Cells Respond to Mechanical Cues of Extracellular Matrix

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Extracellular biophysical properties have particular implications for a wide spectrum of cellular behaviors and functions, including growth, motility, differentiation, apoptosis, gene expression, cell–matrix and cell–cell adhesion, and signal transduction including mechanotransduction. Cells not only react to unambiguously mechanical cues from the extracellular matrix (ECM), but can occasionally manipulate the mechanical features of the matrix in parallel with biological characteristics, thus interfering with downstream matrix-based cues in both physiological and pathological processes. Bidirectional interactions between cells and (bio)materials in vitro can alter cell phenotype and mechanotransduction, as well as ECM structure, intentionally or unintentionally. Interactions between cell and matrix mechanics in vivo are of particular importance in a variety of diseases, including primarily cancer.

Keywords: extracellular matrix (ECM) remodeling ; fibronectin ; cell mechanics ; cancer cells ; stiffness ; forces ; enzymatic degradation ; ion channels ; integrins ; metastasis

1. Cells Can Alter Organization of the ECM in a Biological Manner

The composition and adhesion characteristics of the ECM can be described by the principle of dynamic reciprocity among the cell and its microenvironment. Thereby, the cells experience many mechanical signals. These signals comprise forces that the cells experience from their environment, including neighboring cells, the flow of blood, or the pressure generated in confined spaces. Additionally, the cells utilize their own force-generating mechanism to investigate the mechanical characteristics of the local tissue. Each of these forces can induce a variety of cellular reactions based on shared principles of “mechanotransduction”, in which cells translate mechanical cues into different intracellular biochemical signaling routes. As the list of cellular and tissue-specific events governed by mechanotransduction expands, it is rapidly emerging that forces can elicit specific reactions according to cell type, cellular circumstance, or the way they are perceived through the cell. To obtain both diversity and specificity in reactions, mechanical stimuli must operate in a similar way to biochemical stimuli, in which differences in ligand identity and concentration, detected by a repertoire of receptors, govern a wide array of cellular functionalities. The intricacy of the cellular reaction, thus, results from the wealth of information that is contained in the physical parameters of the mechanical forces, including their magnitude, direction, and dynamics over time, and the capacity of the cells to capture this information. How are force-transmitting molecules capable of recognizing and reacting to these various physical inputs, and how are these molecular reactions incorporated to govern the cellular fate?

Matrix stiffness (synonymously referred to as the elastic modulus or Young’s modulus) of a substance relies heavily on restructuring, crosslinking, and depositing, together with the breakdown of distinct ECM proteins [1]. The accumulation of ECM proteins, which enclose clusters of gel-like hyaluronic acid structures, confers stiffness to the ECM, and the stiffer structures impart resistance to outside pressure stresses on the primary tumors [2]. Cancer associated forces (CAFs), the primary provider of ECM, alter the tumor microenvironment via the expression of lysyl oxidase (LOX), which induces collagen crosslinking during tumor advancement, which is tightly linked to ECM denseness and constitution. The breakdown of protein crosslinking, in return, results in the decomposition of the ECM and reduced stiffness. Collagen constitutes the most prevalent scaffold protein in the ECM and is a key determinant of ECM strength and elasticity in various tissue types. The build-up of collagen and fibronectin causes tensile stress in the circumference of the tumor [3]. The collagen metabolism is disturbed in the course of tumor advancement, which may be reflected in enhanced collagen expression and storage along with increased matrix-metalloproteinase (MMP) activity [4]. In this case, transforming growth factor-β (TGF-β), a key cytokine implicated in cancer cell adhesion and metastasis, is primarily involved in modulating the activity of fibroblasts and the crosslinking of collagen layers in the ECM [3]. The upregulation of TGF-β is implicated in the evolution of desmoplasia in tumors and has been utilized as a proxy indicator for ECM stiffness [3][5]. Integrins relay mechanical cues from the ECM throughout the interaction between tumor microenvironment (TME) and cancer cells by

forming adhesion-plaque complexes and control cancer cell performance through cytoskeletal rearrangement [4]. The activation of the integrin-focal adhesion kinase (FAK) signaling pathway led to the enhanced stiffness of the matrix and, consequently, increased invasion of glioma cells [6]. In a mouse model, upregulated integrins and focal adhesions (FAs) have been linked to elevated matrix stiffness and a stronger invasive potential of mammary epithelial cells [4]. Both FAs and adherens junctions (AJs) act as core components of cytoskeletal assembly and structural architecture, and among their roles is to co-ordinate multiple biochemical signaling circuits. Moreover, the involvement of AJs in the perception of mechanical cues between cancer cells has also been verified. As principal sensors of geometric and mechanical restraints emanating from adjacent cells, AJs orchestrate actin and membrane dynamics to regulate a variety of morphogenetic events and sustain the integrity of the boundary in reaction to extracellular stresses [7][8]. E-cadherin, a major AJ protein in epithelial cells, has been proposed to facilitate the responsiveness of cells to alterations in matrix stiffness through the activation of multiple actin-binding proteins (ABPs) [9]. The stability of the AJs also has an effect on the activity of the mechanotransduction cues, with the AJs exhibiting a stable status at high tension and a more dynamic status at lower tension [10]. Several mechanosensitive ion channels (MSCs) implicated in carcinogenesis, termed “oncogenic channels”, may also participate in the generation of matrix stiffness via mechanotransduction, in complement to their participation in the cardinal phenotypes of cancer cells, involving migration, limitless proliferation potency, resilience to apoptosis, angiogenesis inducement, and invasion [11][12][13]. Piezo1, which functions as a pressure-sensitive, cation-selective mechanical channel positioned at focal adhesions, has been shown to control ECM and enhance tissue stiffness through the activation of integrin-FAK signal transduction. A stiffer mechanical microenvironment increased Piezo1 expression and encouraged the aggression of gliomas [6][14]. Although it has been established that the elevated matrix stiffness is a direct consequence of the activation of CAFs and the enhanced accumulation and crosslinking of extracellular matrix proteins, especially collagen, it is uncertain whether this activating event is implicated in all tumorigenesis pathways in various cancer types and constitutes an early event in tumorigenesis. In summary, dysregulated CAFs and aberrant collagen accumulation in tumor tissue resulted in the enhanced matrix stiffness of the tumor stroma, which positively correlates with tumorigenesis and tumor growth.

1.1. Enzymatic Modification of the Cancer ECM

The ECM constituents, including collagen and fibrin, can be enzymatically broken down. This enzymatic degradation causes the ECM to liberate matrix-tethered biomolecules to guide cell performances. In the interim, the degradation leads to a reorganization of the scaffold that enables the cell to move and invade. The most important enzymes participating in the reorganization of the ECM in the biological framework are metalloproteinases, in particular, the MMP family and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family [15][16]. In comparison to naturally sourced biomaterials, the synthetic polymers may provide improved batch-to-batch stability and improved quality control [17]. Several biochemical responses have been used in the preparation of degradable biomaterials, covering hydrolysis, such as esters, anhydrides, and thioesters, enzyme-sensitive decomposition, such as MMP-degradable crosslinkers or peptides, and stimulus-sensitive break-down, such as photodegradable systems [18]. Cells need sufficient room to grow and adequate external mechanical support to initiate and control cell functionality, which is particularly relevant in cancer growth. Matrix degradation is, hence, crucial for cell activity, notably in 3D microenvironments [19]. Undegradable or space-limiting rigid 3D hydrogels inhibit cell proliferation, growth, and osteogenic differentiation because the dense crosslinking meshes do not offer sufficient room. Conversely, the customizable, biodegradable hydrogels efficiently improve cell proliferation and functionality in the 3D environment. Thus, mesenchymal stem cells in degradable gels composed of methacrylated hyaluronic acid hydrogel crosslinked with MMP-degradable linkers displayed chondrocyte morphology and expressed a high level of chondrogenic biomarkers. In comparison, mesenchymal stem cells in insensitive hydrogels demonstrated restricted cell spreading with a circular morphology [20]. Similarly, cells could not propagate inside highly crosslinked hydrogels that are compromised by non-degradable reticulations [21].

However, what is the situation of enzymatic degradation in cancer and inflammatory diseases? In contrast to the excessive accumulation of ECM, extensive ECM conversion is triggered by the incorrect expression or activity of matrix-degrading enzymes. MMPs, ADAMs, hyaluronidases, plasminogen, and cathepsins have been seen in cancer and are signs of chronic tissue break-down. A number of MMPs, comprising MMP1, MMP2, and MMP9, have been demonstrated to be implicated in both the enhancement and inhibition of cancer progression in breast and lung cancer via their actions on ECM remodeling and subsequent impacts on intracellular signaling structures [22]. In osteoarthritis, for instance, the abnormal generation of fibronectin, versican, and laminin causes modified integrin-mediated FAK/Src signal transduction and a consecutive elevation of MMP2 and MMP9 expression, resulting in matrix integrity deterioration and enhanced ECM break-down [23]. Similarly, the enhanced cytokine output accompanying rheumatoid arthritis leads to the enhanced expression and aggregation of integrin receptors, closely linked to the activation of their signaling pathways, comprising the extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK) subfamily, FAK/Src, and phosphoinositide-3 kinase (PI3K) pathways. This results in the enhanced synthesis of matrix-degrading enzymes like MMP1 and MMP3 [24].

Specifically, the phosphorylation of the JNK subfamily in synovial fibroblasts has been associated with the elevated expression of collagenases, which is concordant with the chronic break-down of the ECM in rheumatoid arthritis [25]. In complement to integrin-driven signaling programs, the activation of a variety of other ECM receptors can aid the transmission of extracellular cues in healthy and diseased tissues.

1.2. Matricellular Proteins

The wording “matricellular protein” has been proposed by Bornstein in 1995. It means that modular, extracellular proteins achieve their functions through tethering to matrix proteins, cell surface receptors, or other molecules, including cytokines and proteases, which, then, interfere with the cell surface. Matricellular proteins are released into the ECM, and even though they can attach to structural ECM constituents like collagen fibrils or basement membranes, they are not assumed to participate in their mechanical functionalities [26][27]. In opposition to the continuous availability of structural proteins in the ECM, the expression of matricellular proteins is strictly controlled to fine-tune their roles in the preservation and healing of injured tissues [28]. It is remarkable that matricellular proteins are abundantly expressed throughout development, whereas their expression in adult homeostatic tissues decreases to a minimal level. Nevertheless, the expression of a number of matricellular proteins is triggered in the regeneration of tissue damage, inflammation, cancer, and other diseases [29][30]. An example of the multiple implications of matricellular protein are thrombospondins (THBSs). THBSs encompass an evolutionarily conserved family of extracellular, oligomeric, multidomain, calcium-binding glycoproteins that are known to co-operate with other ECM constituents and cell surface receptors [31].

2. Cells Can Sense Mechanical Cues Passively When the ECM Exerts a Force onto Them

Tissues can be frequently deformed in shear, elongation, or compression, which are facilitated by either static or cyclic mechanical cues, such as stresses. These mechanical cues of the surrounding ECM environment can be sensed by cells through mechanosensory molecules and receptors. Forces acting on cells and exerted by cells on the extracellular environment lead to tensions and deformations that are perceived by a set of specialized molecules termed mechanosensors. These mechanosensors experience a force-dependent conformational modification that modifies the biochemical functionality of the protein. Forces from the cellular environment are usually first perceived at the cell surface, where the force-producing cytoskeleton also applies tension when it contacts various mechanical surroundings. The adhesion complexes, where cells are connected to the surrounding tissue via FAs and to other cells via AJs, have, thus, turned out to be pivotal hubs in the transmission of forces [32][33]. Cells, nevertheless, have a far wider range of mechanosensors, comprising multiple structurally distinct families of force-sensitive ion channels [34] and receptors for biochemical ligands that react directly to force, such as Notch [35] and plexin D1 [36]. In humans, the pathway comprises the cell surface receptors Notch1, Notch2, Notch3, and Notch4, and their ligands delta-like-ligand (Dll), such as DII1, Dll3, and Dll4, as well as jagged 1 (Jag1) and jagged 2 (Jag2). The Notch receptors and Notch ligands each exhibit an extracellular domain, a transmembrane region, and an intracellular domain. Receptor ligand engagement is able to trigger receptor activation by uncovering a concealed extracellular location in the negative regulatory region (NRR) for peptidases. ADAM10 or ADAM17 split this site (S2 cleavage) to generate the extracellular Notch truncation, which is, thereafter, detected from the γ-secretase complex that splits within the transmembrane domain and liberates the intracellular Notch domain (NICD) from the membrane (termed S3 and S4 cleavage) [37][38]. The liberated NICD is then able to engage transcription factor complexes via CSL, which denotes an abbreviation derived from the species names, CBF1/RBPJκ, Su(H), and Lag-1, and either promote or retard transcription [39], resulting in either a similar cell destiny (lateral induction) or an alternate cell destiny (lateral inhibition). Finally, forces at the cell circumference are transferred by the cytoskeleton to other cellular areas like the nucleus [40], which also comprise mechanosensitive compounds and participate in the cellular reaction to external and intrinsic forces.

Mechanosensors operate through a number of common mechanisms whereby the force-induced conformational alterations influence either molecular interactions or the activity of proteins. Forces are able to directly enhance the protein–protein engagement of mechanosensors through enhancing the lifetime of the linkage, such as catch bond, in contrast to the majority of protein–protein interactions where the lifetime diminishes with force, such as slip bond [41]. In addition, forces can act to shape interactions through protein unfolding or demasking, which can either expose cryptic binding sites (CBSs) [10][42] or perturb binding motifs, such as the cytoplasmic tail of the β1 or β7 integrin subunits, and FilGAP to filamin A [43]. The type of cryptic site differs for several mechanosensors, and the forces can also uncover proteolytic sites [44][45] or motifs involved in post-translational modifications [46]. Multiple membrane-associated mechanosensors are controlled by force-driven alterations of membrane tension, for example, by driving the gating mechanism of mechanosensitive ion channels [47]. Ultimately, the forces of the cytoskeleton can also work to stabilize specific structural configurations of mechanosensors like integrins [48]. Mechanosensors frequently constitute bulky

multimolecular clusters with combined mechanosensors that are regulated by various mechanisms, of which FAs and AJs serve as prototypical models. Mechanical sensors do not work like ordinary on–off switches; instead, their reaction is dependent on certain force characteristics. Forces can impact multiple areas of the cell, but may have varying magnitudes, directions, and temporal patterns, all leading to a distinct reaction and varying biological outputs. The particular mechanisms of force transmission in the single mechanosensors and their organization inside the cell define the capability to distinguish between these various parameters, as will be explained in the following sections.

2.1. How Large Are Cellular Forces?

Cellular reactions to mechanical stimuli including flow, ECM stiffness, and tissue stretch are determined as a function of the magnitude of the forces connected to these stimuli. The magnitude of the force perceived by the cells and the sensitivity of the various mechanosensors in this zone dictate how the cells react to the mechanical stimulus. Even though the molecular principles of force sensitivity are not yet fully understood, a number of mechanisms that enable cells to acquire this knowledge have been elucidated. A molecular rationale for sensitivity to force quantities is mechanosensors that have a threshold for activation force, such as the force needed for CBS to be exposed or the force region where catch bonds are generated. Due to the presence of stable intermediary modes of the force-dependent conformations of the mechanosensors, this level of sensitivity can be even more precisely adjusted. Single molecule force spectroscopy of catch bonds has revealed a minimum of three modes, such as weakly, moderately, and strongly bound, at a variety of force strengths across integrin-fibronectin [49], vinculin-F-actin [50], and von Willebrand factor (VWF)-GPIb [51]. What is still to be discovered, however, is whether these conditions actually occur in the cells and whether they are linked to varying amounts of biochemical activity. Intermediate states can also occur in mechanosensors that incorporate multiple force-sensitive domains which deploy at varying force levels. CBSs in the various rod domains of talin have been shown to unfold at a force of 5 pN for the R3 domain and 10–25 pN for the other domains [52]. Since these rod domains feature various binding partners, this may increase the multiplicity of mechanotransduction routes as a function of the strength of the forces.

Besides the force size-dependent adjustment of individual mechanosensors, the size sensitivity is created by molecular mergers that comprise several mechanosensors with various activation swells. At the same time, it has been demonstrated for ECM stiffness-dependent mechanotransduction through FAs, which involves concomitant integrin-fibronectin catch binding and talin deployment. Since both processes take place solely in a specific force zone, the stiffness becomes an extremely relevant factor [53][54]. The perception of size could be based not solely on the interplay between the mechanosensors within these molecular aggregates, but on their interlocking functioning. For example, tensile forces can not only enhance the association between actin and β-catenin/α-catenin at cadherin adhesions [55], but also trigger the liberation of β-catenin from cadherin to enable its transcriptional role [56], which can possibly be accounted for by varying force thresholds. Size perception can also emerge at the cellular level by activating several types of mechanosensors that are located at a certain distance from one another at various force levels. For example, this is involved in the various mechanisms of protection from nuclear stress depending on the level of stress, with low levels of stress causing the Piezo-induced softening of the nucleus and high levels of stress also leading to the alignment of cells and their actin cytoskeleton in a cadherin-dependent fashion [57].

Different mechanosensors' specific susceptibilities enable the design of circuits where cellular sensitivity to mechanical stimuli can be manipulated. For example, various integrin subtype and ligands [58], several constituents of the identical mechanosensor family, such as talin-1 and talin-2 [59], or splice variants of the same mechanosensor, such as for Piezo-1 [60], can react to a multitude of force magnitudes. In addition, the mechanical condition of the actual cell, such as the actomyosin contractility and cell stiffness, affects the way cells react to external mechanical stimuli by influencing membrane deformability or exerting a preload on mechanosensors that reduces their surge threshold toward ectopic forces. These mechanisms also account for the diversity of cellular reactions to variations in force magnitudes and the intricacy of the regulation of the dynamic region and the tenderness of the cells.

2.2. How Is the Direction of Cellular Forces Regulated?

Since forces represent vector magnitudes that have not only a quantity but also a direction, they inherently deliver directional cues, unlike biochemical signs that need a gradient. Directionality, such as that arising from the direction of blood flow or the direction of tissue stretch, can lead to anisotropic cellular reactions, producing polarized cellular responses. Thus, the directional tension in epithelia leads to the alignment of cell divisions and collective movement following the tension direction due to mechanotransduction across the AJs [61][62]. In a similar way, the majority of cell types align vertically to the direction of uniaxial elongation, thereby focusing on the anisotropic mechanoreaction and the

decomposition of FAs [63]. The regulation of AJ dynamics can also rely on the direction of force, as forces spread vertically to the cell–cell contacts and stabilize the AJs, while parallel shear forces demonstrably lead to their deconstruction [64].

In parallel to the polarization of cell response to directional forces, single mechanosensors can induce various reactions according to the orientation of the forces acting on them. Piezo1 perceives both tensile and compressive forces within epithelia, which can trigger cell divisions or extrusion, respectively [65][66]. Most interestingly, Piezo1 is variably sensitive to each of these opposing forces [67], even though the distinct reactions could also be related to distinct cellular Piezo1 populations and/or the action of the inward calcium flow in compressed and stretched cells, respectively [66]. In addition, it has been demonstrated that several mechanotransduction routes are only enabled in a selective manner when forces are administered in a certain direction. Thus, signal transmission by the mechanosensitive T cell receptor/Major-histocompatibility complex (TCR/MHC) complex in T cells is only accomplished in an efficient manner when the forces act parallel to the attachment interface [68]. In this sense, only unidirectional shear forces on endothelial cells engage integrins and force-sensitive calcium channels to initiate an adequate athero-protective reaction [69][70][71].

The mechanisms used by mechanosensors to translate directional cues into direction-specific cellular reactions are still relatively obscure. The reason for this could be that the arrangement of the mechanosensors in the cell is asymmetric and/or their activation, such as unfolding mechanism of catch bond or CBS unfolding, is optimized when the forces act in a certain geometry. In fact, it has been proposed lately that the stabilization of the link between actin filaments and adhesion complexes relies on the orientation of the forces generated by actomyosin. The catch-bond interplay of vinculin and actin prefers to arise when the forces are directed towards the minus end of actin [50], and a similar directional asymmetry may govern the linkage between *α*-catenin and actin [72]. In addition, the engagement of vinculin with its CBS in talin and that of other force-dependent engagements are more robust when tensile forces are exerted parallel instead of vertical to the bond interface [73]. This geometry constraint of the force-dependent stabilization of actin interference with cell adhesions distorts the structure of actin filaments. In a similar way, the triggering of mechanosensors through external forces can vary according to their inherent geometry and orientation with respect to the force vector. This organization of the mechanosensors is probably subject to anisotropy, so that only some of the molecules are aligned adequately with the direction of force to become activated, while non-aligned mechanosensors may not react or react less strongly. Crucially, anisotropic forces can also be distributed throughout the cell in an isotropic manner via transmission to the cytoskeletal network [74], and thus the anisotropy of the cytoskeleton is expected to underpin the polarized cellular responsiveness to directional inputs.

2.3. How Dynamic Are Cellular Forces?

Forces impacting cells can be fleeting and last on the order of seconds, like acute stresses, or hours and days, like morphogenetic movements or a reorganized ECM. In a similar manner, the cellular mechanoreaction toward these signals take place at different timescales [75][76]. In the course of time, in addition to the fluctuating time duration, the forces can oscillate, e.g., as a result of the pulsating stretching of the arterial walls or the “tugging” effects of the interaction between the cell and the ECM [77]. These oscillating forces lead to various cellular consequences in comparison to static forces, such as the specific activation of cell signaling paths and cellular restructuring through cyclic stretching or hydrostatic pressure [74][78][79][80]. In addition, cells can react to different frequencies of force oscillations, which affects, for example, the degree of cellular orientation to axial loads [81].

Oscillation-dependent reactions can be attributed to the fact that the activation of mechanosensors relies on the dynamics of the force over time. For example, cyclic forces can extend the binding duration of catch bonds in comparison to static forces in that they encourage the transition to a heavily bound condition, as experimentally proven for the α5β1-fibronectin catch bond [82]. Mechanosensors can function as bandpass filters, as the transduction sensitivity changes with the signal frequency. The Piezo has been proven to inactivate quickly following its force-dependent aperture. Consequently, the amplitude of Piezo activity can be changed through repeated forces, and this has been demonstrated to be a function of the stimulation frequency [83]. Talin’s unfolding has recently been found to be synchronized with oscillating forces, although it only operates at specific frequencies [84]. While the functional significance and the underlying structural rationale of these mechanisms are not yet clear, these studies indicate that various mechanosensors can process and convey frequency-dependent mechanical signals in a selective manner.

The loading rate, meaning the velocity with which the forces are exerted, is also a decisive factor for the cellular reaction. For example, stretch levels vary between tissues and are high in fast expanding tissues such as the lungs when breathing in air, and low when morphogenetic movements are taking place. The extent of the forces generated by the cells themselves varies according to the viscoelastic characteristics of the ECM, which can result in varying levels of enhancement of the adhesion and spreading of cells [54][85]. The ability of cell–cell adhesions to sustain mechanical stress

by stimulating actin reorganization also influences the rate of stress [86]. These variations in loading rate could directly affect the efficiency of the transduction of mechanosensors, since the unfolding of cryptic sites and the kinetics of engagement of the resulting mechanosensor interactions rely on the loading rate [87]. Ultimately, the capture of the temporal dynamics of forces relies on the time scale over which the forces vary, in relation to the time scale of the activation and inactivation of the mechanosensors and the rate of their turnover. A discrepancy between these time scales would cause the cells to lack temporal knowledge of the forces affecting them, which would result in a completely dissimilar reaction.

3. Cells Can Interact with One Another

Even though various mechanosensors can trigger specific distinct reactions, they commonly act on the identical cellular processes and are able to orchestrate the reaction. For instance, mechanotransduction via integrins, cadherin-based adhesions, and Piezo governs the progression through several phases of the cell cycle [66][88][89][90][91]. Likewise, the Piezo-driven softening of the nuclei and the E-cadherin-dependent realignment of the cells co-ordinately shield the nuclei from mechanical stresses [57]. Several mechanosensors also operate on the exact same signal path, as shown in detail for the control of the Hippo route (for more detail, see review [92]). In an analogous manner, β-catenin-based transcription is mechanistically activated through its phosphorylation at cadherin adhesions [56], and also through the integrin-based suppression of the destroying complex [93]. Due to these connections, mechanical stimuli affecting various mechanosensors cannot merely trigger analogous biological responses, but also empower diverse mechanosensors to interact and guarantee the robustness (or diversification) of the reaction.

3.1. Neighboring Cells

Co-ordination is not just the result of interaction at the stage of the downstream mechanotransduction routes, but the mechanosensors themselves also impact the way in which the forces are shared and converted by each other. This has been investigated in detail for FAs and AJs, between which the force partitioning is compensated by their linkage via the actin cytoskeleton (for more details, see review [94]). Thus, the enhanced stiffness of the matrix, which is perceived from the integrins, also leads to increased tensile forces on the AJs [95], and, conversely, the AJs act to alter the tensile forces experienced by the integrins [96][97][98][99]. Piezo has recently been found to be linked to FAs and is enabled at points of traction [100][101]. Inversely, Piezo supports the generation of traction forces through FAs and contributes to their sensitivity with respect to substrate stiffness [6][101]. Numerous additional instances of the interaction of single mechanosensors influencing the regulation and function of others both locally (within one complex) and in a distal manner (spanning several complexes, such as adhesions and nucleus) have been revealed [102][103][104][105], which constitute the complexity of the cellular response to mechanical cues.

In addition to the mutual influence of various mechanotransduction mechanisms, the cellular reaction to mechanical forces also depends on their interaction with biochemical factors, such as growth factors. Since mechanotransduction results in the translation of forces into an intracellular biochemical reaction, the forces will act on analogous pathways and cellular events that are governed via these growth factor cues. In addition, forces are able to modulate the identical receptors that are activated through biochemical ligands that regulate the activity of the receptor either at the engagement level of the receptor ligand itself, such as for epidermal growth factor receptor (EGFR) [106], and TGFβ-R [107], in a ligand-independent fashion, such plexin D1 [36] or possibly both, such as Notch [102][103]. Mechanical and biochemical impulses can synergistically activate downstream signaling processes. In contrary, several receptors exhibit specific downstream pathway signaling in reaction to mechanical activation [102] or initiate different signaling routes when activated in response to mechanical stimuli or their biochemical ligand [36].

The biochemical reaction triggered via the mechanosensors can have the effect of regulating the original mechanical stimulus. This biochemical feedback can occur by weakening the force on single mechanosensor molecules, for instance, by inducing FA growth, or by initiating a cellular reaction that cancels the original forces, such as via enhancing proliferation and, subsequently, decreasing tensile forces. In addition to this level of complexity, biochemical processes can influence the cellular force generation mechanism. This can weaken cellular sensitivity to mechanical stimuli [108], and also spread mechanical forces in the tissue, as demonstrated recently through the reciprocal regulation of ERK activity and tensile forces between adjacent cells [109].

3.2. Distant Cells (via Traction-Induced ECM Displacements)

Many cancer cell types exert substantial tensile forces on the enveloping matrix, causing alterations in the ECM that can spread over long distances of tens of cell diameters [110][111][112][113]. When they are embedded in fibrous biological hydrogels like collagen or fibrin, the cells constrict, thereby restructuring and compacting the adjacent ECM fibers. Over a

period of a couple of hours, this restructuring can, then, create a visible fibrous band of aligned and compacted fibers that can mechanically connect neighboring cells and impact the internal molecular status of the cells [114] and their active responsiveness [115]. This type of long-range power transmission from cell to cell via the ECM can be regarded as the transfer or sharing of knowledge between cells and, thus, is referred to as cell–ECM–cell communication. This type of long-range mechanical cell–ECM–cell communication has been found to co-determine multiple biological events, for instance, tissue wounding [115], fibrosis [116], vascularization, capillary burgeoning [117][118], the folding of tissues [119], and the invasion and metastasis of cancer [112][120]. In vivo, fiber alignment bands may act as ECM 'tracks' for cell movement, which could play a part in wound repair, fibrosis, and cancer metastasis [110][121].

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