



# *Annual Review of Cell and Developmental Biology*

## Tissue Biology: In Search of a New Paradigm

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### Keywords

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### Abstract

Animal tissues are made up of multiple cell types that are increasingly well-characterized, yet our understanding of the core principles that govern tissue organization is still incomplete. This is in part because many observable tissue characteristics, such as cellular composition and spatial patterns, are emergent properties, and as such, they cannot be explained through the knowledge of individual cells alone. Here we propose a complex systems theory perspective to address this fundamental gap in our understanding of tissue biology. We introduce the concept of cell categories, which is based on cell relations rather than cell identity. Based on these notions we then discuss common principles of tissue modularity, introducing compositional, structural, and functional tissue modules. Cell diversity and cell relations provide a basis for a new perspective on the underlying principles of tissue organization in health and disease.



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## INTRODUCTION

Tissues are usually defined as collections of cells with shared morphology and function. A canonical view is that there are four main types of animal tissues: epithelial, connective, muscle, and nervous. However, in many contexts it is more natural to think of tissues as organized assemblies of different cell types. With the recent growth in interest in tissue biology, it can be argued that some of the basic notions in that field need to be reframed from the modern perspective to make them internally consistent, generalizable, and informative. In particular, this will help address some of the fundamental gaps in our understanding of biology at the tissue level. These include basic questions about tissue organization: What are the design principles of tissue architecture? Do different tissues represent variations on a common theme, similar to different cell types being variations on the basic design of a eukaryotic cell? Is there some sort of hierarchy of cell types within tissues? If so, what is it based on? Answering these kinds of questions would require developing a new conceptual framework and applying perspectives from other fields with a better understanding of related problems. This, in turn, requires a certain level of abstraction and formalism, freed from field-specific jargon, so that our understanding of tissue biology could be built from first principles.

One perspective that is particularly relevant to tissue biology comes from complex systems theory (Miller & Page 2007, Solé & Goodwin 2000). A complex system is defined as a collection of diverse, interdependent, and interconnected agents that interact with each other according to some rules. A consequence of these interactions is emergent properties of the system (its structure,

function, or dynamic behavior), which are not reducible to the characteristics of individual agents. Tissues have all the features of a complex system: They are composed of diverse, interconnected, and interdependent cell types that interact with each other according to some rules, resulting in emergent properties of tissue structure, function, and composition.

Here we discuss basic aspects of tissue biology from a complex systems perspective. We first review the generation of cell-type diversity during evolution. Diversity has two faces: Intrinsic diversity reflects cell identity, including cell types, subsets, and states. Extrinsic diversity is defined by cells' relations to each other. These relations define cell categories, just as the categories parent or friend are defined by the relations between people regardless of their identities. We then discuss the possible modular units of tissue organization, including compositional, functional, and structural units. Finally, we explore possible rules of cell interactions, leading to self-organization and emergent properties.

## TISSUE ORGANIZATION THROUGH ANIMAL EVOLUTION

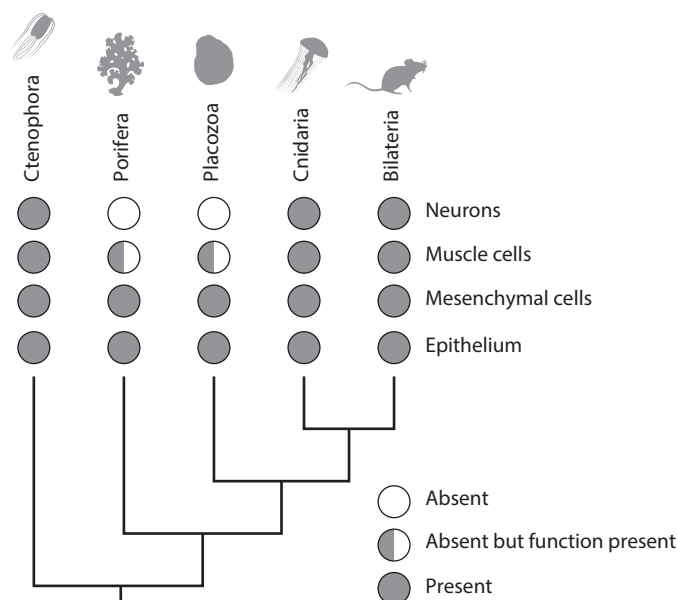
Major events in the evolution of animal tissues and body plans occurred deep in the animal phylogeny. The more recent changes entailed elaborations of the preexisting framework of tissue types, for example, the evolution of a brain by the centralization of the nervous system that originated much earlier in metazoan evolution. Tracing the evolution of foundational animal tissue types, therefore, requires us to infer the tissue composition of the urmetazoan ancestor (the hypothetical most recent common ancestor of all metazoans) and the early events in metazoan evolution.

Metazoa consists of five major lineages: Bilateria, Cnidaria, Ctenophora, Placozoa, and Porifera (Dunn et al. 2014). Bilateria and Cnidaria are sister lineages, but the phylogenetic relationships among the rest of the lineages are not fully resolved. While there is accumulating evidence supporting the Ctenophora-sister model (Li et al. 2021, Whelan et al. 2015) in contrast to the traditional Porifera-sister model, the resolution of the root of the animal tree—which is crucial for inferring urmetazoan traits—remains debated (Telford et al. 2016). Despite this uncertainty, we can still infer the ancestral states of most animal tissues, although with varying degrees of confidence (King & Rokas 2017).

The presence of the epithelial layer in all five major lineages of animals (**Figure 1**) suggests that it is a foundational metazoan tissue that likely existed in the urmetazoan ancestor (Leys & Riesgo 2012). Consistent with the ancient origin of the epithelium, inklings of features associated with epithelial cells are seen even in unicellular relatives of animals. For example, the genes involved in cell-cell adhesion complexes, as well as the main component of the basement membrane, Collagen IV, predate metazoans and are present in unicellular holozoans (Grau-Bové et al. 2017, Miller et al. 2013). Additionally, facultatively multicellular stages in unicellular holozoans such as choanoflagellates form as a single layer of polarized cells similar to an epithelium (Brunet & King 2017), highlighting the role of epithelial cells in defining an organism's boundary, making them the essential tissue type in animals.

Epithelial-mesenchymal units are the elemental building blocks of most animal tissues. Indeed, in addition to the essential epithelial tissue, a mesenchymal cell type is present in all animals: for example, archaeocytes in sponges (Pechenik 2015), fiber cells in placozoans (Smith et al. 2014), and fibroblasts in vertebrates. The timing of the origin of mesenchymal cells was unclear given that the closest living relatives of animals, choanoflagellates, exhibit an epithelial-like polarized cell phenotype. However, Brunet et al. (2021) recently showed that choanoflagellates transition to an amoeboid state in response to stress, suggesting that the mesenchymal phenotype, as well as a mechanism of epithelial-mesenchymal transition (EMT), already existed in the urmetazoan





**Figure 1**

Phylogenetic distribution of major tissues and cell types across Metazoa. Epithelial and mesenchymal cells are present in all animal lineages, suggesting the ancient origin of a minimal epithelial-mesenchymal tissue unit in animals. Silhouettes are from <https://phylopic.org>.

ancestor. The ancient origin of both the epithelial and mesenchymal cells further supports the centrality of the epithelial-mesenchymal unit in animal tissue organization.

Beyond the epithelial-mesenchymal unit, ctenophores, cnidarians, and bilaterians have specialized muscle cells, while Porifera and Placozoa lack specialized muscle cells but some of their cell types are contractile (Pechenik 2015). Thus, although myocytes are not a shared feature of animals, the contractile apparatus is. The inference of the ancestry of myocytes relies on the resolution of the root of the animal tree, but it is parsimonious to reason that the urmetazoan ancestor had a contractile cell type, or at least the contractile machinery.

Inference of the evolution of neuronal tissue also relies on the resolution of the sponge-ctenophore controversy because sponges and placozoans do not have a nervous system. However, cell types expressing neuronal modules, such as the presynaptic and postsynaptic machinery, have been identified in sponges (Musser et al. 2021); and peptidergic neurosecretory cells that likely regulate feeding and locomotion have been identified in placozoans (Pechenik 2015, Smith et al. 2014). Interestingly, ctenophore neurons are distinct from neurons in other animals (Burkhardt 2022, Sebe-Pedros et al. 2018), raising the possibility that the nervous systems of ctenophores and of other animals may have evolved convergently (Moroz 2015). These observations together imply a deep homology (Shubin et al. 2009) of nervous systems in animals. That is, while the urmetazoan ancestor lacked a nervous system, it had functional and regulatory modules that created the preconditions for, and in parallel evolved into, the nervous systems in Ctenophora, Cnidaria, and Bilateria.

In summary, the urmetazoan ancestral body plan was likely bounded by an epithelial layer, perhaps with a mesenchymal amoeboid cell type in the space between the epithelial layers. The epithelial tissue was likely multifunctional and performed contractile as well as sensory and regulatory functions.

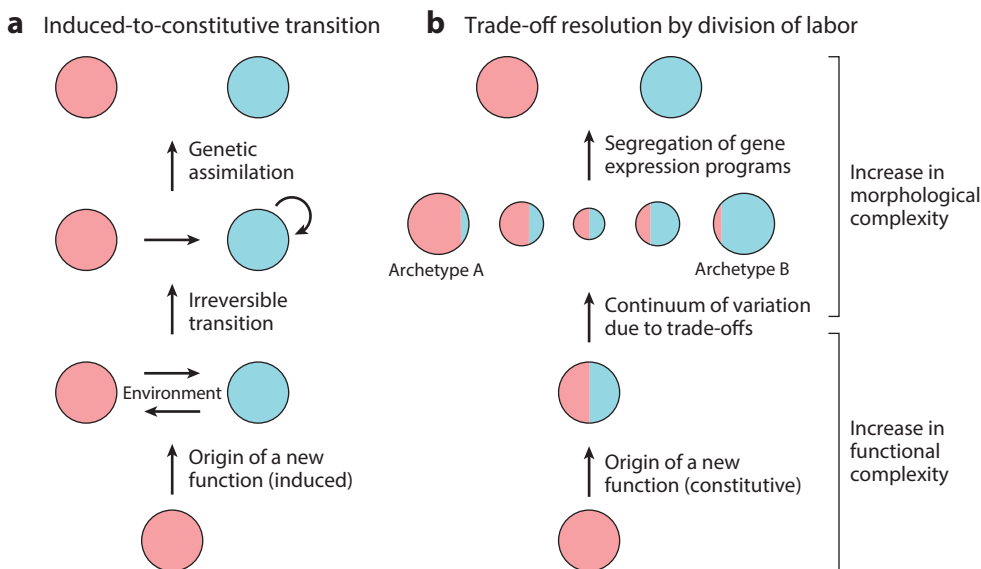
## CELL TYPES AND THEIR EVOLUTION

The inferred tissue composition of the urmetazoan ancestor indicates that the fundamental tissue types and cell type families arose early in animal evolution and subsequently underwent lineage-specific expansion. The progressive expansion of tissue types likely occurred through the diversification of cell types (Arendt et al. 2016) and the evolution of interactions among them.

The cell types in the urmetazoan ancestor were likely multifunctional (Arendt 2008), e.g., epithelial cells possessing contractile machinery, which progressively diversified into functionally specialized cell types. This implies that the increase in morphological complexity over time in metazoan lineages does not necessarily reflect an increase in functional complexity. Making a clear distinction between the two enables us to conceptualize a model of cell type diversification with a two-step process: the addition of a new function to an existing cell type (increase in functional complexity) followed by the segregation of functions into two sister cell types (increase in morphological complexity).

Below we describe a model that outlines two modes by which a cell type can evolve into two sister cell types. The two modes can be summarized as an induced-to-constitutive transition (**Figure 2a**) and trade-off resolution by division of labor (**Figure 2b**), and they are motivated by the temporal-to-spatial transition and division of labor models proposed for the origin of animal multicellularity (Brunet & King 2017).

In the first mode of cell typogenesis, the new function is driven by a gene expression program that is induced by an environmental cue, which can be either a chemical signal or a positional signal based on the cell's anatomical location (Okabe & Medzhitov 2016). At first, this induced state can be a reversible activation or polarization state. Subsequently, the induced gene expression program can evolve to be constitutive. This is akin to genetic assimilation (Waddington 1942, 1953) and can happen mechanistically by bringing the expression of the inducible transcription factor under the control of the lineage-defining transcription factors (Pope & Medzhitov 2018). In other words,



**Figure 2**

Two modes of cell type diversification in evolution. The colors indicate the function performed by the cell type. (a) Induced-to-constitutive transition. (b) Trade-off resolution by division of labor.

cell type diversification takes place via the developmental individuation of the alternative states of the ancestral cell type. This is exemplified by the co-option of an ancestral stress response in the origin of a novel cell type (Love & Wagner 2022), for example, the decidual stromal cells in placental mammals (Erkenbrack et al. 2018) and possibly the metazoan mesenchymal cells (Brunet et al. 2021).

In the second mode of cell typogenesis, the new function is added to the ancestral cell type as a new functional module that is constitutively expressed. Therefore, the two functions of the ancestral cell type are not temporally or spatially delineated but are performed by the same cell. Depending on the nature of the functions, such multifunctionality can result in trade-offs between the two functions such that an individual cell can perform one function effectively only at the expense of the other function. A natural outcome of such a trade-off is that individual cells of the given cell type prefer to perform one function over the other, resulting in a continuum of variation (in function as well as gene expression) among the cells of the given type. The vertices or the extreme positions of the continuous space occupied by the individuals of this cell type in gene expression space represent the so-called archetypes of the given cell type that prioritize one function over the other (Adler et al. 2019, 2023; Hart et al. 2015; Korem et al. 2015). The trade-offs can be resolved over time by exaggerating the continuum of variation, turning off the gene expression program for one function and becoming functionally specialized by selectively retaining the gene expression program for the other function. In this mode, the different archetypes can be viewed as precursors of new specialized cell types. For example, osteoblasts, stem cells, and adipocytes can be viewed as specialist cells evolving from mesenchymal precursor cells that faced a trade-off between extracellular matrix (ECM) secretion, growth factor (GF) production, and triglyceride storage, respectively. The existence of cell type-specific archetypes has been further demonstrated in health (Adler et al. 2019, 2023) and disease (Cook & Wrana 2022, Friedman et al. 2020, Groves et al. 2021, Hausser & Alon 2020, Hausser et al. 2019). Another way of resolving trade-offs is by using a temporal division of labor that is governed by circadian clocks (Partch et al. 2014).

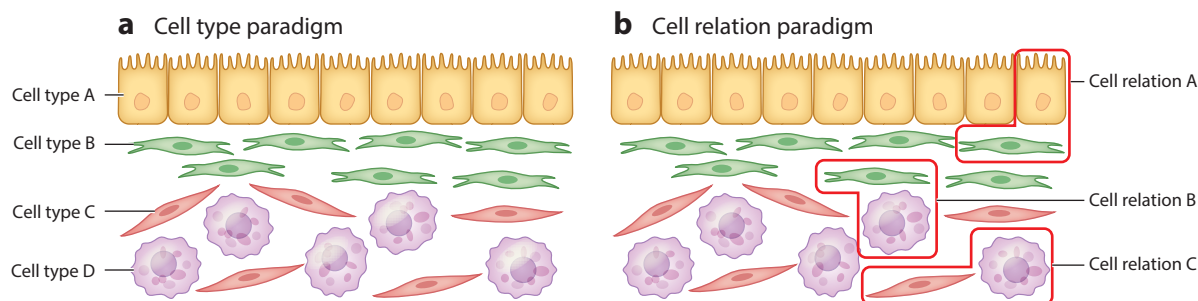
## CELL CATEGORIES BASED ON CELL RELATIONS

The notion of a cell type reflects intrinsic characteristics of cells, including their developmental origin, function, and morphology. To understand cells in their social context, we need a complementary characteristic that reflects the patterns of cells' relations to each other. Relations define cell categories that do not necessarily correspond to their identities (or cell types). The differences in classifications that are based on identity versus relations can be illustrated using a social system as an analogy: Understanding the behavior of a social group using information about individual features (e.g., names, age, sex, and profession) alone is limiting. Knowing how different individuals relate to each other (e.g., parent-child, employer-employee, spousal, and friendship relations) is essential to the understanding of the social structure. These relations define categories of spouses, parents, employees, or friends, and they provide an insight into the organization of a social group that is not available from the knowledge of individual characteristics alone.

Similarly, characterizing cells based on their individual cell type properties is insufficient for understanding their role in tissue organization. To explore cells in their social context, we have to define cell categories where the relevant attribute is not the cell's identity but rather its relations to other cells (**Figure 3**). Below we discuss several examples of common cell relations and their roles in tissue organization.

### Primary-Supportive Relation

Considering the functional organization of tissues, the diversity of cell types can usually be divided into two functional categories: cells performing primary functions of the tissue and cells



**Figure 3**

Tissue organization based on cell types and cell relations, showing a schematic of a tissue where cells are categorized (a) based on their type and (b) based on their relation to other cells.

performing supportive functions that facilitate and optimize the performance of the primary tissue function (Meizlish et al. 2021, Okabe & Medzhitov 2016) (**Figure 4a**). Primary-supportive cell relations appeared early in animal evolution as seen in the primordial epithelial-mesenchymal tissue unit, where epithelial cells perform the primary functions of defense, nutrient acquisition, and maintenance of internal homeostasis, whereas mesenchymal cells provide structural and functional support by the production of the ECM and other secreted factors that support epithelial cells' primary functions.

A primary-supportive relation is also found between neurons and Schwann cells (Gilbert 2010) where the role of Schwann cells is to facilitate the function of neurons. Similarly, pericytes support the function of endothelial cells, and astrocytes provide metabolic and other supportive functions to neurons in the brain.

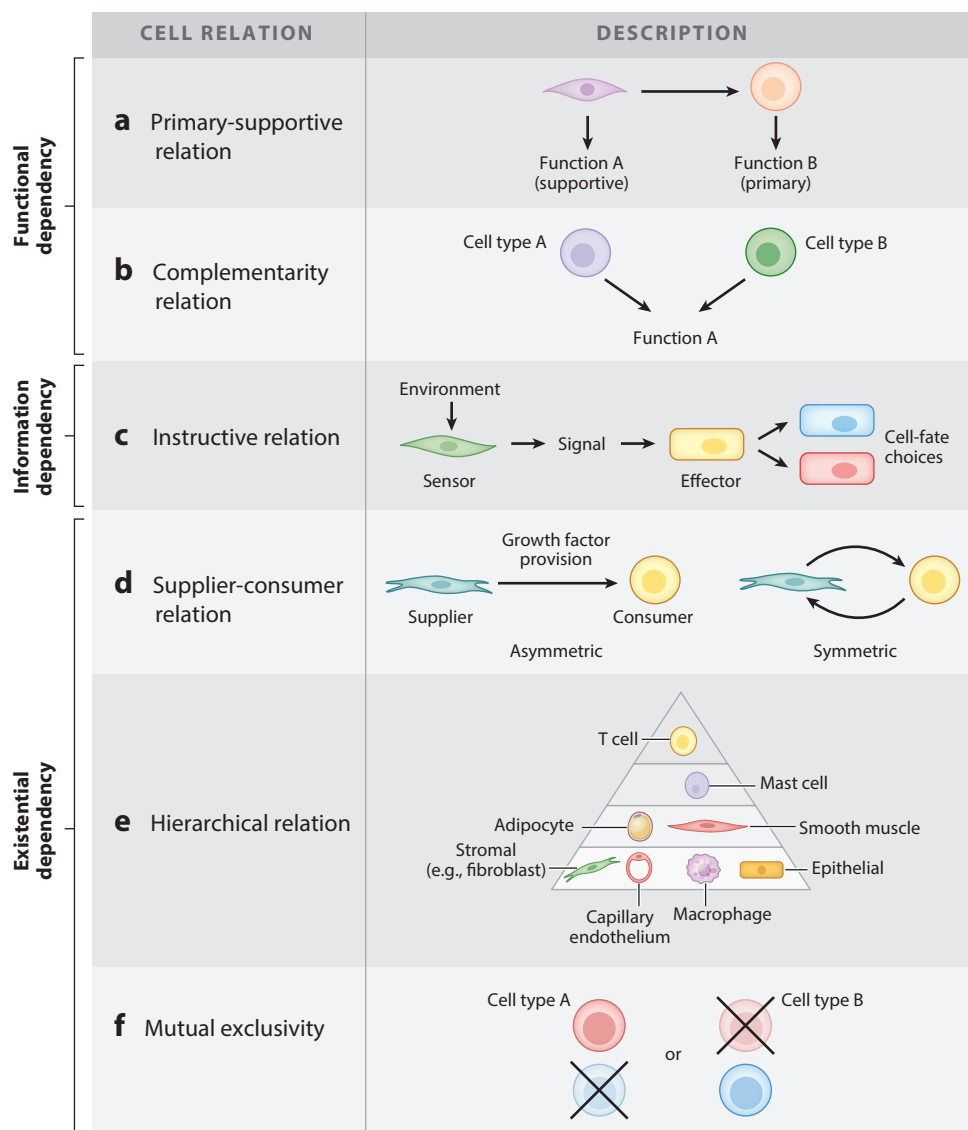
Tissue-specific functions are performed by the primary cell types that vary across different tissues, while supportive cells can be either specialized (as exemplified by glial cells in the brain or pericytes in blood vessels) or universal to most tissues. The latter include fibroblasts, capillary endothelial cells, and tissue-resident macrophages. At least in vertebrates, these cell types perform essential supportive functions, including ECM production, oxygen and nutrient delivery, and maintenance of tissue homeostasis, respectively.

The definition of primary/supportive functions is not absolute but is dependent on the scale at which we are examining the system (Meizlish et al. 2021). For example, the main functions of the intestinal epithelium are digestion and absorption, which are primary functions at the tissue level but supportive at the organismal level, providing nutrients to the organism as a whole. Immune primary defense functions at the immune system level are supportive at the organismal level. Germline cells are the ultimate primary cells that are crucial for reproductive success, whereas somatic cells provide support by allowing germline cells to propagate to the next generation.

## Complementarity Relation

The primary-supportive relation described above is an example of an asymmetric relation: Cell A is supportive for cell B but not vice versa. However, there are situations where the functional division of labor in tissues results in cells equally contributing to a primary function—where they complement each other's function by forming functional units (**Figure 4b**). For example, osteoblasts and osteoclasts have complementary functions in matrix deposition and resorption (Kim et al. 2020), as do fibroblasts and macrophages in general (Meizlish et al. 2021). The columnar and bulbous secretory cells of the rove beetles' tergal gland produce the solvent and benzoquinones, respectively,





**Figure 4**

Summary of cell relations that are universally found across animal tissues. The hierarchical relation in panel *e* illustrates a pyramid of cell hierarchical relations in vertebrates.

that together constitute the defensive compounds secreted by the gland (Brückner et al. 2021). Functional units are also formed by motor neurons and skeletal muscle cells.

### Instructive Relation

The primordial epithelial-mesenchymal tissue unit defines another cell relation that depends on asymmetric information transfer. During embryonic induction, mesenchymal cells produce instructions, such as bone morphogenetic protein (BMP) inhibitors and fibroblast growth factors



(FGFs), that act on Wnt responsive epidermal cells leading to their differentiation into placodes (Fuchs 2007, Hsu et al. 2014). Here, dermal cells contain positional information, while epidermal cells have several fate choices (e.g., to form different skin appendages, depending on their position along body axes). The fate choice of epidermal cells is dictated by signals derived from dermal cells, which in turn are determined by positional information (expression of specific Hox genes in dermal cells) (Chang 2009). This example illustrates the instructive relation: Cell A has information that dictates the fate choices of cell B (**Figure 4c**). Either the information can preexist in cell A (as is the case with positional information) or cell A can acquire the information from its environment. In the latter case, the instructive relation between A and B is equivalent to the familiar sensor-effector relation found in homeostatic circuits: Sensor cells monitor the values of a homeostatic variable and produce signals that instruct effector cells to alter that value in the desired direction (Kotas & Medzhitov 2015). Here, sensor cells have information (about the value of the variable), effector cells have choices to change that value, and the action of effector cells is dictated by the signal produced by sensor cells. Another example of instructive relations is between niche cells and stem cells: Here, niche cells can dictate the fate of stem cells, such as self-renewal versus differentiation. Similarly, dendritic cells detect pathogens and produce cytokines (IL-12, IL-6, etc.) that dictate differentiation of naive T cells into specific effector lineages (Banchereau et al. 2000). In all these cases, there is asymmetric information transfer from one cell to another.

### Supplier-Consumer Relation

The next category of cellular relation we consider is based on existential dependency between cells where cell A depends on cell B for existence in a particular tissue niche. Similar to trophic relationships between organisms in an ecosystem, one cell may rely on resources provided by another cell to survive. These resources can be lineage-restricted GFs, metabolites, and other signals provided by supplier cells that are essential for the survival of cells consuming them. Another type of existential dependency is when one cell type regulates the tissue microenvironment such that it is permissive for the existence of the other cell type, as exemplified in how ECM properties affect cell attachment and survival. In contrast to the sensor-effector relation, which is defined by asymmetry of information, this relation is defined by asymmetry of resources.

Similar to ecosystems, the supplier-consumer relation between cells can be symmetric, resembling trophic mutualism where the two cell types provide GFs for each other, or asymmetric, as in the case of niche cells supplying the physical and nutritional needs of stem cells (**Figure 4d**).

### Hierarchical Relation

Analogous to an ecosystem, tissue organization often shows hierarchy between the different cell types where certain cell types are more crucial than others for the integrity, functionality, and composition of the tissue. For example, although tissue-resident T cells add some functionalities to the tissues they reside in, they are not required for tissue organization. Indeed, elimination of these cells by genetic or other means does not disrupt tissue structure. This is in contrast to fibroblasts, endothelial cells, and macrophages, which are required for normal tissue organization and function (Felix et al. 1994, Hashimoto et al. 2013). We illustrate this in a pyramid of essentiality that is similar to Maslow's hierarchy of human needs in **Figure 4e** (Maslow 1943).

Cell hierarchy is also reflected in the role of a particular cell as a regulator of the tissue composition. This is analogous to keystone species in ecosystems. Keystone species disproportionately affect the ecosystem they are part of. The composition and proportions of species in the ecosystem are highly influenced by the keystones' presence despite the fact that the keystone species may be relatively small in mass or numbers. Similarly, some cell types have a larger impact



on the composition or spatial organization of the tissue than others. These keystone cells do not necessarily correlate with their abundance.

### Mutual Exclusivity

Considering cellular composition across different tissues, we often see that some cell types are mutually exclusive and do not coexist in the same tissue compartment (**Figure 4f**). Mutual exclusivity can occur for several reasons: The presence of one cell type may make the tissue environment not permissive for another cell type, the two cells may compete for the same resources or be functionally incompatible, or the two cells may simply be precluded from existing in the same niche due to the lack of any developmental or physiological scenarios. The importance of mutual exclusivity and its control is illustrated in situations where exclusion is disrupted. Metastasis, endometriosis, and other types of ectopic tissue growth exemplify how the violation of the exclusivity of cells from certain tissues may lead to detrimental pathological states.

## MODULAR ORGANIZATION OF TISSUES: MINIMAL TISSUE UNITS AND HIGHER-ORDER MODULES

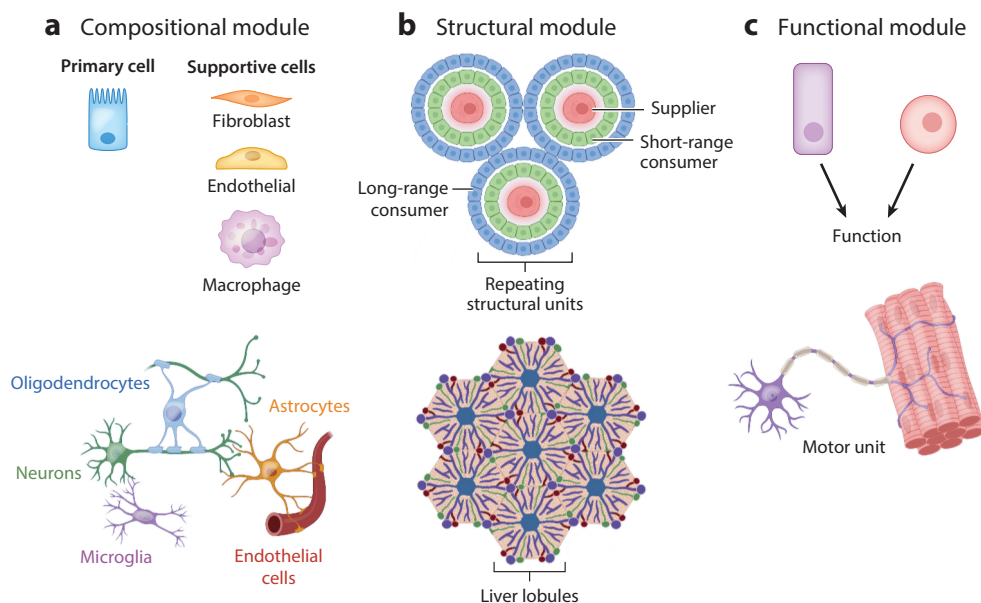
Modularity is a common feature in biological systems (Hartwell et al. 1999, Schlosser & Wagner 2004, Wagner et al. 2007). Modularity describes a complex system of decomposable components, or modules, such that each module consists of elements that interact with each other much more than with elements outside the module. Although modularity is well understood at the cellular and molecular levels, tissue modularity is not well defined. To reveal universal features of tissues, we need to define the modular structure of tissues. Here we consider modularity in tissues from three perspectives: modules for tissue composition, structure, and function.

### Compositional Tissue Modules

The most basic tissue composition originates from the primordial epithelial-mesenchymal tissue unit. The division of cell types in a tissue into epithelial and mesenchymal cells is found in all metazoans, and epithelial-mesenchymal interactions underlie many fundamental developmental processes throughout the animal kingdom (Gilbert 2010, Magie & Martindale 2008, Tyler 2003). All cell types initially derive from the epithelia (of blastula), with mesenchyme and secondary epithelia generated by EMT and mesenchymal-epithelial transition (Acloque et al. 2009, Gilbert 2010, Thiery & Sleeman 2006, Wolpert et al. 2015).

Given its ancient origin and fundamental role in tissue patterning, the epithelial-mesenchymal module can be thought of as a basic unit of tissue organization (Gilbert 2010, Nelson & Bissell 2006, Wolpert et al. 2015). Reciprocal interactions between epithelial and mesenchymal cells are mediated by the members of the FGF, BMP, hedgehog (Hh), Wnt, and Notch families, which control epithelial and mesenchymal differentiation and morphogenesis (Carroll et al. 2005, Gilbert 2010, Hsu et al. 2014, Wolpert et al. 2015). As discussed above, the epithelial-mesenchymal module illustrates both the primary-supportive functional relation and the instructive relation.

In complex metazoans, including vertebrates, the epithelial-mesenchymal unit as a primary-supportive relation is expanded where the mesenchymal cells further diversify into mesodermal cell types with more specialized supportive functions that are nearly universal for vertebrate tissues where they form a minimal unit of tissue organization: These are stromal cells, capillary endothelial cells, and tissue-resident macrophages (**Figure 5a**). Stromal cells are made up primarily of fibroblasts, which are responsible for structural support. Tissue-resident macrophages come in many organ-specific varieties, including microglia (brain), Kupffer cells (liver), osteoclasts



**Figure 5**

Universal modules in tissue organization. (a) Tissue compositional modules are derived from the primordial epithelial-mesenchymal tissue unit based on a primary-supportive relation. (b) Tissue structural modules emerge based on cell relations such as the supplier-consumer relation. (c) Tissue functional modules consist of multiple cell types collectively performing a joint tissue-level function. Figure adapted from images created with BioRender.com; panel a template retrieved from [https://app.biorender.com/profile/alessia\\_neuro/templates/6407435ceb89cce7732d6909](https://app.biorender.com/profile/alessia_neuro/templates/6407435ceb89cce7732d6909).

(bone), and alveolar macrophages (lung) (Ginhoux et al. 2016, Perdiguero & Geissmann 2016). Like macrophages, stromal and microvascular endothelial cells also have tissue-specific characteristics that presumably reflect the diversity of their primary cells (Lemos & Duffield 2018, Potente & Mäkinen 2017).

Most vertebrate tissues contain additional supportive cell types, including tissue-resident lymphocytes (Fan & Rudensky 2016), dendritic cells (Banchereau et al. 2000), and, in some tissues, adipocytes (Zwick et al. 2018) and mast cells (Galli et al. 2011). These represent additional elaborations of cells specialized for particular supportive functions in tissue homeostasis and defense.

In contrast to expansion of the epithelial-mesenchymal unit, there are also examples of contraction of the minimal tissue unit. This is illustrated most dramatically by cartilage, which is essentially made of a single cell type (chondrocyte) surrounded by the ECM it produces (Ross & Pawlina 2011). However, cartilage can be argued to be a special case of tissue composition, just as mammalian erythrocytes lacking a cell nucleus are a special case of a eukaryotic cell structure, in that both are derived features that do not reflect the ancestral design.

### Structural Tissue Modules

In the simplest body plan, the most fundamental structural tissue module consists of two layers of epithelial and mesenchymal cells and the matrix the mesenchymal cells produce. To form this structure, epithelial cells are governed by cell-cell interactions that create an epithelial layer,

and mesenchymal cells are governed by cell-matrix interactions. Most epithelial tissues can be traced back to the primordial epithelial-mesenchymal-matrix design. Other types of tissue show an elaboration of this simple design. For example, neurons follow epithelial patterns where they use cell-cell interactions to regulate their spatial organization. In skeletal muscle, the tendon attaches the muscle to the bone and serves as a matrix resembling a mesenchymal-matrix design. Higher-level spatial arrangements in epithelial tissues, such as tissue polarity and branching morphogenesis (Bryant & Mostov 2008, Newman & Bhat 2009), are patterns that emerge from interactions between epithelial and mesenchymal cells through inductive signals (Briscoe & Small 2015). For example, the epithelial-mesenchymal interaction circuit with short-range positive and long-range negative feedback is an essential feature of Turing's reaction-diffusion model of spontaneous pattern formation (Bailles et al. 2022, Kondo & Miura 2010, Meinhardt & Gierer 2000, Turing 1990).

In vertebrates, minimal structural units in the tissue are formed from multiple copies of higher-level compositional units, spatially organized around blood capillaries. Examples of such structural units include intestinal crypts and villi, liver lobules, brain cortical columns, bone osteons, skin hair follicles, lung alveoli, and renal nephrons. Multiple copies of these units ultimately give rise to tissues and organs with additional features, such as innervation, lymphatic drainage, and mesothelial encapsulation. The design of the structure that is formed is dictated by the supplier-consumer relations in the tissue, particularly by the local availability and diffusion rates of GFs and cytokines (Oyler-Yaniv et al. 2017) (**Figure 5b**).

Although mammalian tissues are an elaboration of the simple epithelial-mesenchymal-matrix design, in some cases the relation to the original design may be obscured by specialized features of morphogenesis. These cases exemplify continuous transformation—a concept from mathematics and topology. In continuous transformation a shape of an object can be modified such that parts of the object may expand/shrink dramatically. As a result, reactive distances between points on the object can change, leading to drastic changes in the overall shape. Similar to this notion, certain tissues do not show recognizable structural modules since they have evolved through the continuous transformation of elementary tissue designs that distorted the original pattern. Such continuous transformation can be seen in the structure of the brain and endoderm-derived organs.

An important feature in defining structural modules is the formation of boundaries that delineate the division between different modules at the organ and tissue levels. The formation of boundaries in the tissue is a self-organized process that eventually leads to compartmentalization in the tissue (Dahmann & Basler 1999, Dahmann et al. 2011, Glen et al. 2019).

## Functional Tissue Modules

Functional units are defined by several cell types that divide labor to collectively perform a joint function. This division of labor can be found on a continuous spectrum from a complementarity to a primary-supportive relation. Examples of functional units based on complementarity relations include motor neuron and skeletal muscle, pericytes and endothelial cells, and osteoclast and osteoblast cells (**Figure 5c**).

Certain functional units can be repeated across different tissues where the identity of the cell types within these functional modules may vary. For example, ECM composition is usually regulated primarily by fibroblasts and macrophages, but in the brain, the ECM is also produced by astrocytes (Wiese et al. 2012).

At the tissue level, the basic functional units are combined into higher-order units, such as lung alveoli, intestinal villi, and kidney nephrons. The higher-order functional units are present in multiple copies and are often organized around microvessels.

## SELF-ORGANIZATION, EMERGENCE, AND SIMPLE RULES

Many tissue characteristics we discussed above, including spatial patterns, composition, and function, are emergent properties, and as such they cannot be explained based on detailed knowledge of individual cells, genes, or signaling pathways involved in tissue organization. Emergent properties are products of systems with a large enough number of diverse components (or agents) that can interact with each other according to some prespecified rules. Therefore, in order to understand a complex system, one needs to define the rules of interactions between its components that produce emergent properties (**Figure 6a**).

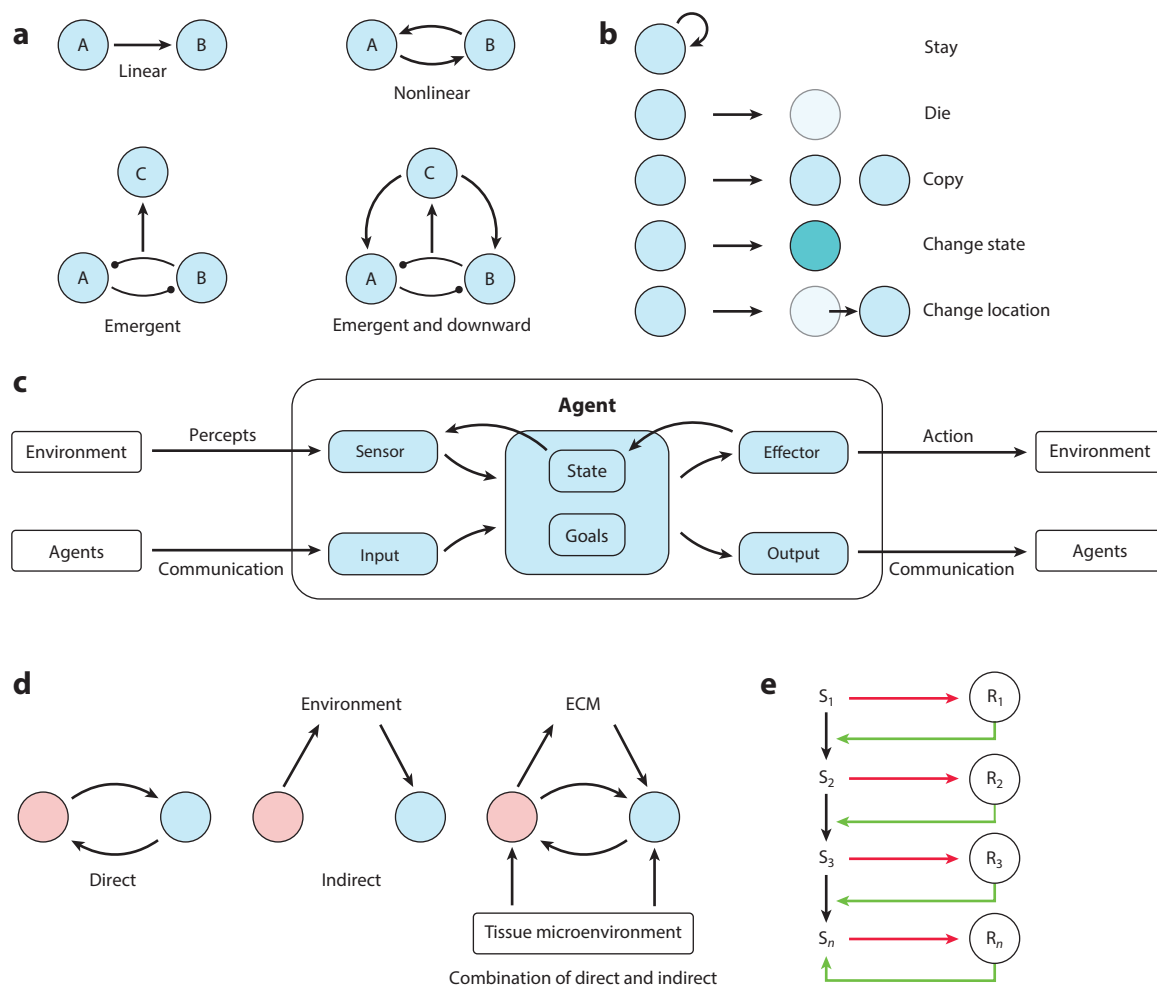
Emergent properties and self-organization are best demonstrated by social insects (Camazine et al. 2001, Solé & Goodwin 2000): Termites can build sophisticated structures, yet individual insects are completely unaware of the final product they collectively generate. There is no centralized control and no blueprint for the individual termites to follow. Instead, each insect operates based on locally available information to execute a few available behavioral programs (Camazine et al. 2001, Solé & Goodwin 2000). The sources of local information can be either pheromones produced by fellow termites or environmental factors, like temperature, humidity, or light. Importantly, the information about the final product does not exist prior to building the nest (unlike information about engineered structures that preexists in the form of blueprints). Instead, this information is generated in the process of building the nest. This type of generative information created in the process of nest construction is also used in animal development to construct tissues and organs (Wolpert et al. 2015).

The example of social insects highlights the general principles of self-organization and emergence based on decentralized control: (a) Individual agents respond to locally available information; (b) this information is encoded in signals that come from other agents either directly or indirectly through the modification of the microenvironment; (c) and agents respond to these signals according to some predefined rules (Camazine et al. 2001). Importantly, even a small number of simple rules is sufficient to generate complex patterns and behaviors—the emergent properties of the system (Camazine et al. 2001). This latter aspect of complex systems is nonintuitive but highly pervasive in nature. As argued before, principles of self-organization explain otherwise mysterious biological phenomena from microtubule assembly to embryonic development (Kirschner et al. 2000).

In the case of tissues, the agents are individual cells that interact with each other and react to their environment according to a set of predefined, cell type–specific rules. The predefined rules that guide cell interactions are based on the cell's goals. For example, homeostasis as a goal leads to feedback interactions that maintain a tissue variable at a fixed level. Based on the interaction rules, the cellular internal state, and its external environmental condition, the cell can take one of several possible actions: It can stay in the same cellular state, die, multiply, or change its state or location (**Figure 6b,c**). To understand self-organization and emergent properties of tissues, it is necessary to define the rules of cell–cell and cell–environment interactions leading to these cellular actions and their biological rationale. Defining the rationale is important because the rules used in biological systems are selected by evolution to achieve particular end results, such as assembling cells into functional tissues and maintaining homeostasis in the face of perturbations.

The rules of cell interactions presumably belong to several programs, with each program being a collection of compatible rules. Some programs are used in core developmental processes, such as tissue polarization, spatial patterning, lumen formation, branching morphogenesis, and compartment boundary formation, where a few families of signals (BMP, FGF, Hh, Wnt, Eph, and Notch) play a prominent role (Carroll et al. 2005, Dahmann & Basler 1999, Gilmour et al. 2017, Newman & Bhat 2009). In addition, it is increasingly appreciated that mechanical forces





**Figure 6**

**Emergence and self-organization.** (a) Patterns of causality: Unlike the simple case of linear causality (A causes B), emergent properties (C) are not caused by A or B but are the consequence of interactions between agents (A and B). If C can further modify A and B, or change their interaction rules, the result is downward causality. (b) Elementary cellular actions: Everything cells can do is a variation on these actions. (c) Cells as agents respond to environmental changes and react based on their internal state and predefined rules based on their goals. Cells have two inputs, environment (percepts) and signals from other cells (communication), and can produce two outputs, acting on the environment and communicating to other cells. Panel c adapted from Wooldridge (2002). (d) Self-organization is a combination of direct and indirect interactions of agents. (e) Stigmergy is a self-organizing process whereby individual agents (e.g., cells) sense and respond to the consequences of their actions on the environment. Here, cells sense an environmental signal ( $S_1$ ). Their response ( $R_1$ ) to  $S_1$  modifies  $S_1$  to another signal ( $S_2$ ), which in turn elicits a response  $R_2$  (from the same or different cell type) to modify  $S_2$  into  $S_3$ , and so on, until the process reaches the final stage, which either does not produce any further signals or produces a signal  $S_n$  that promotes its own maintenance, thus entering a homeostatic mode. In some versions of this process, signal  $S_{k-1}$  may inhibit response  $R_k$  until  $S_{k-1}$  is eliminated by  $R_{k-1}$ . This ensures that the next step in assembly does not start until the previous step is completed. Abbreviation: ECM, extracellular matrix.

play a critical role in tissue development and patterning (Gilmour et al. 2017, Heller & Fuchs 2015). Once the basic tissue framework is established by developmental programs, cells switch to programs that govern tissue composition and homeostasis. The developmental programs can become reactivated during tissue repair and tumorigenesis (Duffield et al. 2013, Krafts 2010), which



presumably are accompanied by transiently switching off the homeostatic programs, as they may be incompatible with tissue repair. Finally, at least for some tissues, there appear to be alternative programs that govern tissue's cellular and ECM composition. Switching from a default program to the alternative program underlies the phenomenon of tissue remodeling—a stable change in tissue composition. For example, periodic tissue remodeling occurs in the female reproductive organs, and inducible tissue remodeling is commonly orchestrated by inflammatory signals.

## RULES OF CELL COMMUNICATION

### Functional Demand and the Control of GF Production

The cellular composition of tissues is determined by the local availability of lineage-specific GFs (Raff 1992), which are required for the survival, proliferation, and differentiation of specific cell lineages, for example, including M-CSF for macrophages, PDGF for fibroblasts, VEGF for endothelial cells, and IL-7 for lymphocytes. Despite the vast amount of empirical data, the logic of control of GF production is largely unknown: How do individual cells within tissues decide which GF to produce, and how much, at any given time to ensure the correct cellular composition and spatial arrangement of cells within tissues? One way this can be achieved is through cell interaction circuits designed to maintain a stable ratio of cell types involved in GF exchange (Adler et al. 2018, Zhou et al. 2018). Cell interaction circuits can explain how GF production can be regulated, but not which GFs are produced. The latter question can be addressed from a perspective of functional demand.

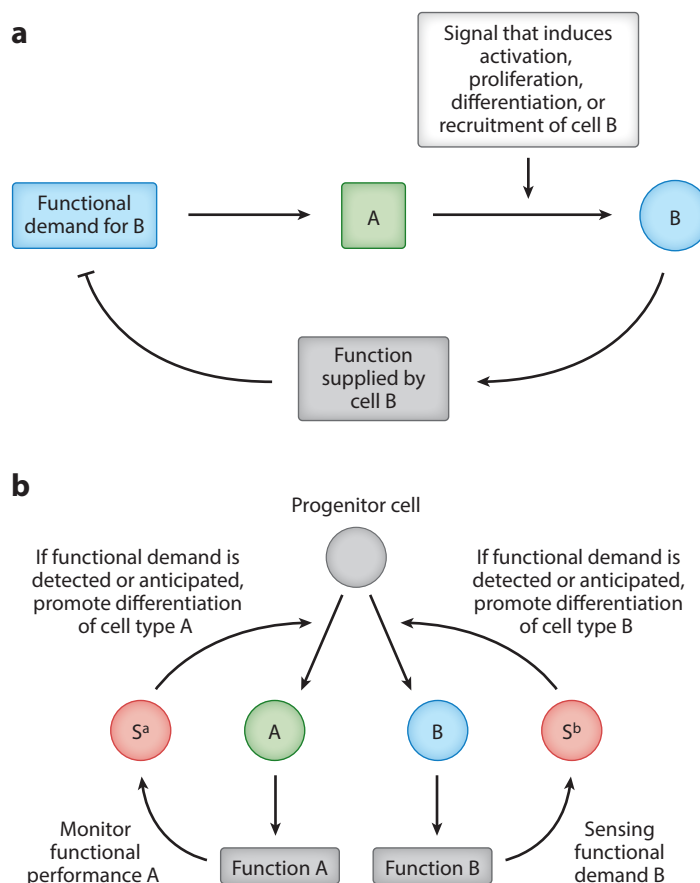
Let us first consider familiar examples to illustrate the general principle. Local tissue hypoxia indicates a demand for oxygen, which is supplied by the blood endothelial cells. Sensing of the hypoxia by the transcription factor HIF-1 $\alpha$  leads to the expression of VEGF, which in turn promotes angiogenesis (Pugh & Ratcliffe 2003). This example suggests a general principle of regulation of lineage-specific GF production: If cell type A is a supplier of a signal S ( $S^a$ ) that controls the proliferation, survival, activation, differentiation, or recruitment of cell type B, then  $S^a$  production by cell A is controlled by sensing demand for the function performed by cell B (**Figure 7a**). In this way, the number or activity of cell B in a given tissue compartment is automatically adjusted to the demand for the function(s) they perform.

A variation on this theme is that signal  $S^a$  controls the differentiation of cell B from its progenitor (**Figure 7b**). This, again, allows for an automatic adjustment of necessary cell type numbers to the functions they need to perform. Examples of this scenario are seen in emergency hematopoiesis, where inflammatory cytokines produced in response to infection affect hematopoietic lineage choices towards myeloid cells at the expense of lymphoid cells (Takizawa et al. 2012). In another example, erythropoietin (EPO), produced by the peritubular fibroblasts in the kidney in response to hypoxia, leads to increased production of red blood cells (RBCs) to meet the systemic demand for oxygen (Liang & Ghaffari 2016). Similarly, IL-13, produced by innate lymphoid 2 cells, promotes the differentiation of mucus-producing goblet cells to meet the demand for increased mucosal barrier function (Vivier et al. 2018). Conversely, reduction in functional demand may lead to tissue atrophy, as seen in the case of skeletal muscle atrophy caused by immobility, or intestinal atrophy in migratory birds and bulk eaters like pythons that go for extended periods of time between meals.

There are several implications from the functional demand perspective: First, there should be a finite set of functional demands, some universal (e.g., oxygen delivery), others tissue-specific (e.g., sensing the absorptive function of enterocytes). Second, for each functional demand there must be a corresponding sensing mechanism. Third, there should be dedicated signals corresponding to each functional demand (such as EPO corresponding to demand in RBCs, and M-CSF





**Figure 7**

Sensing and responding to functional demand. (a) Cell A senses some quantitative measure of the functional performance of cell B and, upon detection of functional demand for B, produces signals that promote the proliferation, recruitment, or activation of cell B. (b) Cell types A and B are derived from a common progenitor and specialize on functions A and B. Cells S<sup>a</sup> and S<sup>b</sup> monitor the functional performance of cell types A and B, respectively. When they detect (or anticipate) functional demands for A or B, they produce signals that promote differentiation towards the A or B lineage, respectively.

corresponding to demand in macrophages). When more than one signal corresponds to a given functional demand, their production is likely to be coregulated.

So far, we have discussed cell interactions with each other and with their microenvironment. We now turn to the ECM, which is another important source of local signals for tissue organization.

### Extracellular Matrix and Stigmergy: Building and Interpreting the Cellular Environment

The ECM is an essential feature of metazoan tissue design (Hynes & Naba 2012, Karamanos et al. 2021). It is an organized assembly of hundreds of different components, including fibrillar proteins (collagens and elastin), glycoproteins (e.g., fibronectin and laminin), proteoglycans, and

hyaluronic acid (Hynes & Naba 2012, Karamanos et al. 2021). The ECM has many critical roles in tissue organization and function: It confers mechanical properties, such as tensile strength, elasticity, and lubrication; it serves as a scaffold for tissue development and spatial organization; it functions as a communication medium, as most GFs and chemokines are deposited on the ECM; it provides ligands for integrins and other adhesion receptors, forming a substratum for cell attachment and movement; and, finally, it is a source of diffusible signals (matricryptins) that are released by limited proteolysis mediated by matrix metalloproteinases (MMPs) (Bonnans et al. 2014, Geiger & Yamada 2011, Hynes & Naba 2012, Nelson & Bissell 2006, Ricard-Blum 2011, Sarrazin et al. 2011, Yurchenco 2011). A special type of ECM, the basement membrane, separates epithelial and mesenchymal cell types and functions as a critical scaffold for the attachment, signaling, and morphogenesis of epithelia (Nelson & Bissell 2006, Yurchenco 2011). The staggering complexity of ECM composition, assembly, and dynamics has been a major obstacle for understanding ECM biology.

The ECM has an important role in mediating indirect interactions between cells in the tissue context (**Figure 6d**). This type of communication through the environment produces a distinct form of self-organization known as stigmergy, which was originally proposed to explain collective behaviors of social insects in nest construction (Grasse 1960). As termites construct their nest, the actions of individual termites generate signals (intermediate steps in nest construction) that are sensed by other termites and elicit their own actions in nest construction, which, in turn, generate new signals promoting new sets of actions. Each termite executes specific actions based on a few hardwired rules in response to local information that is being generated in the process of nest building. For instance, if there is a hole in the wall of the mound, termites interpret the edges of the hole as a signal to add building material until the hole is filled in, at which point there will no longer be a signal to fill in the hole. The same principle of stigmergy is applicable to the construction and interpretation of the ECM.

The complex architecture of the ECM is a product of the stepwise maturation, deposition, assembly, and breakdown of ECM components. Analogous to the termite example, cells may detect the signals generated by the intermediate states of ECM construction and respond to further modify the intermediate states until the final, fully assembled state is reached. At that point, the signals to deposit or modify the ECM would be eliminated and the system will reach a steady state, or homeostasis (**Figure 6e**). Upon damage to the ECM, the intermediate signals are revealed again, triggering the same set of recursive actions that will repair the damage.

The following example illustrates the application of stigmergy to ECM assembly. The formation of a fibronectin matrix starts with fibronectin binding to its receptor,  $\alpha 5 \beta 1$  integrin (Clark 1990) (signal 1), which reveals a cryptic self-assembly site in fibronectin (signal 2), allowing for polymerization (generating signal 3) (Kadler et al. 2008, Zhong et al. 1998). The presence of fibronectin polymer (signal 3) promotes the deposition of collagen fibrils. Finally, collagen association with fibronectin shields it from cellular traction forces and presumably also masks signal 3 to prevent further collagen deposition (Kadler et al. 2008).

The principle of stigmergy may also explain ECM degradation: Proteolysis of Collagen I starts with removal of its C-terminal telopeptide, which reveals the cleavage sites (signal 1) for MMP1, as well as integrin binding sites (signal 2) within the collagen fibrils (Perumal et al. 2008). Cleavage of collagen fibrils by collagenases like MMP1 generates signal 3 (denatured collagen), which is now recognized by gelatinases like MMP2 and MMP9, which complete the collagen digestion (Bonnans et al. 2014). Macrophages are important sources of gelatinases, and denatured collagen (signal 3) acts as a chemoattractant for macrophages, indicating that macrophages sense and respond to the intermediate products of collagen digestion (O'Brien et al. 2010).



In these examples of ECM dynamics, we can see how cells respond recursively to the signals generated and eliminated in the process of ECM assembly and degradation. Different cell types within tissues can execute different sets of rules, which further couples ECM structure and cellular composition, without the need for centralized control or a genetic blueprint that specifies all the details of ECM structure.

### WHAT CAN GO WRONG AND WHY?

Tissue-level diseases are a set of diseases where the intricate balance in the tissue ecosystem breaks such as in neoplastic, degenerative, and fibrotic diseases. Understanding tissues from a cell relation perspective may shed light on the vulnerability of the design features leading to these pathological states. For example, the cell relation between macrophages and fibroblasts that is mediated by GF exchange was recently proposed to explain the tissue vulnerability in response to persistent injury that leads to fibrosis (Adler et al. 2020, Miyara et al. 2023, Wang et al. 2023). Other types of paracrine cell interactions may lead to degenerative or neoplastic diseases depending on the cell communication rules they follow.

An important feature of cell categorization into primary and supportive cells is that the supportive cells are programmed to facilitate the survival, differentiation, and functionality of primary cells. One negative consequence of this blind devotion of supportive cells to their primary cells plays out in scenarios where primary cells turn into cancer cells. In tumor settings, the supportive cells still follow the functions they are programmed to perform, thereby contributing to tumor growth. This is true for endothelial cells (Folkman 2002), stromal cells (Denton et al. 2018, LeBleu & Kalluri 2018), and macrophages (Mantovani et al. 2017, Wynn et al. 2013)—the main supportive cell types that promote tumor development by just doing their job. Additionally, one of the supportive functions of macrophages and stromal cells may involve the protection of primary cells from autoimmune attack, which may explain their contribution to immunosuppression in the context of antitumor immune responses (Denton et al. 2018, Veglia et al. 2018).

### CONCLUSIONS AND PERSPECTIVES

Recent advances in single-cell genomics, ex vivo organoids, and imaging are providing critical data and insights into tissue biology. As organoid technology continues to mature, we should be well-positioned to address fundamental questions about tissue self-organization (Paşca et al. 2022, Serra et al. 2019, Tuveson & Clevers 2019). The current limitation of organoids, however, is the lack of experimental control over ECM composition and the fact that the requisite GFs are supplied to the system externally, rather than being produced by the cells according to their own logic. As this hurdle is being overcome, it should allow for systematic exploration of the rules of GF production and other forms of cell communication that produce emergent properties of tissue architecture. Our goal here is to suggest some of the new perspectives that can help in developing a conceptual framework for tissue biology. The principles uncovered in complex systems theory are particularly relevant and essential for proper understanding of tissue organization as a product of the execution of simple rules of cell interactions. We argue that defining the full catalog of these rules will result in a modern paradigm of tissue biology and will help us understand, and ultimately treat, associated diseases.

### DISCLOSURE STATEMENT

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