A Study on Implications of Dynamic Remodeling & Homeostasis Of the extracellular matrix for the cancer diseases

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Abstract: Dynamic remodeling of the extracellular matrix (ECM) is essential for development normal organ homeostasis. Life-threatening pathological conditions arise when ECM remodeling becomes excessive or uncontrolled. Here, we focus on how ECM remodeling contributes to cancer disease, which present challenging obstacles with respect to clinical treatment, to illustrate the importance and complexity of cell-ECM interactions in the pathogenesis of these conditions. ECM remodeling is crucial for tumor malignancy and metastatic progression, which ultimately cause over 90% of deaths from cancer. Here, we discuss current methodologies and models for understanding and quantifying the impact of environmental cues provided by the ECM on disease progression, and how improving our understanding of ECM remodeling in these pathological conditions is crucial for uncovering novel therapeutic targets and treatment strategies. This can only be achieved through the use of appropriate in vitro and in vivo models to mimic disease, and with technologies that enable accurate monitoring, imaging and quantification of the ECM.

Keywords: extra cellular matrix, pathogenesis, homeostasis, quantification

Introduction

The extracellular matrix (ECM) is one of the most important regulators of cellular and tissue function in the body. Tightly controlled ECM homeostasis is essential for development, wound healing and normal organ homeostasis, and sustained dysregulation can Result in life-threatening pathological conditions. The importance of correct biochemical and biophysical ECM properties on the regulation of cell and tissue homeostasis is illustrated by the fact that the ECM is deregulated in many different types of disease. In this Perspective, we focus on how ECM composition and remodeling is now thought to be crucial for tumor genesis and metastatic progression in cancer disease. We also discuss recent progress in developing physiologically relevant qualitative and quantitative models, as well as advancements in technologies that enable accurate monitoring, imaging and quantification of the ECM. Together, these technologies will help us dissect both the spatial and temporal dynamics of ECM homeostasis, and promote our understanding of the underlying mechanisms that influence cell-ECM interactions in the context of multiple disease types. Finally, we close by examining how recent advances in this field might allow targeting of the ECM to provide new therapeutic approaches for treating cancer disease.

ECM composition and functionMatrix components

The ECM is defined as the diverse collection of proteins (and so ph value) and sugars that surrounds cells in all solid tissues. This tissue compartment provides structural support by maintaining an insoluble scaffold, and this in turn defines the characteristic shape and dimensions of organs and complex tissues. The ECM is mainly composed of an intricate interlocking mesh of fibrillar and non-fibrillar collagens, elastic fibers and

glycosaminoglycan (GAG)-containing non-collagenous glycoproteins (hyaluronan and proteoglycans). Although the ECM has historically been perceived as fulfilling a primarily structural and hence biomechanical role, the ability of the ECM to provide the contextual information responsible for controlling both individual and collective cellular behavior has been increasingly recognized in recent years.

Following intracellular synthesis, ECM components are secreted into the interstitial matrix that surrounds and supports cells, and is the main provider of structural scaffolding for tissue. This matrix also plays a key role in protecting cells by acting as a compression buffer when tissues are subjected to deforming stresses. The interstitial matrix found in most but not all tissues consists mainly of the fibrous collagen type I, which, together with fibronectin, confers mechanical strength to tissues (Erler and Weaver, 2009). Although collagens are collectively the most abundant component of the ECM, the differential expression of individual interstitial ECM components underpins the specific functions of many organs and tissues. For example, chondroitin sulfate, a sulfated GAG that is usually found attached to proteins as part of a proteoglycan, is highly expressed in the ECMs of connective tissues such as cartilage, tendons, ligaments and major arteries, where it helps to maintain the structural integrity of the tissue. By contrast, secreted protein acidic and rich in cysteine (SPARC), a matricellular glycoprotein that was initially termed osteonectin, was originally identified in bone, where it binds collagen and Ca^{2+}, initiating nucleation during bone mineralization (Termine et al., 1981). However, SPARC has also been shown to be secreted by non-epithelial cells in non-ossifying tissues (Sage et al., 1984) during development and tissue repair, where it mediates ECM remodeling and turnover, and cell-ECM interactions (Engel et al., 1987; Sage et al., 1989; Funk and Sage, 1991; Lane and Sage, 1994; Murphy-Ullrich et al., 1995; Chlenski and Cohn, 2010). External mechanical loading of tissues can also modulate ECM composition in some tissues. For example, in situations in which mobility is impaired, there is a decrease in the proteoglycan content of articular collagen and in bone mineral density, but these increase with exercise (Bird et al., 2000; Rittweger et al., 2006; Rittweger et al., 2009), suggesting that ECM composition is modulated by both intrinsic and extrinsic stimuli.

In addition to the interstitial matrix, extracellular basement membranes (BMs) are a specialized form of sheet-like ECM to which epithelial cells can anchor and which interact directly with the epithelium and endothelium. These membranes mainly consist of collagen IV, laminins, entactin (also known as nidogen) and heparan sulfate proteoglycans (Erler and Weaver, 2009). BMs play a key role in epithelial cell function, providing cues for orientation that help to establish and maintain apicobasal polarity and cell differentiation.

The ECM serves many functions in addition to providing structural support. Macroscopically, the ECM physically segregates cells and organs and acts as a protective cushion – for example, by regulating hydrostatic pressure within tissues and organs. At the microscopic level, this highly dynamic molecular network is also capable of regulating cellular behavior through modulation of, among other things, proliferation, cytoskeletal organization, cellular differentiation and receptor signaling (Paszek and Weaver, 2004; Kass et al., 2007). Such ‘outside-in’ biochemical signaling mechanisms rely on the precise spatial organization of ECM ligands to integrate complex signals in a regulated manner (Hynes, 2009). The biophysical properties of the matrix also regulate cellular mechanosensory pathways – through global substrate rigidity (a phenomenon defined as mechanotaxis or durotaxis) (Lo et al., 2000; Wong et al., 2003; Hadjipanayi et al., 2009) or extracellular tension (known as tensotaxis) (Beloussov et al., 2000) – that prompt cells to detect and respond to changes in tissue biomechanics (Yu et al., 2010). In addition, the ECM also sequesters and hence acts as a ‘local depot’ for a wide range of growth factors and cytokines. For example, tissue injury can trigger protease activities,

leading to a rapid release of signaling molecules [such as transforming growth factor-□ (TGF□) (Wipff et al., 2007; Wells and Discher, 2008)], which in turn allows a swift and local growth-factor-mediated activation of cellular functions without de novo synthesis.

Structure and mechanical function

Functionally, discrete tissues and organs have markedly distinct biomechanical properties (Fig. 1), which are subject to change during the course of development or during pathogenesis (Butcher et al., 2009).

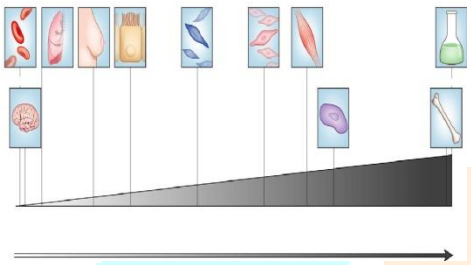

Fig. 1.Variations in tissue stiffness. The biomechanical properties of a tissue in terms of stiffness.

The biomechanical properties of the ECM are tightly controlled by the specific composition and concentration of matrix components, and also by post-translational modifications, such as glycosylation, transglutamination and cross-linking (Erler and Weaver, 2009).

Collagen cross-linking occurs in both a regulated and non-regulated manner, typically via enzyme-mediated or non-enzyme-mediated processes, respectively. Regulated collagen cross-linking is almost exclusively mediated by lysyl oxidase (LOX) and the LOX family of secreted amine oxidases (Csiszar, 2001; Kagan and Li, 2003), and primarily occurs during developmental processes and wound healing. LOX family members catalyze the cross-linking of collagens (and elastin) through oxidative deamination of lysine residues. The importance of correct LOX expression and the resulting collagen cross-linking is exemplified by the fact that LOX-knockout mice die at birth due to collapse of their lethally fragile diaphragm and cardiovascular system (Maki et al., 2002; Hornstra et al., 2003). Clinical manifestations of reduced LOX activity (which can result from nutritional copper assimilation deficiencies) are also seen in two X-linked recessively inherited disorders: Menkes disease and occipital horn syndrome (OHS) (Royce et al., 1980; Kaler et al., 1994). Osteolathyrism is another collagencross-linking deficiency, and is brought on by chronic ingestion of *Lathyrussativus*, a plant that is rich in the LOX inhibitor□-aminopropionitrile (BAPN). Conversely, elevated LOX activity levels are clinically associated with increased fibrosis and can be detected in the sera of patients with liver cirrhosis (Murawaki et al., 1991; Kagan, 1994; Kagan, 2000). Chronic increases in the level of circulating LOX have also been shown to increase collagen cross-linking and result in stiffening of heart tissues, compromising cardiac function (Sivakumar et al., 2008).

Non-enzymatic collagen cross-linking usually occurs through glycation (Schnider and Kohn, 1980) and transglutamination (Mosher and Schad, 1979; Mosher et al., 1979), or as a result of increased biglycan and proteoglycan levels (Wiberg et al., 2003). Such collagen cross-linking acts to stiffen the ECM, although this process occurs much more slowly than its enzymatic alternative (Avery and Bailey, 2006). However, structural ECM proteins exhibit a remarkable longevity in vivo, often measured in years as opposed to hours for intracellular proteins: types I and II collagen in human skin, articular cartilage and intervertebral disc exhibit 15-, 95- and 117-year half-lives, respectively (Verzijl et al., 2000; Sivan et al., 2008). On such a timescale, glycation-mediated collagen cross-linking becomes important and is thought to play a key role in many age-associated diseases, including degenerative eye disease, pulmonary fibrosis, arterial stiffening and cardiovascular disease, and neurodegeneration; such manifestations are increasingly accelerated in diabetes patients who exhibit

chronically elevated blood-glucose levels (Bunn et al., 1978; Frank, 1991; Vitek et al., 1994; Sasaki et al., 1998; Glenn and Stitt, 2009).

Cell-ECM interactions

Cellular responses are tissue and context dependent in terms of both biochemical and biomechanical cues (Bissell and Radisky, 2001; Yu et al., 2010). Hence, understanding the complex processes surrounding ECM production, modification and remodeling, and relating these processes to physiological changes in the biochemical and biomechanical properties of the ECM, are key to determining how microenvironmental changes influence cellular responses. These considerations are especially important in the development of anti-cancer therapies, which might be able to target aspects that are dysregulated in the cancer disease.

Manipulating and quantifying the changes in ECM

To study the effects of the ECM on cellular behavior in vitro in a meaningful way, it is necessary to manipulate and quantify the biochemical and biomechanical properties of the ECM in a controlled manner. Matrix stiffness, for example, can easily be modulated in vitro by overlaying a thin layer of matrix on either tunable polyacrylamide (Wong et al., 2003; Paszek et al., 2005; Levental et al., 2009) or polydimethylsiloxane (PDMS) (Cortese et al., 2009) substrates of a specific pre-defined stiffness. Matrix stiffness can also be modulated in vitro through modulating the in situ cross-linking of native ECM components (Butcher et al., 2009) either enzymatically, using LOX (Erler et al., 2009) and LOX family proteins (Barry-Hamilton et al., 2010), or through non-enzymatic reactions such as glycation using ribose or glucose (Paszek et al., 2005; Erler et al., 2006; Kass et al., 2007; Erler et al., 2009; Levental et al., 2009). ECM properties can also be similarly modulated in vivo, to some extent, either through overexpression of cross-linking enzymes, such as LOX, or by inhibition of matrix-degrading enzymes (Erler et al., 2006; Ahn and Brown, 2008; Levental et al., 2009). Processes such as fibrosis can be induced using irradiation or other agents, such as bleomycin to induce pulmonary fibrosis and carbon tetrachloride or dimethylnitrosamine to induce liver fibrosis. These treatments induce rapid inflammatory and fibrotic responses in target organs, leading to increased ECM deposition and remodeling that mimic pathological progression of the disease. Such approaches have greatly facilitated the identification of key players that mediate fibrotic disease progression (Kagan, 1994; Ebihara et al., 2000; Friedman, 2004; Pardo and Selman, 2006; Iredale, 2007).

The quantitative assessment of ECM properties is a requirement if the functional effects of complex remodeling processes are to be understood. Changes in matrix composition and stiffness can be measured in vitro, in vivo and ex vivo. Common methods include staining tissues for biochemical markers by immunohistochemistry or immunofluorescence to characterize changes in ECM composition. In addition, histological methods such as the use of Masson's trichrome and picrosirius red to stain collagens can be used to examine collagen structure and quantify collagen linearization and orientation (Levental et al., 2009) (see Fig. 3). Although such standard procedures can provide highly informative data on matrix changes during development and disease progression, they give only a static snapshot of the ECM and cannot capture its complex dynamics. To address this limitation, specialist techniques [such as echocardiography and sonoelastography (using sound) and second harmonics imaging (SHG; using light) with two-photon microscopy of whole tissues ex vivo and in vivo] can be used to analyze the ECM, particularly the collagen structure, and quantify collagen linearization in a non-invasive manner (Levental et al., 2009). Similarly, these techniques have been used to monitor the interactions of epithelial and stromal cells with tumors, as well as the initiation of

collagen remodeling (Brown et al., 2003; Condeelis and Segall, 2003; Perentes et al., 2009; Wolf et al., 2009). Most important, however, is the ability to monitor events on a temporal scale rather than relying on endpoint assays to help understand both ECM dynamics and the resulting cellular behavior. Recent work by Giampieri et al. involving non-invasive intravital SHG imaging identified the paradigmatic role of TGF during the intermediate steps of tumor progression. This work highlights how temporal switches in TGF expression induced by local microenvironmental cues can dramatically affect cell migration, intravasation into blood and lymphatics systems, and colonization of secondary sites (Giampieri et al., 2009).

Techniques such as atomic force microscopy (AFM) can be used to generate extremely high-resolution images of ECM structure (Graham et al., 2010) and, with the upcoming force-mapping modality experiments that many atomic force microscopes are capable of, local force measurements can be taken to evaluate matrix elasticity and stiffness at the micron scale. Non-destructive tissue AFM can be carried out on standard cryosections in a manner that preserves biomolecular structure and allows visualization of both intra- and extracellular structure at a micro- to nanometer resolution. Owing to the non-destructive nature of the technique, experimental intervention can be applied both pre- and post-imaging and, more importantly, it allows the combining of ultrastructural imaging with current clinicopathological microscopy techniques (Graham et al., 2010).

Also of interest are the viscoelastic (i.e. time-dependent) properties of tissues and matrix at the cellular level. Shear rheology is a standard technique used for measuring ECM and tissue stiffness at the macroscopic level. At its simplest, this approach measures torsional stress and strain, from which it is possible to calculate the elastic modulus (in Pa) as a function of strain rate. At the same time, measurements of mechanical compression and nano-indentation (a commonly applied means of testing the mechanical properties of materials by indenting the test material with a diamond tip while measuring the force-displacement response) can also provide high-resolution measurements of matrix and tissue elasticity, because nano- indentation can achieve lateral resolutions of ~15 m (Akhtar et al., 2009b). However, a common problem with all of these techniques is that the method of interrogation can greatly affect outcome, so careful experimental design must be implemented; stiffness values are typically calculated as a function of experimental measurements and depend precisely on how and which variables are measured.

Although the techniques described above provide accurate and useful quantitative data on the biomechanical properties of matrix and tissue, most are generally considered invasive and/or destructive methodologies (Gueta et al., 2006). Hence, there is a need to develop methods to measure elastic properties and stiffness of tissues and matrix in a non-invasive manner for clinical application. The elastic properties of tissues is one of the elements that provides the image contrast in technologies such as magnetic resonance and ultrasound elastography, which are routinely used in the clinic (Barbone and Bamber, 2002). For example, clinical in vivo imaging of malignant breast tumors tend, on elastography, to appear stiffer than benign breast tumors; in particular, a halo of stiffer tissue is frequently observed at the tumor margin (invasive) edge of the tumor (Jeff Bamber, personal communication). These observations can prove invaluable in helping to guide treatment regimens at the bedside. At the bench, however, science seeks to quantify such observations to increase our understanding of how tissue biomechanics are related to disease progression.

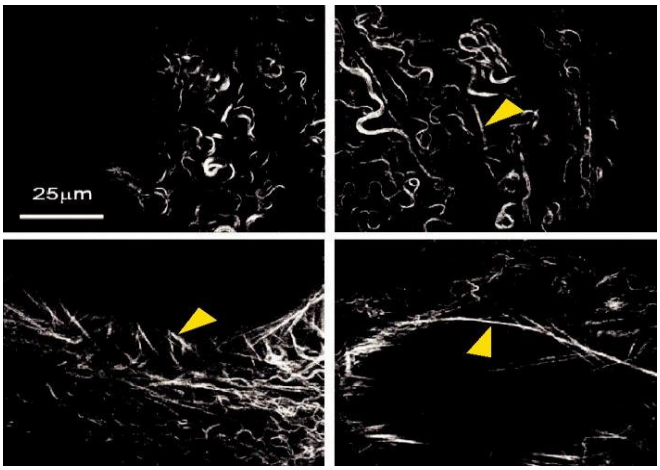

Fig. 3. Second harmonic generation (SHG) imaging of collagen fibril linearization during mammary gland tumorigenesis

New technologies based on fluorescence resonance energy transfer (FRET) (Jiang et al., 2004), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) (for a review, see Scherer et al., 2008a) are being developed to image the dynamic status of ECM remodeling, including visualization of MMP activity (Scherer et al., 2008b; Littlepage et al., 2010). Similarly, advances in □-ultrasound, optical coherence tomography (OCT), optical acoustic microscopy and scanning acoustic microscopy (SAM) (Akhtar et al., 2009a) are currently under development to facilitate quantitative measurement and imaging of stiffness at the microscopic scale (Jeff Bamber, personal communication) (Low et al., 2006). In addition, increasing the resolution and versatility of many of the above techniques will be possible with improved contrast agents, such as so-called 'smart probes', which are MRI contrast agents that can be used to study ECM components (Spuentrup et al., 2005; Stracke et al., 2007; Miserus et al., 2009), soluble proteins such as growth factors and MMPs (Tsien, 2005; Scherer et al., 2008a; Scherer et al., 2008b), specific immune- or tumor-cell populations (Reynolds et al., 2006; Korosoglou et al., 2008; McAteer et al., 2008; Radermacher et al., 2009), and even physiological conditions such as hypoxia (Fig. 4) (McPhail and Robinson, 2010). These contrast agents are typically highly selective, specific and undergo enhanced activation on interacting with their target. In summary, new techniques that image the dynamics of cell-ECM interactions to non-invasively quantify remodeling of the ECM at the sub-millimeter level and, more importantly, on a temporal scale will ultimately provide additional resources for basic research and in the clinic..

Cancer

Tumor development is a complex, dynamic and progressive process that involves both cellular and environmental cues. The tumor microenvironment is mechanically and biologically active and, more importantly, is dynamic, as is highlighted by the fact that it is continuously and progressively remodeled (Yu et al., 2010). It is well known that interactions between cells and an altered microenvironment can drive malignancy. Conversely, tumor cells can manipulate their microenvironment to enhance their own survival, thereby creating a positive tumorigenic feedback loop. Thus, it has been proposed that, once established, tumors should be considered functionally discrete organs (Bissell and Radisky, 2001). Interestingly, cells with a tumorigenic genotype can become phenotypically normal if the environmental context is appropriately manipulated, and there is increasing evidence that it might be possible to restore aggressive breast cancer cell lines to a near-normal phenotype by manipulating environmental cues and simultaneously inhibiting multiple signaling pathways (Bissell and Radisky, 2001). Thus, it is becoming increasingly clear that tumors should be studied in a physiologically relevant context.

It has long been known that tumor-derived ECM is biochemically distinct in its composition compared with normal ECM. Furthermore, reports have demonstrated that the tumor stroma is typically stiffer than normal stroma (~400 Pa compared with 150 Pa, respectively), and that breast cancer tissue can be tenfold stiffer than

normal breast tissue (150 Pa versus 1.5 kPa, respectively) (Kass et al., 2007; Butcher et al., 2009; Levental et al., 2009). More recently, increased matrix stiffness and ECM remodeling were observed in pre-malignant tissue (~350 Pa in pre-malignant tissue versus 150 Pa in normal tissue), and this increase was shown to contribute to malignant transformation in the breast (Levental et al., 2009). Pronounced changes in ECM homeostasis, which in some respects mimic those that occur in fibrotic diseases, play a crucial role in tumor progression. They occur owing to disruption of the balance between ECM synthesis and secretion, and owing to alterations in the normal levels of matrix-remodeling enzymes such as LOX (Payne et al., 2007) and MMPs (Jodele et al., 2006; Strongin, 2006; Kessenbrock et al., 2010).

The ECM: Its clinical importance

The dysregulation of ECM homeostasis is a common driving factor in cancer. In line with this, the manifestations of these diseases can overlap: organ fibrosis has been shown to drive malignant transformation, and cancer-associated fibrosis and desmoplasia are implicated in primary tumor growth and metastatic dissemination. It has long been known, for example, that there is a clear clinical correlation between breast tissue density and cancer risk (Wolfe, 1976b; Wolfe, 1976a; Boyd et al., 2002; Boyd et al., 2007). However, although there are numerous treatments available to treat cancer, there are currently no approved treatments that directly target the mechanisms of fibrosis. Given that the ECM plays a pivotal role in the progression of both types of disease, we discuss below the potential of the ECM as a therapeutic target.

The targeting of ECM-remodeling-enzymes to prevent the changes in ECM homeostasis that promote disease progression has received much interest in terms of developing antifibrotic therapies and is now becoming an increasingly attractive therapeutic approach for preventing cancer progression. However, this strategy is not straightforward: for example, early attempts to treat hypertrophic fibrotic scarring and keloidal scars focused on targeting collagen cross-linking with □-aminopropionitrile (BAPN; an inhibitor of LOX). Although this therapy effectively reduced collagen cross-linking and scarring when applied topically, clinical trials were halted owing to toxicity of the drugs, and there has been limited progress since. However, targeting LOX activity has shown more promise in treating cancer: inhibition of LOX was shown to reduce primary tumor growth and mechanotransduction in the mammary epithelium (Levental et al., 2009). Furthermore, LOX inhibition prevents the formation of invasive branching structures in collagen in vitro, the invasion of tumors in vivo, and abrogates BMDC recruitment and the establishment of metastases in vivo. It also destabilizes already-formed metastases by reducing their growth, prevents further metastases and increases host survival (Erler et al., 2006; Erler et al., 2009). Although this suggests that the tumor progression in these models directly depends on LOX and its effects on ECM properties, the exact mechanism by which LOX inhibition is protective remains unknown and is currently being investigated. Nevertheless, these data support the idea that antagonizing matrix modifications, and cross-linking in particular, is a promising cancer prevention strategy. Indeed, LOX seems an excellent therapeutic target and inhibitors are now in development for use in the clinic.

Conclusion

Tightly controlled ECM homeostasis is crucial for regulating many essential cellular processes, allowing for correct organism development, wound healing and normal tissue homeostasis. When this homeostasis is perturbed, an aberrant ECM can contribute to pathological conditions, including fibrotic disease, tumor progression and metastasis (as discussed in this Perspective). The pathological conditions caused by aberrant ECM changes are responsible for millions of deaths worldwide, and present a challenging obstacle

with respect to clinical treatment. Investigating the processes underlying perturbation of homeostasis, the consequential changes in biochemical and biomechanical ECM properties, and the resulting nature of altered cell-ECM interactions will allow us to identify therapeutic targets for clinical benefit across multiple diseases. Among the challenges is to identify effective ways to spatially and temporally monitor these events in a non-invasive and quantitative manner. The hope is that monitoring and therapeutically targeting the abnormalities in the ECM and cell-ECM interactions that are associated with pathological conditions will soon become standard clinical practice.

Given that evidence implicating the ECM in disease progression is rapidly accumulating, new therapies are continuously entering pre-clinical and clinical trials. Studies across multiple disease types, particularly cancer, are aiming to target various factors that regulate ECM homeostasis; several of these factors have shown promise, including the previously mentioned collagen cross-linker LOX (Erler et al., 2006; Le et al., 2007; Erler et al., 2009; Le et al., 2009; Levental et al., 2009), the MMP inhibitor Marimastat (Goffin et al., 2005; Rosenbaum et al., 2005), anti-tenascin-C therapies (Hicke et al., 2006; Reardon et al., 2008) and anti uPA/uPAR (Berkenblit et al., 2005), among others. Such studies continue to unravel the commonalities between diseases involving the ECM, including fibrosis and cancer; identifying these commonalities will not only help to develop novel therapeutics, but will also increase our understanding of the underlying pathological mechanisms. As we move forward, we must always be aware that tissues and organs are made up of both cells and surrounding ECM.

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