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The dynamic tumor extracellular matrix: Biophysical cues, cellular crosstalk, and disease progression

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The interplay between diverse cell types and their extracellular matrix (ECM) is fundamental for multicellular life. The ECM is a complex meshwork of fibrillar proteins and soluble factors. Cells and their surrounding ECM interact bidirectionally, whereby cells deposit their tissue-specific ECM and remodel it enzymatically and by exerting contractile forces. The ECM in turn modulates cellular functions like gene expression, proliferation, and motility. A careful balance of this interaction is key for homeostasis, and is lost during cancer progression. Different cell types constituting a tumor including cancer and stromal cells, contribute to an imbalanced cell-ECM crosstalk within the tumor. Cumulatively, this leads to a tumor ECM characterized by particular features like increased stiffness and viscoelasticity, altered alignment, bundled fibers, etc. In this review, we discuss the advances in our understanding of the tumor ECM architecture and the multicellular interactions that help achieve it, with a special focus on increasing granularity in disentangling the contributions of individual tumor ECM features in disease progression.

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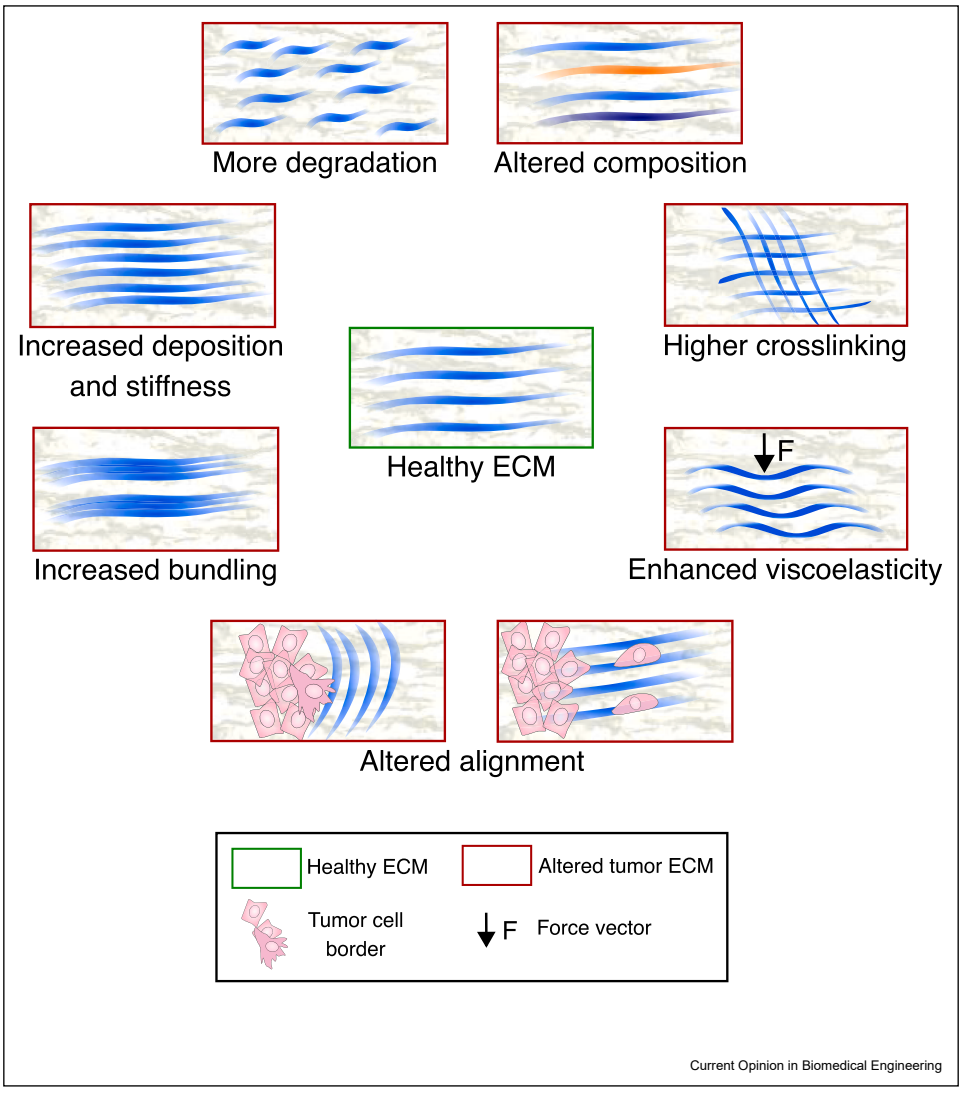
Introduction: mechanical cues and molecular signals in the tumor microenvironment

Tissues and organs of a multicellular organism are composed of cells embedded in their extracellular matrix (ECM). The size and shape of the different cell types and their ability to generate and organize their microenvironment underpins distinct organ-specific tissue features. The ECM is a dynamic and complex meshwork of different structural proteins (e.g., collagens, fibronectin, and elastin), proteoglycans, enzymes, growth factors, cytokines, chemokines, etc. These compositional characteristics, in addition to serving as chemical signal reservoirs, contribute to the emergent physical, topographical, and mechanical properties of the ECM such as stiffness, porosity, degradability, viscoelasticity, and plasticity [1,2]. The dynamic remodeling of these ECM features is vital for tissue homeostasis. However, when ECM remodeling becomes dysregulated, it can contribute to pathological conditions such as cancer [for an extensive overview of ECM remodeling in normal and pathological cancer contexts, refer to Refs. [1,3]]. The cancer-associated ECM differs from the healthy ECM both in composition and biophysical properties in a way that favors the different steps of invasion and metastasis (Figure 1) [4]. For instance, in solid tumors, the ECM exhibits straightened and bundled collagen fibers aligned either parallel or perpendicular to the tumor [5,6]. This often results in tumors being stiffer than the surrounding stroma. The genesis and consequence of an altered tumor ECM are associated with dysregulated proteome and genome expression profiles of cancer and stromal cell (e.g., fibroblasts and immune cells) populations, with active synergy supporting tumor progression.

Cells respond to the integrated physicochemical cues provided by the ECM, and, in turn, actively remodel the ECM to regulate key functions such as proliferation, differentiation, and motility—including migration, invasion, intravasation into the circulation, and extravasation at a distant organ. Integrins are the primary receptors governing cellular responses to ECM signals [7]. Integrin-ECM engagement and activation triggers the formation of integrin adhesion complexes (IACs). IACs, 'adhesome' protein hubs regulating cellular tension and contractility, motility, and downstream signaling, impact transcription in numerous ways including transcriptional co-activators like YAP/TAZ. IACs are central to cellular mechanoresponses, and while their structure and composition differ between 2D cell culture and 3D tissues, their dysregulation is considered to be a common feature of fibrotic and cancerous phenotypes [2,7].

Figure 1



ECM alterations in the TME. Various alterations in the tumor ECM promote cancer progression. These include changes in ECM composition and increased deposition of matrix components, e.g., collagen, leading to altered matrix stiffness and architectural changes reflected in the extent of proteolytic degradation, crosslinking, bundling, alignment, and viscoelastic properties of the ECM.

The entire collection of cellular and acellular components (the ECM) of a tumor constitutes the tumor microenvironment (TME). A large body of literature has established the genetic and phenotypic variations of cells within the TME, leading to the 'hallmarks of cancer' that cumulatively promote cancer progression [8]. Furthermore, ECM alterations are reported in multiple cancer types, suggesting that a dysregulated ECM should also be considered a 'hallmark of cancer' [4].

In this review, we summarize the recent developments in our understanding of tumor ECM remodeling events. We will focus on the role of cancer-associated cellular and ECM components, and how their crosstalk impacts the architecture of the TME and contributes to disease progression.

The physical microenvironment in cancer: mechanical determinants of tumor progression

The ECM and its remodeling play pivotal roles in cancer progression (Figure 1). Growing evidence is uncovering the mechanisms by which heterogeneous cancer cell populations sense and respond to the altered physical properties of the tumor ECM. These changes in ECM structure not only affect tumor cell signaling but also

determine whether cells undergo single verses collective cell migration, ultimately shaping the invasive behavior of the tumor.

While a stiffer ECM is a well-established alteration associated with the TME, how cellular properties adapt or scale in response to ECM rigidity is not well known. A recent study culturing MDA-MB-231 breast cancer cells and HT-1080 fibrosarcoma cells on soft and stiff ECM substrates for 40 generations revealed clonal outgrowth of rare subpopulations adept on the soft ECM [9]. This selection process is in contrast to the 'cancer evolution' idea, which suggests that cancer cell populations evolve over time to the changing ECM and TME. Strikingly, the rare subpopulation cells exhibit stiff-like phenotypes when cultured on soft ECM, mediated by elevated RhoA activity, and are highly migratory. Similarly, osteosarcoma U2OS cells plated on defined ECM combinations such as collagen-I/laminin, can adopt a stiff-like cell-spreading behavior on soft substrates [10], regulated by a YAP-independent mechanism involving a balance between adhesion strength and acto-myosin contractility. Although performed *in vitro*, these studies highlight that cellular responses to stiffness are context- and matrix-composition-dependent.

The presence of genetically distinct cancer cell subpopulations better suited to either a stiffer or softer microenvironment may aid the different steps of the metastatic cascade, during which cancer cells encounter tissues with distinct mechanical properties. Evidence suggests that subpopulations preferring stiffer ECMs could support dissemination away from the primary tumor. For instance, cell populations mechanically primed on a stiff substrate exhibit higher invasion, storing mechanical memory either transcriptionally [11], or through ECM remodeling to enable future invasion events [12]. Moreover, breast carcinoma acini in stiff, but not soft, 3D hydrogels invade by tangentially breaching the basement membrane through a non-proteolytic mechanism requiring synergy between increasing cell volume and focal adhesion kinase (FAK)- and Rho-dependent cell contractility [13]. In a more translational setting and beyond bulk stiffness, application of a convolutional neural network coupled to automated force measurements (STIFMap) has allowed mapping of sub-tumor regions in fixed patient samples with different stiffnesses based on collagen staining [14]. STIFMap data indicate a correlation between specific stiffer areas within tumors and adhesome components such as integrin β1, contractility marked by phosphorylated myosin light chain 2 (pMLC2), and an epithelial–mesenchymal transition (EMT) gene signature, all key features of disseminating cancer cells.

Further downstream in the metastatic cascade, soft-adapted subpopulations may become advantageous. This is corroborated by the analysis of intra-tumoral stiffness in breast cancer, identifying a histone deacetylase 3 (HDAC3)-dependent mechanism that leads to clonal selection on soft intra-tumoral niches, enhancing the different steps of brain metastasis such as blood–brain-barrier breach and colonization [15]. Hence, although increased tumor bulk stiffness is established as a poor prognostic factor and might aid cancer cell dissemination out of the primary tumor, a more refined understanding of how intra-tumoral stiffness variations contribute to the metastatic cascade is needed. Furthermore, the various physical properties of the ECM (such as fiber alignment, bundle size, stiffness, plasticity etc.) are expectedly interdependent, and cancer cells generate specific architectures for progression as described below.

Several lines of investigation have started to tease apart heterogeneous and specific ECM architectural features that govern tumor cell characteristics (Figure 1). In a mouse-derived breast cancer organoid model, modulating collagen fiber bundling versus bulk matrix stiffness has different effects on single-cell and collective modes of cell invasion [16]. While single-cell invasion is enhanced by both increased stiffness and bundle size, collective invasion needs matrix alignment and is inhibited by a generic increase in matrix stiffness [16]. Interestingly, increasing collagen density, which is accompanied by enhanced compaction and reduced pore size, appears to support collective invasion in epithelial MCF-7 and in metastatic 4T1 breast cancer spheroids [17]. Such collective invasion in dense collagen occurs independently of cell–cell adhesions, although inhibiting cell–cell contacts promotes cellular individualization among collectively migrating cells. Tumor ECM alignment patterns, including tumor-associated collagen signatures (TACS1-3), are considered to have prognostic value. TACS define the degree and orientation of collagen alignment around the tumor [5]. In breast cancer, TACS3, defined by straightened collagen fibers reoriented perpendicular to the tumor boundary, is the worst predictor of survival. Interestingly, spatial mapping in melanoma and breast carcinoma has revealed intra-tumoral TACS patterns, with TACS2 and TACS3 occurring proximal and distal to the tumor boundary, respectively [18]. Correspondingly, invading carcinoma cells show increasing Rho-associated protein kinase (ROCK)-dependent pMLC2, single-cell ameboid invasion, and mechano-inflammatory transcriptional signatures progressing from the proximal to the distal regions, with the worst patient outcomes associated with more distal invasion. Collagen-I alignment, rather than absolute concentrations seem critically important for these effects. Efforts are underway to gain more nuanced and refined TACS (TACS1-8) indicative of patient prognosis and mechanisms of cell dissemination out of the primary tumor [6]. However, the molecular details and the significance of the expanded TACS palette in governing migratory or invasive modes remain elusive.

An increased ability to decouple and independently measure specific ECM parameters can provide insights

into specific features sensed by cells. For instance, enhanced ECM viscoelasticity, independently of stiffness, promotes hepatocellular carcinoma progression through an integrin β1—tensin-1—YAP signaling axis [19]. Mechanistically, this is achieved through increased deposition of advanced glycation end-products, and consequent alterations in collagen organization leading to lower connectivity, higher bundling, and shorter fiber length. Further, elevated viscosity increases NHE1-TRPV4-RhoA-mediated contractility and drives breast cancer cell migration, extravasation, and lung colonization [20]. Given the interdependence of several ECM mechanical properties, more refined methods are being developed to assess the effect of individual ECM parameters such as viscoelasticity, confinement, and fiber architecture on cellular behavior (Box 1).

Box 1. Methods to assess individual ECM parameters' impact on cancer cells

Development in biomaterials and methods have enabled us to tease apart specific mechanical parameters of the ECM and measure cell responses. Hydrogels, natural or synthetic, are often used for *in vitro* 3D cell culture. Altering buffer conditions and, consequently, collagen-I polymerization kinetics results in different fiber architecture, without significantly changing the gel's matrix stiffness [47]. Synthetic polyisocyanide-based hydrogels allow control over mechanical properties while keeping the polymer's concentration and gel microstructure constant [48]. Similarly, alginate-based hydrogels are used to study the effect of ECM viscosity independently of stiffness, pore size, and ligand concentration on tumor growth and EMT [49]. Mixing different materials is another approach to independently tune mechanical parameters. For instance, EKGel, a mixture of gelatin and cellulose nanocrystals, has been used to investigate the growth of tumor spheroids within ECMs of varying stiffnesses without altering ligand concentration [50]. Further, ECM fiber alignment can be controlled in cell-derived matrices produced in specific templates, for example by seeding fibroblasts around an agarose mold [51]. Bioprinting techniques are useful to produce ECM with a defined architecture, but they come with limitations in resolution and throughput. Filamented light biofabrication seems to be a promising solution to overcome these limitations [52]. The continued progress in models mimicking specific *in vivo* ECM parameters has the potential to capture cellular responses to individual ECM properties, permitting us to better understand and predict tumor cell behaviors in a dynamic TME. Being able to image the ECM and to measure its mechanical properties in tissues is essential to understand the native ECM properties in tumor tissue and to replicate those properties in *in vitro* experiments. In addition to existing techniques using genetic modifications or protein-specific probes or labeling, new universal ECM probes have been developed that allow live imaging of the whole ECM architecture directly in tissues. These probes are either based on N-hydroxysuccinimide (NHS) ester labeling of proteins [53] or on glycan binding [54]. Moreover, techniques to measure *in situ* the mechanical properties of tissues are being developed. The most recent advance is light sheet elastography, which combines light sheet microscopy, allowing high-resolution imaging of live tissues, and shear wave elastography to measure tissue stiffness at cellular resolution [55]. Combining such advanced mechanical characterization tools with ECM structure imaging could allow us to precisely profile the TME's ECM properties.

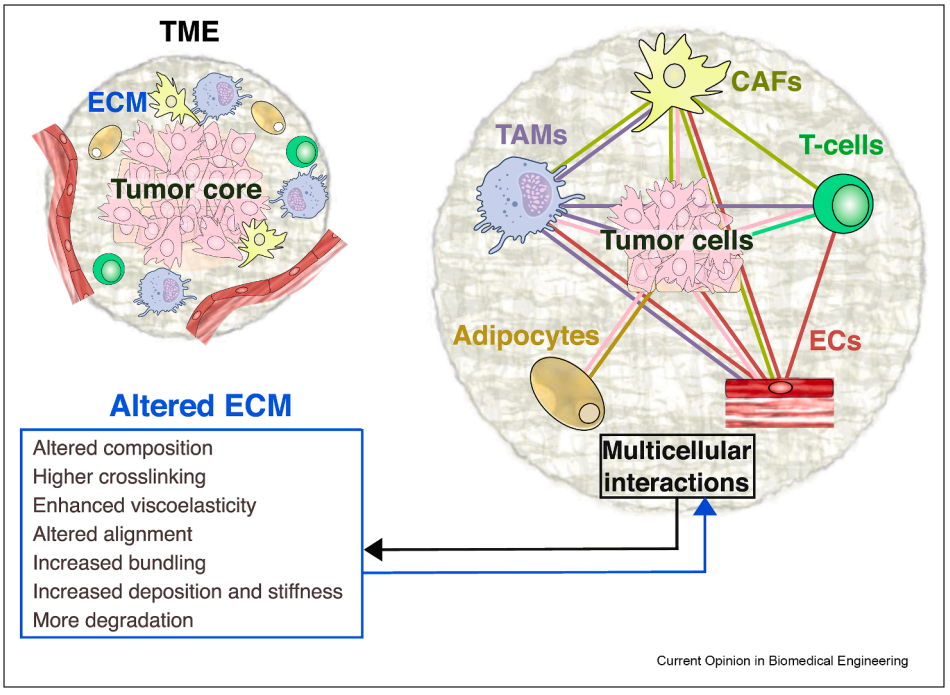
Architects of progression: multicellular remodeling of the tumor ECM

The TME is an evolving ecosystem with a dynamic cellular component composed of cancer cells, cancer-associated fibroblasts (CAFs), myeloid and adaptive immune cells, adipocytes, and endothelial cells [21]. These cell types influence cancer cell behavior directly, through paracrine signaling, or through ECM remodeling (Figure 2).

CAFs are well recognized as the primary ECM remodelers within the TME, and they contribute to an altered tumor ECM through various mechanisms [22,23]. Briefly, CAFs are the major depositors of tumor collagens, corroborated by a recent systematic analysis of single-cell RNA sequencing (scRNA seq) datasets, which also established the collagen-signatures of different CAF subtypes [23,24]. CAFs also secrete ECM-modifying enzymes. The lysyl oxidases (LOX) induce collagen crosslinking [25], and collagenases support matrix remodeling and ECM degradation, helping tumor cell invasion. The physical and mechanical characteristics of the ECM are interdependent, and the above changes subsequently lead to increased ECM stiffness and viscoelasticity, and contribute to an altered alignment (Figure 1), promoting cancer progression. Interestingly, *in vitro*, CAFs deposit integrin-β5 decorated tracks, called 'CAF tracks,' which steer cancer cell migration and durotaxis [26]. However, the existence and significance of 'CAF tracks' *in vivo* remain elusive. In addition to remodeling the ECM, CAFs also interact with cancer cells directly. In a mouse intestinal tumor model, CAFs encapsulate the incipient tumor cells and compress them to elevate the intratumoral pressure and increase cancer cell density [27]. Such compression induces cytoplasmic YAP localization and reduces cancer cell proliferation, indicating a prohibitory role of CAFs in tumor progression. On the contrary, in head and neck squamous cell carcinoma (HNSCC), single-cell-level multiparametric histology has revealed active, invasion-inducing CAF communication specifically with cancer cells exhibiting partial EMT [28], highlighting that the outcomes of a CAF-cancer cell interaction are cancer-dependent. Reciprocally, cancer cells from the primary tumor can prime metastatic sites by reprogramming resident fibroblasts. A study using breast cancer as a model found systemic circulating activin A (ActA), secreted by the cancer cells, to induce collagen deposition in the lung and promote lung metastasis [29].

Infiltrating immune cell populations can be directly influenced by resident tumor ECM characteristics. In a triple-negative breast cancer model, longer and more aligned collagen fibers near the tumor margin hamper T-lymphocyte infiltration [30]. Moreover, the tumor

Figure 2



Multicellular interactions within the TME. The cellular component of the TME includes different cell types like tumor cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), T-cells, endothelial cells (ECs) and adipocytes. An active crosstalk between these cell types regulates their function and the tumor ECM properties. Such intercellular interactions may happen directly or indirectly through an altered tumor ECM. ECM, extracellular matrix; TME, tumor microenvironment.

ECM stiffness and composition also regulate macrophage differentiation patterns [31]. In ovarian cancer, tumor-associated macrophages (TAMs) are linked to poor prognosis. In a corresponding model system where macrophages are cultured in decellularized omental metastases, ECM-induced macrophage differentiation into TAM-like phenotypes was associated with high-stage disease progression, positively correlating with the expression of five ECM components—fibronectin (FN1), versican (VCAN), matrix remodeling associated 5 (MXRA5), collagen 11 (COL11A1), and secreted frizzled-related protein 2 (SFRP2) [31]. Patients with a higher expression of this ECM signature show lower overall survival. Furthermore, these ECM-educated macrophages might reciprocally remodel the tumor ECM through active integrin—ECM interactions that are also important for macrophage recruitment to the tumor niche [32,33]. Indeed, pan-cancer TAM mapping shows these populations to be highly heterogeneous, consisting of 23 different clusters, reinforcing the limitations of the conventional M1/M2 dichotomy, particularly in the TME [34]. Interestingly, among these, the cluster enriched in ECM-modifying TAMs exhibited several overexpressed collagen genes. Additionally, other adaptive immune cells such as CD8+ T cells remodel the tumor ECM through expression of collagen-crosslinking LOX enzymes in a post-chemotherapy metastasis model, aiding cancer cell seeding [35].

Endothelial cells also play an important role in tumor progression, and a stiffer tumor ECM alters endothelial cell mechano-signaling, increases vascular compression, and causes hypoperfusion, eventually leading to faulty vascularization [36]. A recent study in lung adenocarcinoma has highlighted the potential of anti-angiogenic therapies in cases of elevated collagen deposition accompanied with poor immune infiltration. These so-called 'cold and armored' tumors, with increased collagen and ECM stiffness, support angiogenesis through SOX18 upregulation in endothelial cells, triggered by tumor cell-derived vascular endothelial growth factor A (VEGFA) expression [37], and were sensitive to anti-angiogenic therapy.

Although several cell types within the TME seem to independently influence tumor progression, growing evidence is uncovering the role of complex cellular crosstalk and an altered ECM in this process (Figure 2) as discussed below.

Interconnected components: cellular crosstalk in the TME

In the multicellular TME, there is a complex crosstalk among several cell types, which in turn affects the ECM architecture. Among these cellular components, CAFs are the chief architects of the tumor ECM. Strikingly, scRNA seq from breast cancer patients indicates that CAFs also have the highest cell—cell interactions within the TME [38], the most prevalent occurring between CAFs and TAMs. In addition, a three-way circuit analysis demonstrates the existence of a CAF—cancer-cell—TAM signaling axis. Functionally, the CAF—TAM interaction leads to an upregulation of pro-tumorigenic migratory, chemotactic, and inflammatory genes in TAMs and increased collagen deposition in the ECM by CAFs. Addition of cancer cell-conditioned medium alters the growth dynamics and signaling in this interaction, providing a glimpse of the complex communication network within the TME [38]. Similarly, in colon cancer, CAFs communicate with monocytes and endothelial cells, employing nicotinamide phosphoribosyl transferase (NAMPT)-associated pathways—including NAMPT-integrin—predictive of an immunosuppressive TME [39]. In addition to regulating TAMs, CAFs promote T-cell exclusion from tumors, leading to immune suppression. They achieve this by forming physical cellular and ECM barriers, depositing dense collagen fibers, preventing T-cell entry, and driving T-cell marginalization [22,40].

The occlusion of T-cells by a stiffened and fibrotic TME is further aided by TAM-mediated metabolic rewiring. In a breast cancer model, TAMs respond to a stiffer ECM by activating an autocrine TGF-β signaling loop, leading to collagen VI synthesis, arginine depletion, and a corresponding ornithine increase in the TME [41]. This leads to decreased CD8+ T-cell proliferation, protein translation, and compromised anti-tumor immunity. Similarly, in a colon adenocarcinoma murine model, macrophage depletion in late-stage tumors causes altered collagen alignment and increased T-cell infiltration, likely driven by a *TRPS1-TCF4-COL3A1* axis in the carcinoma cells and fibroblasts [42]. Strikingly, a recent tumor array approach (skin tumor array by microporation; STAMP) showed that early inflammatory monocytes and neutrophils produce T-cell chemoattractants that promote a 'resolved' tumor immune phenotype, in which pancreatic ductal adenocarcinoma tumors are eliminated by the immune cells [43]. The STAMP approach identified a unique CAF subtype, called ChemoCAF, acting upstream to produce chemokines recruiting monocyte/neutrophil, and eventually T-cells. Importantly, the study showed that tumors can generate spontaneously heterogeneous immune phenotypes that change over time. Certain TAM subsets, mapped in a pan-cancer analysis, are indeed positively associated with T-cells [34], indicating that the tumor-promoting or -suppressive roles of the macrophage—T cell interactions are context-, disease-stage- and tumor-subset-dependent, and likely change over the course of tumor development. Hence, tracking the history of the tumor immune environment can have predictive therapeutic value.

Another indirect mechanism of promoting an immunosuppressive TME is improper vascularization due to a remodeled tumor ECM [36]. Endothelial cells and tumor immune cells bidirectionally regulate each other [extensively reviewed in Ref. [44]]. However, the exact molecular details of the endothelial cell-immune cell crosstalk remain elusive. CAFs are also known to regulate endothelial cell function and angiogenesis. Perivascular CAFs in B16F10 melanoma and MH6419 pancreatic cell-derived tumors support tumor vascularization through an activating transcription factor 4 (ATF4)-driven pro-angiogenic secretome [45].

Lastly, tissue resident adipocytes influence tumor progression. For example, through insulin-like growth factor-binding protein 2 (IGFBP2)-mediated paracrine signaling, resident adipocytes inhibit breast cancer invasion [46]. However, the possible link between these adipocyte-associated pathways and the ECM architecture remains to be thoroughly studied.

Understanding the tumor microenvironment: future directions

The fast-evolving, cutting-edge omics and sequencing technologies are providing key insights into the cellular and acellular components of the TME. These have provided increased granularity of our understanding of the constituents of the TME and highlighted the complex interplay between multiple cell types within a tumor and their bidirectional crosstalk with a dynamically remodeled ECM. Furthermore, refined biophysical methods are enabling specific ECM parameters to be tailored and measured independently to further expose the precise roles of the ECM in driving cellular phenotypes, highlighting functionally and clinically relevant dysregulations in the TME. The integration of computational models and neural networks with large publicly available datasets has elucidated the cell types and molecular signatures contributing to ECM alterations, and moreover, has unraveled inter-cellular interactions and plasticity, ultimately driving tumor progression [34,38]. It is evident that the TME composition and architecture are dynamic and context-specific. Further, although models looking at pathways within one cell type or interactions between two cell types have uncovered important regulatory signatures, the TME is a complex and interconnected network, which might behave differently than predicted by reductionist models. This is often reflected in contrasting

phenotypes in different cancer models or at different stages of cancer progression, and result in therapeutic failures [30,42,43]. This highlights the need to aim for more advanced models and, ideally, the inclusion of more of the relevant cell types when studying particular pathways as compensatory mechanisms might hamper favorable outcomes.

From a cell biological perspective, the mechanoresponsive signaling pathways in several of the above contexts remain to be studied. Although many phenotypes are dependent on contractility, the role of cell-ECM adhesions and the exact molecular pathways involved remain elusive. As the TME is a 3D space with a physico-chemically dynamic ECM and evolving cell–cell contacts, established pathways in the 2D setting might not directly translate to the TME. A mechanistic understanding of these pathways in innovative models capturing the 3D TME can help discern the causes of ECM alterations, and has the potential for more predictive power, especially in an ever-changing TME.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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

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