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# Tissue Biology: In Search of a New Paradigm

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## Keywords

cell type, tissue organization, tissue modules, cell relations, cell categories, evolution, self-organization

## 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 and 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

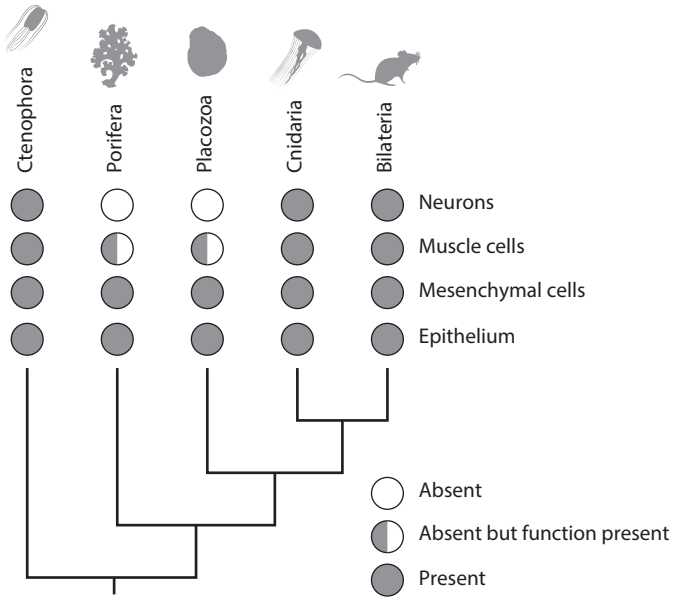


**Figure 1**

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.

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