakly oxygenated tumors and increased malignancy [91]. Cancer cells are capable of enduring oxygen-derived environments by changing the transcription of several genes linked to angiogenesis [92]. It is well recognized that hypoxia-inducible factors (HIF) are an important role in controlling this intracellular cancer cell response to hypoxia. HIF-1α, a transcription factor belonging to the HIF family, has been linked to higher MMP and collagen formation, according to recent research [93]. It is significant to note that HIF-1α has the ability to promote LOX accumulation, which eventually stiffens the adjoining matrix. Last but not least, it has been demonstrated that HIF-1 activates transcription factors linked to the epithelial-mesenchymal transition (EMT), a phenomenon involved in decreasing the polarity and adherence of cells to one another, enhancing the invasive behavior of cancer cells [94, 95].

Unfortunately, throughout clinical studies, the majority of treatments that explicitly target MMP activity had subpar results. There are a few plausible causes for the subpar clinical results. First of all, late-stage cancer patients were those chosen to get MMP-inhibiting medicines. MMPs are recognized to contribute to the beginning and development of tumors, as was previously mentioned. MMP inhibitors could work better in people who are at an earlier stage of the disease [96].

2.6. Mechanical Stress's Effects on Tumor Growth and Treatment

As cancer spreads, structural elements including ECM, cancer-associated fibroblasts (CAFs), and cancer cells become more visible, which causes tumors to expand quickly in size and stiffen. One of the few readily observable mechanical characteristics of tumors that helps doctors anticipate malignancy and prognosis is the fast increase in stiffness [97]. Internally produced pressures enable the tumor to displace nearby healthy tissue and invade neighboring regions as it grows and becomes stiffer. Thus, these forces created within the tumor and those brought on by interactions with its surroundings directly aid tumor growth. Tumor cells experience both fluid and solid stress as a result of these mechanical forces [98].

Typically, the non-fluid elements of the tumor produce solid tension. The discovery that blood and lymphatic arteries are mechanically squeezed in the course of tumor development provided the first support for the presence of solid stress within tumors. In tumors, growth-induced solid stress builds up when the cancer cells multiply quickly [99]. Cells multiply quickly during this phase, placing strain on the tumor's microenvironment and ultimately the adjacent healthy tissues. Additionally, to the solid stress produced by the tumor itself, the adjacent tissue's efforts to thwart tumor growth also cause external solid stress [100]. In a nutshell, solid stressors have a direct impact on the evolution of tumors in two ways. First, they impart direct mechanical stress to tumor cells, altering their genetic expression and causing them to become more malignant and invasive. Second, solid stress distorts lymphatic and blood arteries to cause hypoxia [101]. As the name implies, fluid stresses are caused by forces that the fluid components of the tumor produce. This comprises

the shear forces brought on by capillaries, interstitial fluid movement, microvasculature, and blood and lymphatic flow inside the vessels. The shrinkage of blood/lymphatic arteries by solid stress has a significant impact on the fluid stress placed on the surrounding epithelial tissue, proving that these stresses are in fact intricately linked [102]. Vascular constriction increases the vessel's resistance to lymphatic flow by narrowing its cross-sectional area, which also raises shear stress, increases interstitial fluid volume, and lowers perfusion rates. The capacity of lymphatic arteries to remove extra fluid from the tumor is severely restricted by this decline in perfusion rates and flow, which eventually raises interstitial fluid pressure in nearby tumor tissue. Additionally, the efficiency of chemotherapy and immunotherapies is significantly harmed by the constriction of blood and lymphatic arteries [103].

Cancer cells are in a completely different physiological environment within tumors due to elevated solid and fluid stress. Mechanically acting strain and compression on the cells triggers pathways that lead to tumor formation, boosts cell proliferation, and encourages mass migration [104, 105]. In addition to having more stiffness, cancer cells also create more force than surrounding tissues, making them more vulnerable to it. While measuring the solid stress within tumors has shown to be significantly more difficult than measuring the bulk stiffness of tumors, this problem is not insurmountable [106]. Individual tumor cells are now being measured for solid stress by researchers. Recently, Nia et al. presented the experimental methodology for in-situ 2D mapping of solid stress [107].

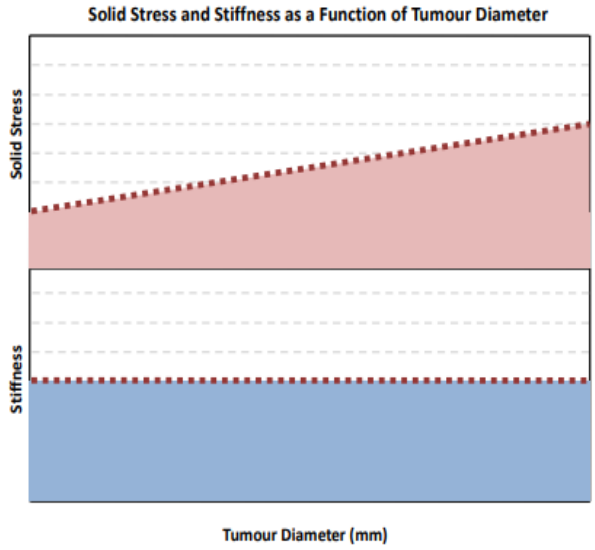

Fig. 6. How solid stress and stiffness change with tumour diameter. Greater solid stress within the tumour is related to increased tumour diameter since the ECM's stiffness remains constant [1].

Investigators use preset geometry to encase the tumor in agarose gel and record distortion after making a small hole to achieve this mapping by carefully releasing the solid tension in tissues [108]. Using both mathematical modelling and experimental investigation, the following key discoveries were made as shown in Figure 6: the stiffness remains constant, solid stress grows linearly with tumor size, and neighboring tissue of healthy nature considerably adds to the solid stress within the tumor. The results imply that the tumor's stiffness is independent of the solid stress applied to the tumor cells [1].

3. CONCLUSIONS

This review addresses the intricate and complex role of the ECM in tissue-genesis and cancer progression. Over the past 20 years, research has shown how critical the ECM is in controlling key physiological processes such as determination of stem cell lineage, cell migration, and its propagation. Consequently, perspectives on cancer have shifted to view it as a disease marked by both uncontrolled cell development and microenvironment instability. Throughout all stages of cancer growth, the apparently static extracellular matrix undergoes dynamic remodeling due to complex interactions among cancer cells, resident cells, and acellular components. Our understanding of the role of extracellular matrix (ECM) in cancer development has advanced, highlight possible therapy targets for lowering the propensity of cancer to spread. However, the temporal sensitivity and specificity required to successfully slow down the propagation of the tumor cells are revealed by the failure to efficiently target wide protein ranges, such as MMPs and collagen.

Neoplastic cells in tumors endure increased mechanical stress when they multiply quickly, which mechanically stimulates tumorigenic pathways, promotes migration, and causes hypoxia. Investigating the correlation between mechanical stress in tumors and their detrimental behavior as well as angiogenesis is crucial while doing cancer

research. These signaling pathways that link external mechanical stress to malignant behavior provide excellent therapeutic targets to halt the spread of cancer. Understanding the link between elevated solid stress and angiogenesis pathways will also provide light on potential improvements in medication delivery.

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5. CONFLICT OF INTEREST

The authors declared to no conflict of interest.

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