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Systems approaches to uncovering the contribution of environment-mediated drug resistance

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ABSTRACT

Cancer drug response is heavily influenced by the extracellular matrix (ECM) environment. Despite a clear appreciation that the ECM influences cancer drug response and progression, a unified view of how, where, and when environment-mediated drug resistance contributes to cancer progression has not coalesced. Here, we survey some specific ways in which the ECM contributes to cancer resistance with a focus on how materials development can coincide with systems biology approaches to better understand and perturb this contribution. We argue that part of the reason that environment-mediated resistance remains a perplexing problem is our lack of a wholistic view of the entire range of environments and their impacts on cell behavior. We cover a series of recent experimental and computational tools that will aid exploration of ECM reactions space, and how they might be synergistically integrated.

1. Tumor cell-environment interactions are multi-factorial

Environmental factors play a crucial role in dictating sensitivity or resistance of cancer cells to drug treatment (Fig. 1). Advances in biomaterials and bioprinting technologies have made it possible to mimic the 3D tumor microenvironment and evaluate how specific extracellular matrix (ECM) compositions, ligands, geometries, and biophysical properties influence drug response more accurately. However, a consensus understanding of how environment-mediated drug resistance (EMDR) limits the efficacy of targeted therapies remains elusive. The presence of cell-to-cell intrinsic differences, multi-factorial environmental inputs, and combinations of resulting phenotypes in and around tumors present an overwhelmingly large parameter space affecting drug response. Given these challenges, we propose that a combination of modeling techniques tailored for high-dimensional analysis, alongside high-throughput experimental approaches to interrogate engineered tumor microenvironment (TME) variations, is critical to integrate and summarize this vast space, unify findings across studies, and generate data-driven hypotheses and biological insights related to EMDR.

1.1. Cell intrinsic differences lead to clonal diversification

Before directly addressing EMDR, we must acknowledge how clonal heterogeneity drives drug response characteristics. Intratumoral heterogeneity can be subdivided in two broad categories—environmental and cellular—resulting in complexity that must be considered when studying ECM-cell interactions. Isolation and systematic characterization of cancer cells has significantly advanced our understanding of the *cell-autonomous heterogeneity* present within the tumor [1,2]. Genome sequencing studies have uncovered that tumors are both spatially and temporally heterogeneous, leading to major challenges in finding therapies effective for all cells in a tumor. As just one of numerous examples, Yates *et al.* analyzed the spatial distribution of subclones for twelve cancers. Eight showed significant spatial heterogeneity in cells with point mutations, and two showed heterogeneity in copy-number changes. Interestingly, they noted the degree of heterogeneity in triple-negative breast cancer correlated to tumor size, although the causality is not clear [3].

Environmental heterogeneity arises when regions within the TME contain distinct environments that modulate disease progression. For instance, the pancreatic TME consists of locally confined sub-tumor microenvironments with distinct fibroblast plasticity, tumor immunity, and treatment response states revealed by regional transcriptomic and proteomic measurements [4]. Additionally, tumors are formed by heterogenous subpopulations of intrinsically different cells that evolve in response to their environment; consequently, each subpopulation has

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distinct input–output responses to the TME. A substantial amount of work has been dedicated to investigating the emergence of subclonal populations defined by their genetic diversification in response to the selective pressure imposed by drugs [5–8]. In breast cancer, sequencing 303 tumor samples from 50 patients enabled investigators to map the spatial and temporal clonal evolution of tumors. They were able to identify causal genetic alterations present in specific subclones with increased resistance to chemotherapy and metastatic capacity [3]. However, while clonal subpopulations within tumors have now been extensively profiled for their selection and relative fitness within the tumor ecosystem, this has yet to be evaluated within the context of their local TME (Fig. 1) [9].

1.2. Cell-ECM interactions

The ECM is a collection of sugars, proteoglycans, and proteins that collectively provide attachment, scaffolding, and, via integrin binding, initiate receptor-mediated signaling in resident cells, which plays a critical role in regulating tumor growth and metastasis [10]. Tissues that nurture the formation of successful metastases have a distinct ECM profile [11], and thorough analysis of these sites has revealed that each tissue has a distinct profile of adhesive matrix proteins and physiological stiffness [12–20]. Inspired by this, Barney *et al.* designed bone-, brain-, and lung-inspired biomaterial platforms by varying the composition and density of ECM proteins [21]. When they cultured bone-, brain-, or lung-tropic cell lines on these ECMs, they found coordination of ECM with EGF regulation of spreading rate, area, displacement, and chemotactic index. They also demonstrated that these ECM-specific responses could predict breast cancer metastasis. The clear next step is to take these ECM-specific biomaterials to drug response studies.

Several studies have indeed demonstrated that integrin-binding to the ECM drive therapy resistance and blocking these interactions has emerged as a potential strategy to overcome integrin-mediated drug resistance [22–24]. For instance, administration of a β_1 integrin inhibitory antibody (AIIB2) reduced tumor volume and increased the efficacy of ionizing radiation in human breast cancer xenografts [25]. A 3D spheroid system demonstrated that matrix-attached ovarian cancer cells developed resistance to dual inhibition of PI3K/mTOR, while inner matrix-deprived cells underwent apoptosis. The ECM-driven adaptive mechanism included upregulation of nutrient deprivation and cellular stress programs that sensitized cells when targeted [26]. Lee *et al.* developed a miniaturized 3D cell-culture array (DataChip), which spotted up to 1080 cell-seeded collagen or alginate gels onto glass slides [27]. This assay, although miniaturized, yielded accurate cytotoxicity information when comparing its IC_{50} values to those in conventional well-plate assays. These high-throughput 3D systems will enable toxicity analysis of drug candidates and their metabolites at the early-stage of drug development process (Fig. 2) [28]. Examples of combinatorial ECM screening approaches include that from Beachley *et al.*, who spotted ECM from 11 different tissues and quantified cell growth over a large panel of cell types, including three different cancer cell lines [29]. Although not explored yet, this would be an excellent system to screen for EMDR across tissue specific ECMs. Mabry *et al.* designed a synthetic hydrogel in a high-throughput multi-well plate, where they can vary

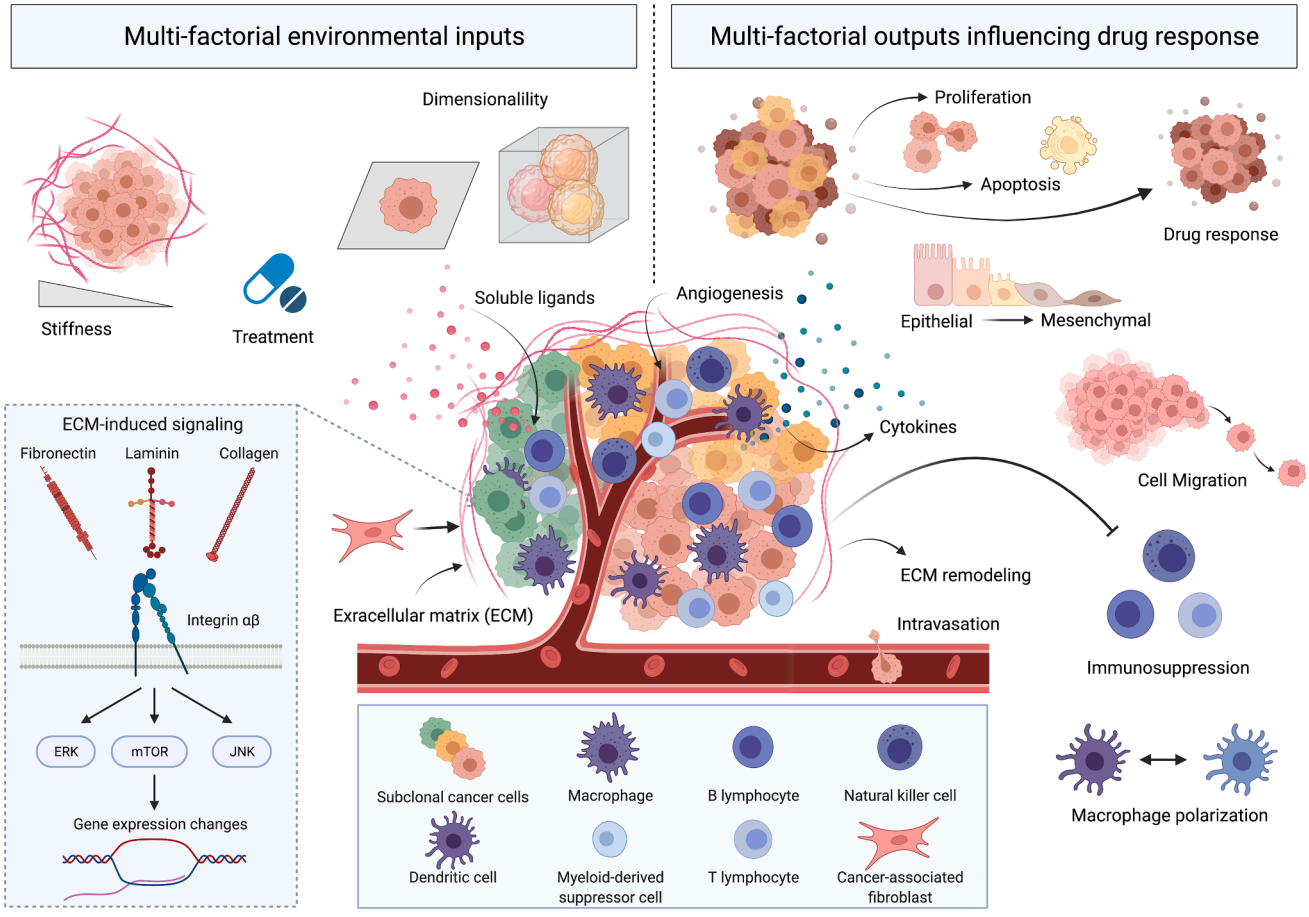

Fig. 1. Tumor cell responses to their environment are multi-factorial. There are multiple factors that can affect tumor cell behaviors. Dimensionality (2D or 3D), stiffness of the culturing materials, topography of the surface, addition of growth factors, shear forces or interstitial fluid pressure can change how tumor cells behave. Outputs are also multi-factorial. Within the same tumor, cells can show different proliferation profiles, drug responses, immune responses, and ECM remodeling due to their intra- and inter-tumor heterogeneity.

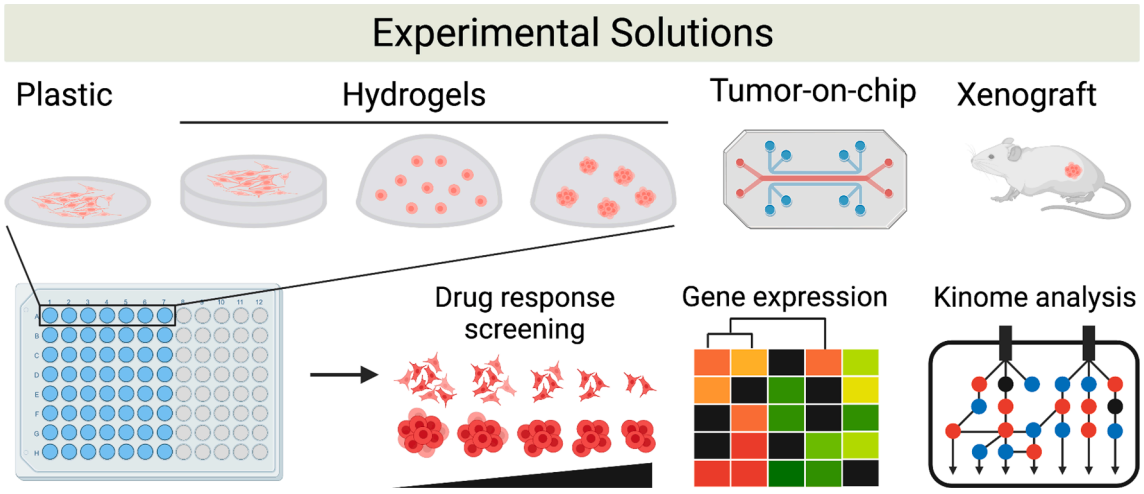

Fig. 2. Experimental solutions to reflect multiple environmental inputs and outputs. To consider physical and biological factors that affect cancer cell behavior, different culturing platforms such as 2D plastic, 2D hydrogels, 3D hydrogels with single cells, 3D hydrogels with spheroids can be used. These can be made on high-throughput system, like 96-well plates. Tumor-on-chip is another platform that reflects tumor microenvironment with microfluid system. Tumor xenografts, although not high throughput, are physiologically closer to the actual tumor microenvironment. With these platforms, drug response, gene expression, and kinome analysis can be done to study multi-factorial outputs.

several parameters including the types of peptides, peptide concentration, and matrix modulus dynamically while cells are embedded [30]. Thus far, this lab has used this and similar approaches to study vascular interstitial cells during fibrosis, and it would be an excellent tumor ECM progression model for cancer.

These studies and others also emphasized the importance of dimensionality, or the geometry in which cells grow, when attempting to recreate the TME [31,32]. In fact, directly comparing CRISPR screens in 2D monolayers and 3D lung-cancer spheroids revealed that many 3D cancer growth-specific vulnerabilities are not recapitulated in 2D [33]. The role of focal adhesion proteins in driving cancer cell dissemination is similarly distinct between 2D and 3D environments [34]. However, systematic comparisons of different dimensionalities can reveal how individual cellular components retain their functional role, but differing importance comes from a shift in the overall rate limiting processes. For example, Meyer *et al.* identified that, while migration growth factor responses differ between 2D and 3D, initial membrane protrusion responses were identical [35]. A mechanistic understanding of which specific components within the ECM and molecular interactors in cancer cells modulate these phenotypic responses will improve our ability to manipulate these responses.

1.3. The physical traits of the TME

The biophysical properties of the TME (*e.g.*, ECM modulus) generate forces that are sensed by cells via integrins, the cytoskeleton, and mechanosensitive ion channels, and strongly influence cell behavior [36]. Modulus is an intrinsic property that describes the extent to which the ECM resists deformation in response to an applied force. Increased modulus is commonly observed in tumors relative to healthy tissue across many cancer types [37–40], typically through ECM deposition by stromal cells, especially cancer associated fibroblasts (CAFs) [41], or via mechanical stresses from cell contraction and tumor growth [36]. The density and identity of ECM proteins deposited by tumor stroma dynamically stiffens the ECM: *e.g.,* type I collagen imparts tensile strength, and elastin gives tissue its elasticity. Several studies support a prevailing hypothesis that ECM stiffness impacts tumor metastases [42,43]. Solid stresses can also be generated by increased tissue volume and increased interstitial fluid pressure. The impact of these mechanical factors in treatment response has gained continued attention. However, their role in EMDR and cancer recurrence has been underappreciated and a deeper molecular understanding of the pathways engaged might lead to further therapeutic opportunities. We will highlight some of the emerging studies and tools developed for this exact topic here.

Schwartz *et al.* developed an approach to study drug responses in cells cultured on a 2D environments or in 3D hydrogels [44]. This study revealed that cells were more resistant to receptor tyrosine kinase (RTK)-targeting drugs, such as sorafenib and lapatinib, when cells were cultured on high modulus 2D hydrogels or when spheroids were cultured in high modulus 3D hydrogels. This agrees with a prior study from Nguyen *et al.* who showed that several cancer cell lines were more resistant to sorafenib when they were cultured on a stiffer 2D biomaterials [45]. They went further to show that gene expression differences were not sufficient to explain the observed drug resistance. They combined multiple linear regression analysis with quantification of the activation of a small panel of receptor tyrosine kinases in and on those environments to reveal that blocking MEK phosphorylation alongside these targeted therapies could overcome EMDR and reduce tumor burden *in vivo*.

Both prior studies show the value in incorporating tunable biomaterials into high-throughput formats, but their limitation is that although they tuned modulus and geometry, they were limited to single ECM proteins. Brooks *et al.* overcame this limitation when they studied ovarian cancer drug resistance in an omentum-inspired 3D hydrogel [46]. They generated 3D tumor spheroids in microwells and encapsulated them in the 3D hydrogels that had the stiffness and protein composition of omentum tissue. The tumor spheroids showed increased sensitivity to Carboplatin, Doxorubicin, LY2606368, and Mafosfamide compared to those cultured on 2D tissue culture polystyrene, which they were able to correlate to observed clinical response with paired primary patient derived samples [46].

1.4. Soluble ligands are released by cancer and stromal cells

Paracrine signaling between cancer and stroma also initiates receptor-mediated signaling to tumor cells, further driving disease progression. For example, TGFβ, IL-6, IL-8, EGF, and hepatocyte growth factor (HGF) produced by CAFs have emerged as potential drug resistance targets [41,47]. IL-6 and IL-8 exert pro-migratory effects on cancer cells [48], and IL-6 further affects apoptosis, cell growth, angiogenesis, and antioxidant metabolic programs that ultimately protect cells from therapy [49]. Similarly, autocrine and paracrine release of TGFβ promotes epithelial-to-mesenchymal transition (EMT), cancer cell migration, and invasion [50–52]. HGF is the cognate ligand of the RTK c-Met,

which regulates tumor growth, migration, and resistance to tyrosine kinase inhibitors (TKIs) [50,51,53,54]. Importantly, crosstalk between response to combinations of these soluble factors can additionally serve as a drug resistance mechanism. For instance, CAFs respond to TGFβ inhibition by increasing release of HGF, which in turn enhances cell invasion [55–58]. Furthermore, cancer cells reprogram their energy metabolism from mitochondrial oxidative phosphorylation to glycolysis-mediated ATP production to fuel uncontrolled cell proliferation in tumors. This metabolic switch occurs in response to hypoxia common to tumors, activating a response system that upregulates glucose transporters and glycolytic enzymes, and increases the release of reactive oxygen species (ROS) [59,60]. Recent work by Oren *et al.* observed a strong relationship between the proliferative capacity of persister cell subpopulations and antioxidant expression signatures. They subsequently validated that the EGFR inhibitor osimertinib induces an increase in ROS and showed that the fraction of proliferative persister cells increased significantly upon ROS neutralization using the ROS scavenger N-acetylcysteine [61].

Clearly, soluble factors in the TME are crucial mediators of EMDR. Whether and how these signals should be targeted, however, will depend on their exact role in the TME. For instance, these soluble factors might alter tumor cell responses to their environment, promote survival and other phenotypes directly, or promote tumorigenic responses indirectly through changes to the TME. Systematic studies of soluble and ECM signals will help to identify the unique or overlapping role of each. A sophisticated study to do exactly this, Lin *et al.* generated 210 unique microenvironments to explore in parallel how they shape the inhibitory effects of lapatinib [62]. They tested four ECM compositions and seven ligands, on either 2,500 Pa or 40 kPa elastic modulus substrate polyacrylamide gels and measured cell proliferation, HER2 expression and phosphorylation, and cell morphology across four different cancer cell lines. Interactions between soluble factor responses can be observed *in vivo* as well. For instance, trastuzumab or lapatinib elicited responses in HER2-amplified breast cancer metastases when they were situated in mammary fat pad but not in the brain, where the combination of a HER2 inhibitor with an anti-VEGFR2 antibody was required to slow tumor growth [63]. In a second study, HER3 blockade was needed to overcome resistance conferred by the brain microenvironment to PI3K inhibition [64].

1.5. Multiple cell phenotypes, in combination, define the resistance capacity of cancer cells

Drug resistance is typically quantified via a direct or surrogate measure of cell number. However, the ability of tumors to sustain growth in the presence of treatment is defined by cooperation between phenotypic responses. Drug treatment can lead to potent differences in cell response, hidden by simply quantifying cell number [65]. Resistant tumor cells that undergo EMT result in both drug resistance and increased metastatic capacity [66,67]. Resistance to cancer immunotherapies is driven, at least in part, by mechanisms such as T-cell exhaustion, immune suppressive cell populations, and inhibitory cytokines and metabolites that immunologically suppress the tumor microenvironment [68]. Furthermore, cancer and other resident cells (*e.g.,* CAFs) reciprocally respond to tumor environmental signals by remodeling their ECM. This response can be subdivided in three broad categories: (1) ECM deposition affecting the biochemical and mechanical properties of the environment, (2) the proteolytic degradation of the ECM weakening migratory barriers and promoting the invasive ability of cancer cells, and (3) integrin-mediated cell-ECM binding causing non-proteolytic physical breaching of the base membrane facilitating cancer cell invasion [69]. For these reasons, drug resistance must be viewed as the coordination of multiple phenotypes to overcome the inhibitory effects of therapy.

The drug response and resistance mechanisms of RTK inhibitors effectively illustrates the importance of determining the role of individual factors within an overall environment. Our labs and others have shown that a common form of RTK inhibitor resistance is derived from alternative "bypass" RTKs that can reactivate essential survival signaling [70–73]. While each RTK has some propensity for this signaling redundancy, different growth factors vary in their resistance-conferring capacities. For instance, lung adenocarcinoma cells treated with the EGFR inhibitor erlotinib can be made resistant by HGF or FGF much more so than EGF, IGF, HRG, or PDGF, and each growth factors' resistance conferring capacity could be explained by its ability to activate a common downstream pathway [70,74]. Beyond merely inducing cell proliferation, RTK-mediated bypass resistance can also activate collateral malignant programs that, in combination, limit therapy efficacy and direct disease progression. For instance, resistance through AXL activation associates with more advanced diseases stages as the receptor sustains cells that have undergone EMT resulting in increased metastatic capacity [66,73,75,76]. The TME can also modulate drug response through these same signals. While these bypass mechanisms mean that there are many possible environmental factors that can contribute to resistance, systematically identifying which factors may lead to similar downstream consequences would help to build a catalog of which are capable of conferring bypass resistance.

Together, these observations indicate that no one environment will faithfully represent the complex cell-ECM interactions that exist in a living tumor. High-throughput screening methods that systematically evaluate the impact of hundreds of tumor-inspired microenvironments can circumvent these limitations to help uncover resistance or sensitivity-driving environmental cues. These data can then be complemented with transcriptomics, proteomics, and/or phosphoproteomics information to uncover the signaling programs that transduce such cues and give rise to the resulting phenotypic responses (Fig. 2). Provided this huge space of inputs and outputs, a set of experimental and computational methods to systematically disentangle what specific microenvironmental factors, signaling changes, and phenotypic expressions drive drug resistance will be necessary.

2. Unique challenge of multi-factorial problems like environment-mediated resistance: Exploring the space of possibilities

A central challenge in understanding how environment contributes to tumor cell resistance is that the "space" of environmental factors is so large. Different environmental factors interact, creating context-specific responses unless one considers the entire range of possible environments. On the other hand, it becomes impossible to measure response to all possible environments. Even in large-scale profiling studies, it can be difficult to "map" between studies to determine which responses occur through common mechanisms, and which represent distinct pathways. A similar problem in mapping arises when considering the relevance of *in vitro* systems to *in vivo* responses: first, there are many factors that can be mimicked *in vitro*, but it is not clear which are essential to creating an accurate (or minimally necessary) representation of the *in vivo* environment; second, the *in vivo* environment itself is not monolithic, and contains microenvironments that vary in their composition. The answer cannot simply be larger studies, as the scale difference is modest compared to the overwhelming range of environmental factors. For instance, testing 10 parameters defined by the categories above, in combination and in triplicate, would require 300,000 measurements (Fig. 3A).

A similar challenge exists in the use of many-parameter computational models. Optimization requires exploring which among many possible inputs leads to optimal outputs. However, the curse of dimensionality dictates that problems quickly become intractable, even for computational exploration, as the number of parameters increases (Fig. 3B). Solutions to this problem from computational applications offer lessons for studying the ECM environment.

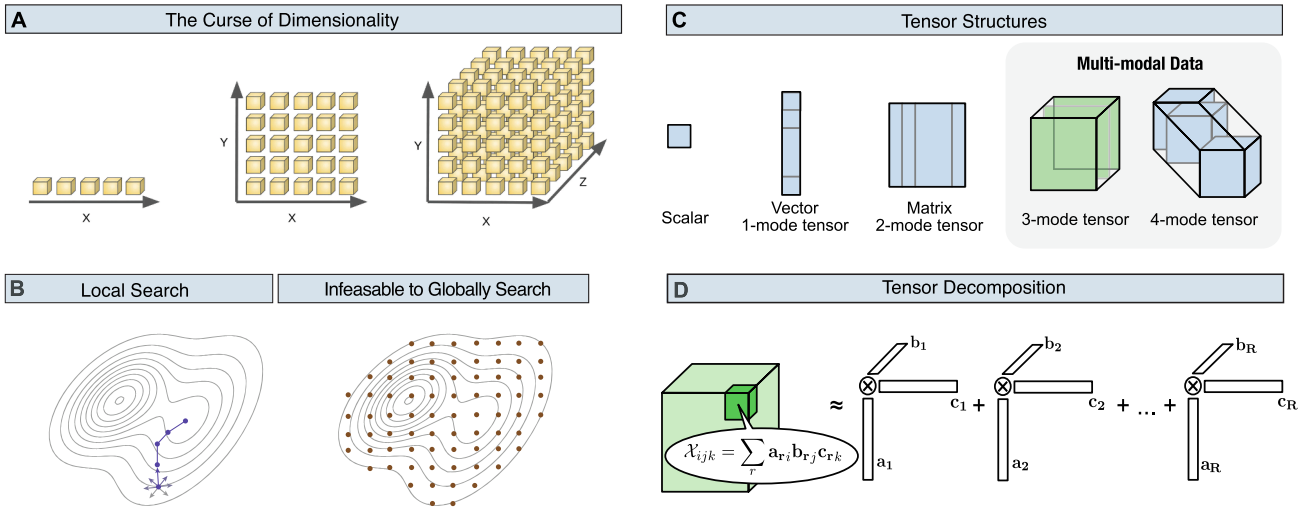

Fig. 3. Computational solutions to mapping EMDR. A) The vast "space" of environmental factors that affect cell response prevents an accurate experimental and computational representation of EMDR. B) Optimization is achieved through a local exploration within the neighborhood of an existing optimal solution. However, because of the curse of dimensionality, this can require an impossibly large number of local searches to fully explore the multi-factorial space of EMDR. C) Multi-modal data includes different variables that combinatorically influence the ECM-mediated cell responses. D) Dimensionality reduction using tensor decomposition can vastly simplify multi-modal patterns.

3. Computational solutions to reduce the space of ECM responses

Computational approaches can provide a solution to parsing the overwhelming space of ECM environment possibilities and their effects on drug response. These methods can help visualize multi-factorial space, optimize experimental design for desired outcomes, and integrate observations with prior knowledge. To do so, computational methods work off two general principles—recognition of certain general patterns, and the use of pre-defined patterns based on prior knowledge. Both approaches have shown success in making sense of cells' responses to their environment and have future opportunities for improvement.

A particularly promising solution to exploring many-parameter responses is finding low-rank structure within a space of possible responses. For instance, when exploring how cells respond to a panel of soluble factors, the responses can be visualized with a technique like principal component analysis (PCA), which identifies a low-rank structure within matrix data (conditions × measurements). However, cell responses are not only multi-dimensional but multi-modal, meaning that *types* of variables, such as soluble ligands, treatment, and ECM biophysical or biochemical properties, can be present in all possible combinations, and induce cell phenotype changes through their combination (Fig. 3C and 4). For instance, Lin et al examined cell responses to lapatinib with different soluble ligands, ECMs, and matrix stiffnesses, with or without lapatinib treatment. These different *groups* of factors were tested in all possible combinations. Such structured data can be organized as a 4-mode tensor where axes represent ECMs, ligands, matrix stiffness, and treatments. Moreover, this data is still multi-dimensional given that many measurements were made. For these cases, higher-mode generalizations of PCA exist. These methods, broadly referred to as tensor decomposition techniques, can be remarkably effective at dimensionality reduction even beyond PCA (Fig. 3D) [77]. For instance, Farhat *et al.* recently profiled the response of several immune cell populations to cytokines at several concentrations over time, resulting in a four-mode tensor (cell types × time × ligand × concentration) [78]. Tensor-based decomposition reduced the data to ~ 2% of its original size, while preserving 90% of the variance in the original 2,880 measurements, by recognizing that just two overall patterns existed across the different parameters [78]. Importantly, this reduction is far beyond what would have been achieved by PCA, and additionally helped visualize the effect of each mode by separating their effects (*e.g.,* the effect of time). Tan *et al.* similarly explored how tensor decompositions can reduce antibody serology data in which the antigen targeting and immune interactions of antibodies are profiled across subjects and time [79]. There too, they observed that dimensionality reduction in tensor form could further reduce data into component patterns, and that its visualization was improved by separation of each mode's effect. Dimensionality reduction in this form can also help to harmonize data across studies. For instance, it has been used to identify patterns across microbiome studies, overcoming inter-study batch effects and sparse, irregular sampling [80]. Common patterns exist among all the ECM factors we have described above, as well, where substantial dimensionality reduction can reduce the search space of experiments.

As an illustrative example of the biological conclusions one can derive from multi-modal dimensionality reduction, we performed PARAFAC decomposition on a microenvironment microarray (MEMA) dataset of MCF10A breast epithelial cells. 182 cellular properties were measured across 57 ligand treatments and 48 ECM environments, forming a 3-mode tensor [81] (Fig. 4A). First, PARAFAC can reduce the data more effectively than PCA—by 98% while still explaining 60% of the variance (Fig. 4B). This makes it easier to identify patterns in how ECM composition, soluble factors, and interactions between both affect the measured cell response. The influence of each mode within a component is multiplied together to reconstruct the data, making interpretation straightforward. For instance, component 2 illustrates the effect of elastin and nidogen, across a range of soluble ligands, affecting cytoplasmic shape properties. These results additionally show how one can draw overall conclusions about the data. For example, component 2 varies more extremely with ECM environment, while component 1 is much more responsive to soluble ligands' presence. Finally, tensor decomposition can facilitate the integration of various data sets, provided they have one mode in common. Here, one could expand the shown tensor (Fig. 4A) into a 4-mode tensor incorporating measurements from different cell lines across the same ligands and ECMs [82,83]. This can help ensure that the cell-ECM interactions discovered are conserved across relevant cell line models.

Alternative solutions to the curse of dimensionality are methods that still enable optimization for some desired output. Broadly, optimization is often performed computationally using either gradients, which indicate the direction of iterative improvement, or surrogate models that act as a stand-in to represent the search space. Both techniques have been applied, for example, in protein design. For instance, directed evolution

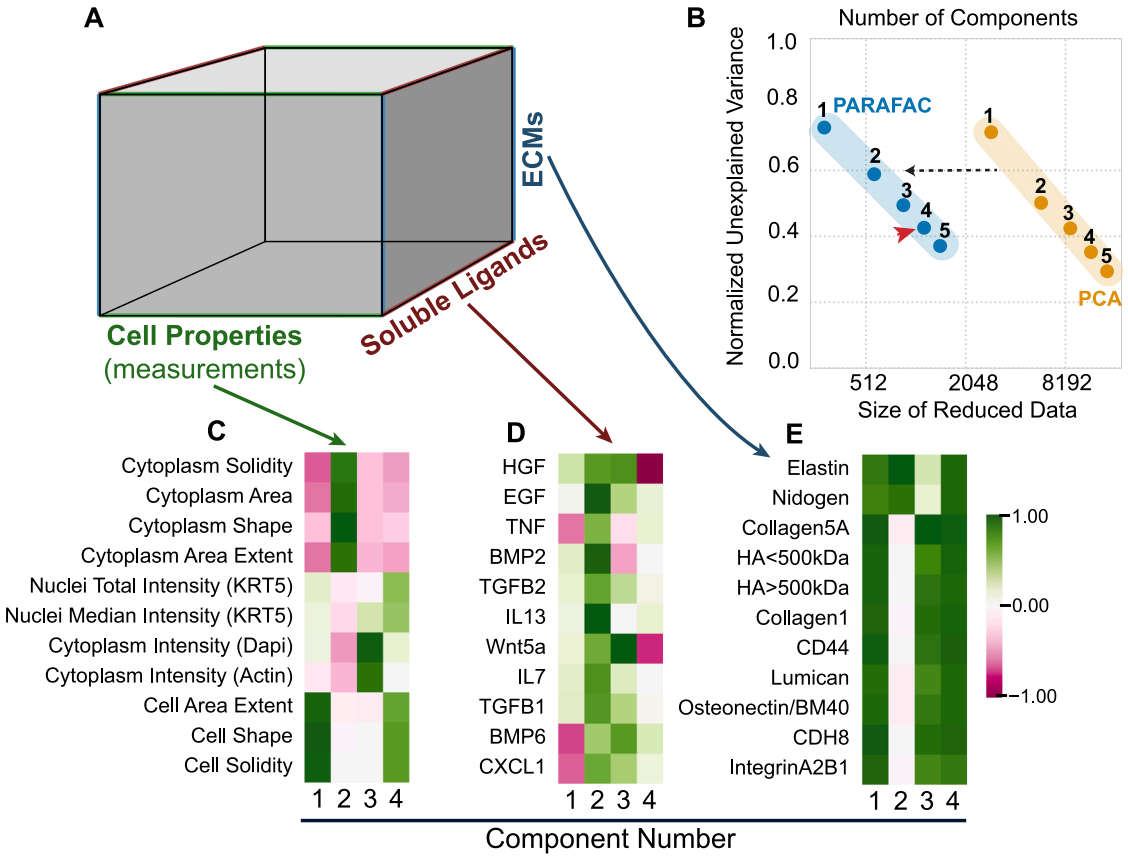

Fig. 4. Illustrative example of multi-modal microenvironment microarray (MEMA) dimensionality reduction. (A) MEMA data in a 3-mode tensor format containing the measured cell properties across various ECM environments and soluble ligands [79]. (B) PARAFAC reduces the MEMA data set by 98% compared to its original size, clearly outperforming PCA across different component numbers. (C–E) Upon decomposition using 4 components (red arrowhead in B), the resulting weights explain the combinatorial effects of the different factors within each mode, namely soluble ligands (D) and ECMs (E) affecting cell properties (C). Note that only a part of the data was shown for simplicity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is essentially a series of local searches within the neighborhood of the existing optimal solution (Fig. 3B) [84]. Surrogate modeling using generative models like Gaussian processes has been widely applied for optimizing protein design when combined with evaluating libraries of variants [85–87]. These techniques might similarly be applied to ECM environments to optimize some desired outcome such as in the design of regenerative tissue scaffolds.

4. Outlook

Though the TME is seemingly vast in the possible combinations of environments and responses, solutions exist for systematically characterizing such problems. Overcoming drug resistance induced by the tumor environment will continue to benefit from tighter integration of experimental solutions to systematically measure environmental responses, and computational solutions to make sense of these measurements. As outlined above, multi-modal dimensionality reduction solutions will be especially critical to this effort as they provide a solution for globally characterizing the space of possible ECM environments. There is good reason to expect that, despite the large number of environmental factors, common patterns exist in the types of responses they elicit, and therefore significant gains are possible through dimensionality reduction. We expect that, as progress is made in characterizing these responses, the ECM environment will one day be considered tractable to profile in a comprehensive way. Comprehensively capturing the influence of the ECM environment will in turn greatly improve our ability to elicit durable treatment responses in cancer.

CRediT authorship contribution statement

Marc Creixell: Writing – original draft, Visualization, Writing – review & editing. **Hyuna Kim:** Writing – original draft, Visualization, Writing – review & editing. **Farnaz Mohammadi:** Visualization, Writing – review & editing. **Shelly R. Peyton:** Writing – original draft, Visualization, Supervision, Writing – review & editing. **Aaron S. Meyer:** Conceptualization, Writing – original draft, Visualization, Supervision, Writing – review & editing.

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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