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Review article

Mechanisms of physiological tissue remodeling in animals: Manipulating tissue, organ, and organism morphology

Kaylinnette Pinet, Kelly A. McLaughlin *

Allen Discovery Center, Department of Biology, Tufts University, 200 Boston Ave., Suite 4700, Medford, MA, 02155, United States

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ABSTRACT

Tissue remodeling is broadly defined as the reorganization or restoration of existing tissues. Tissue remodeling processes are responsible for directing the development and maintenance of tissues, organs, and overall morphology of an organism. Therefore, studying the regulatory and mechanistic aspects of tissue remodeling allows one to decipher how tissue structure and function is manipulated in animals. As such, research focused on investigating natural tissue reorganization in animal model organisms has great potential for advancing medical therapies, in conjunction with tissue engineering and regenerative medicine. Here we discuss the molecular and cellular mechanisms responsible for tissue remodeling events that occur across several animal phyla. Notably, this review emphasizes the molecular and cellular mechanisms involved in embryonic and postnatal physiological tissue remodeling events, ranging from metamorphosis to bone remodeling during functional adaptation.

1. Introduction

Tissue remodeling is broadly defined as the structural reorganization or renewal of living tissue. Tissue remodeling events can be subdivided into two categories: physiological and pathological tissue remodeling. Physiological tissue remodeling is a normal, endogenous process, whereas pathological tissue remodeling is an abnormal process occurring post-injury or disease. Pathological remodeling has been extensively described elsewhere (Chen et al., 2017; DeLeon-Pennell et al., 2017; Hendrix and Kheradmand, 2017; Liu and Khalil, 2017; Lu et al., 2011; Parrish, 2017; Zhou et al., 2018), thus this review focuses on physiological tissue remodeling. There are several biological processes across animal species that fall within the ambit of physiological tissue remodeling (e.g., dauer formation in *C. elegans*, metamorphosis in *X. laevis*, and mammary tissue remodeling in humans). These remodeling events have rarely, if ever, been juxtaposed. This review endeavors to compare and contrast the molecular and cellular mechanisms responsible for these and other tissue remodeling events in animals; highlighting the aspects of tissue remodeling that are conserved across diverse animal phyla. This approach provides us with the opportunity to understand the significant influence that tissue remodeling processes have over tissue, organ, and organismal morphology and function within the animalia kingdom. To that end, below we address two thematic questions: 1) What molecular and cellular processes are fundamental for tissue remodeling? and 2) What regulatory mechanisms control physiological tissue remodeling in embryonic, juvenile, and adult animals?

The first thematic question cannot be discussed without acknowledging that the remodeling of tissues depends on the breakdown and reformation of the extracellular matrix (ECM). Alterations to the ECM can prompt a range of cell behaviors such as cell growth, proliferation, movement, migration, differentiation, or apoptosis (Chen and Khalil, 2017; Gilmore, 2005; Hynes, 2009; Ishizuya-Oka et al., 2000; Lorda-Diez et al., 2015; Meredith et al., 1993; Stoker et al., 1968). Due to their ability to break down the ECM, proteinases (e.g., matrix metalloproteinases [MMPs]) are principally responsible for carrying out the reorganization of the ECM during tissue remodeling. Many previous studies have focused on characterizing proteins that regulate ECM function and maintenance (Bonnans et al., 2014; Hynes and Naba, 2012; Keeley and Mecham, 2013; Wada, 2013). Ultimately changes in the ECM, combined with subsequent cellular responses, work in concert to drive morphological changes and define tissue function. However, it is important to note that the relationship between the ECM and cells is not unidirectional; fibroblasts can influence the organization of the ECM because they are the main depositors of ECM components and proteinases into the extracellular space (Stopak and Harris, 1982). Thus, in a remodeling environment, there is always an inherent feedback loop between cells

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* Corresponding author. Biology Department, Center for Regenerative and Developmental Biology, Allen Discovery Center at Tufts University, Tufts University 200 Boston Avenue, Suite 4700, Medford, MA, 02155-4243, United States.
E-mail address: kelly.mclaughlin@tufts.edu (K.A. McLaughlin).

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and the ECM (Fata et al., 2004; Paiva and Granjeiro, 2017; Praxenthaler et al., 2018; Song and Dityatev, 2018; Wang and Khalil, 2018; Zhou et al., 2018).

Answering the second thematic question requires one to recognize that tissue remodeling processes are critical to an animal's health and survival, at all stages of life. Evolutionarily pre-programed tissue remodeling events can occur either at specific points during an animal's life cycle (e.g., interdigit regression in embryos, metamorphosis, or non-metamorphic maturation) or continuously throughout their lifespan (e.g., cartilage or adipose remodeling) (Choe et al., 2016; Denver, 2008; Holzer and Laudet, 2013; Lorda-Diez et al., 2015; McMenamin et al., 2014; Paiva and Granjeiro, 2014; Schwedes and Carney, 2012). The biochemical pathways responsible for the initiation and regulation of tissue remodeling events within and across animal species are certainly variable, but there are several conserved regulatory mechanisms. For example, the changes in morphology seen during metamorphic and non-metamorphic transitions from juvenile to adult life stages in insects, amphibians, and fish (Fig. 1) are often initiated by hormonal endocrine signaling (e.g., ecdysone and thyroid hormone signaling) and subsequent downstream effects on transcription (Holzer and Laudet, 2013; Ishizuya-oka et al., 1998; Laudet, 2011; Schreiber, 2013). More discrete changes in morphology, such as adipose tissue or mammary gland remodeling in humans, can be triggered by a variety of stimuli including endocrine, paracrine, or autocrine signaling mechanisms (Paiva and Granjeiro, 2014, 2017).

Understanding the underlying processes that mediate and control physiological tissue remodeling in diverse animal model systems will provide valuable insight into the development and maintenance of tissue function and morphology. In addition, evaluating the evolution of tissue remodeling mechanisms across diverse taxa will offer a more profound interpretation of these complex phenomena. Furthermore, such knowledge could inspire novel strategies for the medical treatment of malformed or deformed tissues.

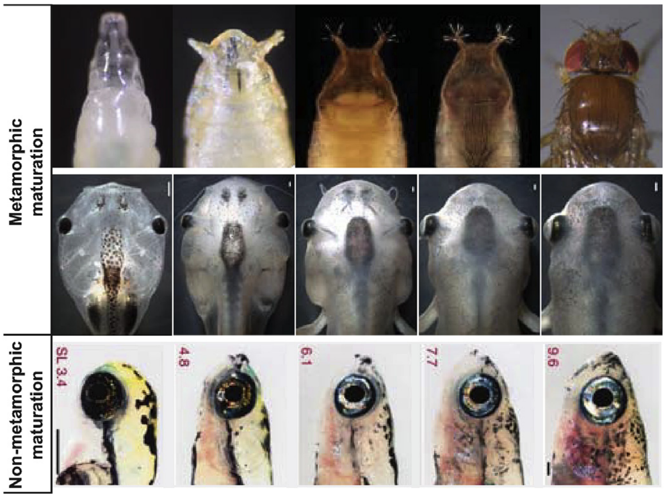

Fig. 1. Tissue remodeling alters head morphology during metamorphic and non-metamorphic maturation. *D. melanogaster* and *X. laevis* larvae undergo complete metamorphosis to transform into adults. During metamorphosis in *D. melanogaster,* tissue breakdown, growth, and remodeling transform the rudimentary larva into an adult with highly sophisticated sensory features (e.g. compound eyes, antennae, and mouth). During metamorphosis in *X. laevis,* remodeling of cartilage, bone, muscle, and nerve tissue within the craniofacial region also causes morphological changes. These morphological changes include the repositioning of their eyes from a completely lateral position to a more dorsal and forward-facing position, degradation of their gills, alterations to their epithelial tissue composition, structural changes to the brain, and reformation of their jaw. *D. rerio* do not undergo complete metamorphosis, however craniofacial morphology is altered during maturation as a result of growth and tissue remodeling. Scale bars for *X. laevis* and *D. rerio* images = 500 μM and 250 μM, respectively. *D. melanogaster* images were provided by Sci-inspi and Dr. Phillip Freda. *D. rerio* images modified from *Parichy* et al. (Parichy et al., 2009).

2. What molecular and cellular processes are fundamental for tissue remodeling?

Tissue remodeling cannot be fully understood by simply focusing on the behavior of cells within a tissue; the extracellular space also plays a pivotal role. The extracellular space is a complex environment composed of both the extracellular fluid and an intricate network of macromolecules referred to as the extracellular matrix (ECM) (Fig. 2). Changes in tissue morphology often result from alterations to the composition and architecture of the ECM, which in turn releases bioactive components into the extracellular fluid that affect cell behavior (Paiva and Granjeiro, 2017; Smith et al., 2012). The extracellular space is particularly important for connective tissues, like cartilage and bone, because they are comprised primarily of ECM and relatively few cells. Consequently, in order to control tissue remodeling - the extracellular space and the characteristics of the ECM - must be tightly regulated.

2.1. Characteristics of the extracellular matrix (ECM) impact tissue morphology and function

The ECM is one of the most important regulators of cellular and tissue function in an organism. It is comprised of a massive network of proteins, polysaccharides, and proteoglycans that have been produced by cells and it plays a pivotal role in tissue homeostasis, development, regeneration, and wound healing (Hynes and Naba, 2012; Keeley and Mecham, 2013). The major protein components of the ECM in animals are collagens, elastins, laminins, and fibronectins (Keeley and Mecham, 2013). These proteins provide strength, elasticity, and organization to the ECM in animal tissues. Depending on the animal, the main polysaccharide components include glycosaminoglycan (GAG) chains or poly-N-acetylglucosamine (chitin) chains (Ayerst et al., 2017). There is also a large percentage of proteoglycans within the ECM (Keeley and

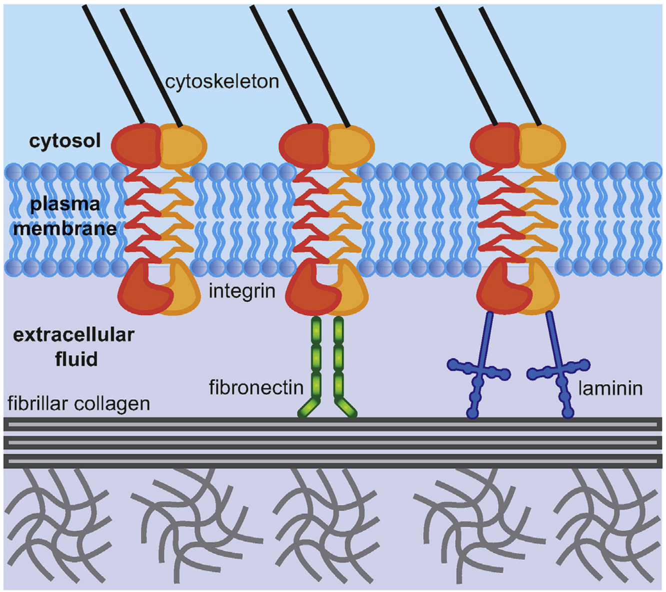

Fig. 2. Basic composition of the animal extracellular matrix (ECM). The ECM contains proteins, glycoproteins, polysaccharides, and proteoglycans. The polysaccharides and proteoglycans form hydrated gels which are the structural basis of the ECM. Collagens are the main protein component of the animal ECM; they form fibers capable of organizing the ECM. Fibronectin and laminin are glycoproteins that bind to collagen and the transmembrane integrin proteins. Integrins are anchored to cytoskeletal proteins, providing a direct link between the ECM and the cytoskeleton.

Mecham, 2013). Proteoglycans are macromolecules consisting of glycosaminoglycans with a covalently linked core protein feature; hyaluronic acid is the only GAG that does not typically form covalent bonds with proteins (Bohaumilitzky et al., 2017; Hynes and Naba, 2012). Together, GAGs and proteoglycans form hydrated gel-like structures in which other ECM protein components then become embedded (see Fig. 2). The exact composition of the ECM determines how much structural support it provides to the cells anchored to it.

While virtually all cells interact with the extracellular matrix, fibroblasts have an exceptionally inter-reliant relationship with the ECM. Fibroblasts are a broad class of cells that not only inhabit the ECM but are also responsible for producing and remodeling the different structural components of the ECM. Fibroblasts secrete various ECM macromolecules into the extracellular space, as well as direct the organization of the ECM by aligning fibrillar collagens (Stopak and Harris, 1982; Tamariz and Grinnell, 2002). Therefore, these cells can manipulate the composition and architecture of the ECM, affecting the overall structure of a tissue. Because the ratio of ECM volume to cell volume in structural connective tissue (e.g., cartilage, bone, tendons, and adipose tissue) is drastically skewed towards the ECM, the configuration of the ECM can have a dominant effect on connective tissue function.

In chordate and vertebrate animals, there are specialized fibroblasts that secrete and organize the ECM of cartilage and bone tissue, known as chondrocytes and osteoblasts, respectively (Chiara and Ranieri, 2009). These and other fibroblasts define connective tissue characteristics by exporting specific combinations of various ECM constituents into the matrix. For example, cartilage tissue is elastic and can withstand some compressive forces; traits than can be attributed to the chondrocytes, because they export a higher percentage of proteoglycans (e.g., aggrecan) into the ECM of cartilage tissue (Chiara and Ranieri, 2009). Therefore, the diverse native function of connective tissues can be attributed to the manipulation of the ECM by fibroblasts. This is easily seen in the endochondral ossification events that occur in amphibians as they shift from a cartilaginous skeleton to an osseous skeleton; chondrocytes and osteoblasts carry out this skeletal tissue reformation. To convert cartilage into bone, chondrocytes break down the cartilage from within, allowing osteoblasts to populate the tissue and form a denser polysaccharide-rich ECM that is ultimately hardened by mineralization. Afterwards the animals are left with osseous skeletal tissue that can withstand a great deal of compression without deformation, optimal for living outside of water (Chiara and Ranieri, 2009; Sharir et al., 2008).

In the non-connective tissues of animals (e.g., epithelial, nervous, and muscle tissue), there may be less extracellular space overall, but the ECM is still a major factor in tissue morphology and function. For example, the ECM of cardiac tissue acts as a scaffold for cardiomyocytes and it provides a tensile material through which the cardiomyocytes' contractile forces can propagate, allowing for the heart's primary function: pumping blood (Baicu et al., 2003; Pandey et al., 2018). Alteration to the ECM of heart tissue can therefore modify heart function. Similarly, embryonic and post-embryonic remodeling of vascular networks through angiogenesis and vascular regression are key to maintaining and optimizing the distribution of oxygen and nutrients throughout the body (Udan et al., 2013a; Wang and Khalil, 2018). In the circumstance of cardiovascular network remodeling in vertebrates, increased blood pressure or hypoxic conditions within tissues trigger compensatory, but ultimately reversible, expansion and branching of blood vessels (Fraisl et al., 2009; Udan et al., 2013b).

2.2. Fibroblasts and myeloid cells utilize metalloproteinases to degrade the ECM and promote tissue remodeling

To fully understand the underlying mechanisms that mediate tissue remodeling, it is vital to examine the protein families known to alter ECM structure. The ECM of an animal is by no means static, even in mature animals there is a constant turnover of ECM macromolecules. While fibroblasts work tirelessly to build up the ECM, proteinases are also hard at work degrading ECM proteins. The major proteinase superfamily responsible for degrading the collagens and glycoproteins of the ECM are the zinc metalloproteinases (metzincins), which include matrix metalloproteinases (MMPs) and adamalysins (ADAMs and ADAMTSs) (Masciantonio et al., 2017). Most MMPs, ADAMs, and ADAMTs are secreted as inactive proenzymes and are activated inside the extracellular space via cleavage by proteases, organic agents, pH change, or other factors (Cui et al., 2017). There is a wide range in the number of MMPs present amongst various animal species; most vertebrates have at least twenty MMP genes, while the *Drosophila* genome has only two (Table 1) (Fanjul-Fernández et al., 2010; Fu et al., 2009; Page-McCaw, 2008). The evolutionary divergence and expansion of MMP genes along the chordate lineage suggests a correlation between specialized tissue remodeling processes and the number of MMP genes (Fanjul-Fernández et al., 2010; Fu et al., 2009; Wyatt et al., 2017). Interestingly, mice and *Drosophila* knock-out studies reveal that single and double MMP knockouts may result in embryonic defects, but not lethality (Page-McCaw et al., 2003; Shi et al., 2008). This supports the notion that metalloproteinases are primarily utilized for ECM and tissue remodeling processes, not *de novo* tissue formation.

Fibroblasts are most frequently associated with producing ECM degrading proteinases, but other metalloproteinase-expressing cells exist, including mesenchymal stem cells (MSCs) and differentiated myeloid cells (e.g., megakaryocytes, macrophages, and neutrophils). One reason for cells to secrete MMPs into the ECM is to clear a path for cell migration. Thus, it makes sense that highly migratory myeloid cells, macrophages in particular, express several MMPs (e.g., MMP 1–3, 7–14, and many more) (Chou et al., 2016). Although macrophages are often associated with inflammatory responses, they also participate in tissue remodeling events. For example, recent studies revealed that macrophages play a critical role in the post-embryonic remodeling of juvenile *Danio rerio* (zebrafish) epithelial tissue, giving rise to the characteristic striped phenotype of adult zebrafish (Eom and Parichy, 2017). The heavily pigmented melanophores within the zebra-like stripes are directed into a sharp linear formation through organizational cues received by xanthophores. It is macrophages, however, that literally traffic airinemes (filament-based cellular projections) from the surface of xanthophores to the melanophores, allowing the xanthophores to communicate with the melanophores via cell vesicles (Eom and Parichy, 2017). Thus, the MMP-based migratory capabilities of macrophages have been proven to serve as an effective tool for promoting the long-distance cell communication necessary for physiological tissue remodeling.

Table 1
The number of MMP genes varies across animal phyla.

Phylum	Class	Species	# MMPs	Source
Chordata	Mammalia	*H. sapien*	24	Fanjul-Fernández et al. (2010)
		M. musculus	23	Fanjul-Fernández et al. (2010)
	Amphibia	*X. laevis*	22	www.xenbase.org
	Actinopterygii	*D. rerio*	26	www.zfin.org
Platyhelminthes	Rhabditoophora	*S. mediterranea*	4	Isolani et al. (2013)
Arthropoda	Insecta	*D. melanogaster*	2	Page-McCaw et al. (2003)
Nematoda	Chromadorea	*C. elegans*	6	www.wormbase.org
Cnidaria	Hydrozoa	*H. vulgaris*	~15	(Page-McCaw, 2008; Sarras, 2017)

After cells secrete proteases that breakdown the ECM, another equally important family of proteins is needed to ensure newly created ECM is protected from subsequent degradation. This protective capacity is regulated by cells, like fibroblasts and myeloid cells, that secrete tissue inhibitors of metalloproteinases (TIMPs) into the extracellular matrix. TIMPs are proteins that regulate metalloproteinase activity and thus, control ECM degradation (Bourboulia and Stetler-Stevenson, 2010; Brew and Nagase, 2010). Mammals possess four different TIMP proteins (TIMP 1–4) and all other animal model systems surveyed thus far express at least one TIMP homolog (Brew and Nagase, 2010). These proteinases and proteinase regulators both act within the extracellular space of an organism, although they are often anchored to cell membranes or the ECM (Murphy, 2017). Briefly, TIMPs are capable of binding to active metalloproteinases, subsequently preventing them from enzymatically cleaving ECM substrates. For example, human mesenchymal stem cells are known to produce MMP-2 during endochondral and vascular remodeling, but at the same time MSCs can release enough TIMP-2 to completely negate any MMP-2 enzymatic activity within the stem cell sustaining perivascular niche that they reside in (Lozito and Tuan, 2011). The release of TIMPs by MSCs is thought to be a perivascular matrix-protective mechanism, capable of preventing vascular basement membrane (VBM) degradation by MMP-2 or MMP-9 (a.k.a. gelatinase-B) under physiological remodeling conditions, such as during endochondral ossification (Lozito and Tuan, 2011; Ortega et al., 2004).

2.3. *During tissue remodeling, alterations to the ECM prompt cellular responses*

When the ECM is altered by modulating metalloproteinase or TIMP activity, cells in contact with the ECM directly or indirectly detect these changes and respond accordingly. Depending on the stimulus and intracellular signaling pathways that are activated, the response of cells within and attached to the ECM may be to proliferate, die, migrate, differentiate, or modify transcription of target genes (Kühn et al., 2004; Lang and Bishop, 1993; Meredith et al., 1993) (Fig. 3). A simple mechanism through which MMPs can influence cell communication and behavior, is through the cleavage of cell membrane receptors. For instance, when a metalloproteinase (i.e., ADAM17) cleaves and inactivates a receptor on the surface of a cell (i.e., tumor necrosis factor α receptor), it alters the repertoire of signaling molecules that a cell can detect (Masciantonio et al., 2017). Furthermore, both metalloproteinase and TIMP activity within the ECM can mediate cell signaling during tissue remodeling in many ways; either protein family can assist in the release, activation, or inactivation of signaling molecules (Hynes, 2009).

The biochemical actions of metalloproteinases and TIMPs have broad implications for cells adhered to the ECM. Cells are generally anchored to the ECM via integrins, which are heterodimeric transmembrane proteins that form attachments between the cytoskeleton of cells and ECM glycoproteins. Thus, it is not surprising that reorganization of the ECM can result in altered tension between the ECM and cytoskeleton, as well as altered integrin signaling, both of which are rapidly detected by the cell. Interestingly, cells that suddenly find themselves unanchored or attached to an incompatible ECM tend to undergo apoptosis (Gilmore, 2005; Meredith et al., 1993). Therefore, a straightforward effect that metalloproteinase degradation of the ECM can have on cell behavior is the induction of apoptosis, as observed during intestinal remodeling and tail resorption in metamorphic tadpoles (Das et al., 2006; Gross and Lapiere, 1962; Ishizuya-Oka et al., 2000). Cooperatively, TIMP inhibition of MMP activity can preserve the ECM and promote cell survival in the tissue areas that must remain untouched by remodeling events, as seen with human mesenchymal stem cell niches (Lozito and Tuan, 2011). However, it should be noted that cause and effect between MMP/TIMP actions and cellular responses are rarely straightforward.

For instance, the actions of MMPs can encourage the proliferation of cells, just as easily as they can promote cell apoptosis. Cleavage of heparan sulfate proteoglycans (HSPGs) by MMPs during adipose tissue remodeling demonstrates this fact. HSPGs that are usually sequestered within the ECM are freed once cleaved by metalloproteinases (Yayon et al., 1991). The cleaved HSPGs can then diffuse throughout the extracellular fluid and act as a positive or negative cofactor for critical paracrine and autocrine signaling molecules including fibroblast growth factor (FGF), bone morphogenetic protein (BMP), WNT, and hedgehog (Kuo et al., 2010; Yayon et al., 1991). The net effect of freeing HSPGs depends on which growth factors they interact with and whether they act as positive or negative cofactors, but if we limit our focus to their positive influence on FGF10 efficacy during murine embryonic adipose tissue formation and remodeling, then HSPG cleavage by MMPs ultimately serves to promote adipocyte proliferation (Ohta and Itoh, 2014; Yamashita et al., 2018). This embryonic adipose tissue growth and remodeling markedly alters the overall morphology of these animals and serves to bolster the energy reserve function of the adipose tissue.

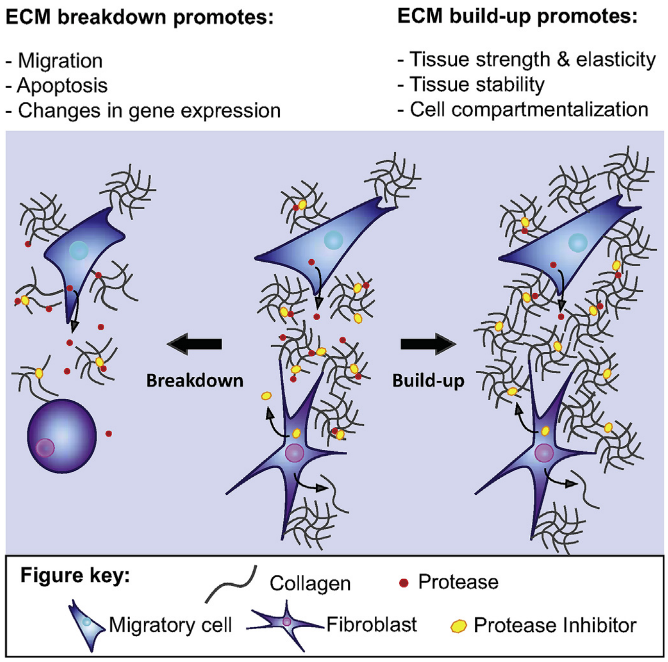

Fig. 3. ECM Remodeling Influences Cell Behavior. The presence and composition of the ECM affects cell behavior through many mechanisms. For example, cells expect to be anchored to the ECM via integrins and if they become completely unanchored, they undergo apoptosis. Yet, degradation of the ECM is essential to cell migration and tissue reformation. Furthermore, the degradation or build-up of the ECM strongly influences the availability and diffusion of bioactive compounds (growth factors, cytokines, and hormones), particularly those that are normally bound to ECM structural molecules (e.g. VEGF and TGFβ).

Given the utility of MMPs and TIMPs during tissue remodeling, there has been a great deal of focus on their role in cancer and other forms of pathological tissue remodeling (Bourboulia and Stetler-Stevenson, 2010; Liu and Khalil, 2017). As a result, their pathological roles have essentially overshadowed their endogenous functions during natural tissue and organ remodeling events. It would be beneficial for researchers to also focus on examining how MMPs and TIMPS are successfully applied in animals to carry out physiological tissue remodeling. For that reason, this review primarily describes MMPs, TIMPs, and ECM remodeling in the context of physiological remodeling. For reviews focused on the triggers and mechanisms of pathological tissue remodeling see (Bonnans et al., 2014; Chou et al., 2016; Kessenbrock et al., 2015).

3. What regulatory mechanisms control physiological tissue remodeling in embryonic, juvenile, and adult animals?

Physiological tissue remodeling allows for the establishment, maintenance, and adaptive alteration of an organism's normal tissue morphology. Thus, physiological tissue remodeling is beneficial to the overall fitness of an organism and, in many situations, is necessary for survival. Whether tissue remodeling occurs in an embryo, juvenile, or adult animal, it occurs either at evolutionarily pre-defined timepoints along the life cycle, like metamorphosis in flatfish, or in response to environmental cues, like allometric resizing in planaria.

3.1. Embryonic tissue remodeling is driven by biophysical inputs, autocrine signaling, and paracrine signaling

Generally, morphogenesis in an embryo cannot be explicitly attributed to tissue remodeling because a tissue must first exist before it can be remodeled. However, there are many embryonic processes that rely heavily on the remodeling of embryonic tissues to establish tissue and organ function, such as tissue regression, angiogenesis, and endochondral bone formation. Though embryonic tissue formation is largely driven by developmental gene regulatory networks, tissue remodeling during embryogenesis is significantly influenced by biophysical factors, thus embryonic remodeling is initiated at specific times during development and responds dynamically to the environment (Bonnans et al., 2014; Jülicher and Eaton, 2017).

A classic example of embryonic tissue remodeling is interdigit regression, during which the digits of vertebrate embryos are sculpted out of limb buds. Interdigital tissue regression is primarily achieved through the induction of cell death between the presumptive digit tissue regions (Lorda-Diez et al., 2015; Montero et al., 2016). One of the many redundant triggers of cell death during limb bud remodeling includes vascular tissue remodeling. Counterintuitively, limb bud interdigital tissue regression is preceded by increased vascularization rather than vascular regression. Researchers have proposed that this increased vascularization promotes reactive oxygen species production and subsequent DNA damage-induced apoptosis (Eshkar-Oren et al., 2015; Montero et al., 2016).

The remodeling of the primary vascular plexus is also an excellent example of embryonic tissue remodeling. For animals with blood vascular systems (vertebrates), there are two major phases of vascular development in embryos: vasculogenesis and angiogenesis (Udan et al., 2013a). Differentiation of stem cells is the dominant mechanisms through which vasculogenesis occurs, while tissue remodeling is the dominant mechanisms through which angiogenesis occurs. During angiogenesis, blood vessel fusion, splitting, sprouting, and regression transforms the primary vascular plexus into a mature network (Udan et al., 2013a).

The main biophysical factors that influence and refine vascular remodeling are low oxygen levels within tissues (hypoxia) and the mechanical stress felt by vascular cells due to blood flow (hemodynamics) (Fraisl et al., 2009; Udan et al., 2013b). Cells under hypoxic stress, upregulate angiogenic growth factors, such as vascular endothelial growth factors (VEGFs), FGFs, and transforming growth factors (TGFs), which then cue angiogenic sprouting of blood vessels into the hypoxic tissue through paracrine signaling. Similarly, vascular cells under mechanical stress upregulate growth factors and utilize paracrine and autocrine signaling to promote the widening of blood vessels. In both the sprouting and expansion of blood vessels, the binding of ligands to growth factor receptors on vascular cells upregulate MMPs to facilitate ECM remodeling (Wang and Khalil, 2018). In conjunction with blood vessel expansion and sprouting during vascular remodeling, regression refines the vascular network via the retraction of temporary or superfluous blood vessels within an embryo, like the transient hyaloid vasculature of developing retina (Yoshikawa et al., 2016). Clearly, the maturation of vascular networks, through remodeling, plays a significant role throughout morphogenesis. Furthermore, angiogenesis and vascular regression extend beyond embryonic life stages as they also coincide with the remodeling of virtually all tissues in juvenile and adult animals.

Endochondral bone formation in vertebrates is another tissue remodeling dominated process that begins during embryogenesis and continues at least through adolescence. Unlike direct intramembranous ossification, endochondral ossification involves transitioning from a cartilaginous tissue template to mineralized bone. The reformation of cartilaginous tissues into osseous tissue encompasses chondrocyte induced vascularization of the cartilage, recruitment of osteoprogenitors, chondrocyte apoptosis or transdifferentiation, and ECM transformation by osteoclasts and osteoblasts (Javaheri et al., 2018; Mackie et al., 2011). All of which is coordinated through systemic hormone signaling (e.g., growth hormone and thyroid hormone) and local growth factor signaling (e.g., VEGF and FGF) between and within several cell populations (Mackie et al., 2011; Provot and Schipani, 2005). The main biophysical factor that influences endochondral ossification during embryogenesis, and later in life, is mechanical loading (Robling and Turner, 2009).

3.2. Tissue remodeling during juvenile animal maturation is controlled by conserved endocrine hormone signaling pathways

Across several animal phyla, tissues are molded into adult forms during juvenile life stages, sometimes quite drastically. For example, *Drosophila melanogaster* larvae have a body plan that is radically different than that found in adult flies, and it is only through extensive remodeling of existing larval tissues that the target adult morphology can be achieved (Bainbridge and Bownes, 1981). The extensive remodeling process that most insect, several amphibians, and numerous fish undergo to dramatically alter their morphology during maturation is referred to as complete metamorphosis (Holstein and Laudet, 2014; Laudet, 2011). During metamorphosis, muscle tissue is modified, neural networks are rewired, sensory organs are altered, some structures disappear (e.g., gills, tails), new structures are created (e.g., limbs, wings), and connective tissue is reshaped. The maturation of non-metamorphic animals is also dependent on tissue remodeling, the morphological effects are merely subtler. Alterations to tissue structure and overall morphology in metamorphic and non-metamorphic juvenile animals is largely regulated by systemic endocrine signaling (Table 2).

Tissue remodeling during maturation serves the evolutionary purpose of optimizing an animal's fitness under the environmental pressures that the adult must face (Holstein and Laudet, 2014). For example, larval *Xenopus laevis* (African claw-toed frog) and *Paralichthys lethostigma* (Southern flounder) undergo metamorphic remodeling of craniofacial

Table 2
General triggers of systemic post-embryonic tissue remodeling responses in various animal model systems.

Trigger	Remodeling Response	Model System(s)	Source
Ecdysone hormone	Metamorphic remodeling of virtually all tissues and organs	Ecdysozoans: *D. melanogaster, M. sexta,* etc.	(Hiruma and Kaneko, 2013; Rewitz et al., 2013)
Thyroid hormone	Metamorphic remodeling of most tissue and organs	Chordates: *Xenopus*, Pleuronectiformes (Flatfish), Amphioxus (Lancelets), *Ciona*, etc.	(Laudet, 2011; Schreiber, 2013)
Prolactin hormone	Remodeling of mammary glands, uterine lining, placenta	Mammals: Humans, Mice, Rats, etc.	(Flint et al., 2006; Muraoka-Cook et al., 2008)
Parathyroid hormone	Bone remodeling	Vertebrates: Humans, zebrafish, *Xenopus*, etc.	(Chiara and Ranieri, 2009; Paiva and Granjeiro, 2014)
Growth hormone	Bone and adipose tissue remodeling	Vertebrates: Humans, mice, *Xenopus*, etc.	(Berryman et al., 2011; Hadjidakis and Androulakis, 2006; Huang and Brown, 2000)

cartilage, bone, muscle, and nerve tissue that results in the dramatic repositioning of their eyes from a lateral position in the juveniles to dorsal placement in the adults (Figs. 1 and 4) (Hoskins, 1990; Hoskins and Grobstein, 1985; Schreiber, 2013). This striking morphological change appropriately accompanies their shift in behavior, from filter feeding animals dependent on panoramic vision to avoid predation, to predatory adults dependent on stereoscopic vision to catch their prey (Buchholz and Shi, 2018; Denver, 2013; Dittrich et al., 2016; Holstein and Laudet, 2014; McMenamin and Parichy, 2013; Rewitz et al., 2013; Schreiber, 2013).

The dramatic remodeling of tissues and organs in metamorphic organisms is initiated via the activity of several endocrine hormones, such as ecdysone and thyroid hormone (Holstein and Laudet, 2014). Both ecdysone and thyroid hormone (TH) production in invertebrates and chordates, respectively, is initiated by the endocrine gland system (e.g., the corpora allata and prothoracic gland in *Drosophila* or the pituitary gland in *Xenopus*) at the appropriate life stage (Denver, 2013; Hiruma and Kaneko, 2013). Once produced, the prohormones enter the blood stream and are systematically distributed throughout the animal's body, making it possible for a single hormone to affect the morphology of the entire organism (Fig. 4). Of course, because all the animal's tissues are simultaneously exposed to the hormone, additional regulatory mechanisms

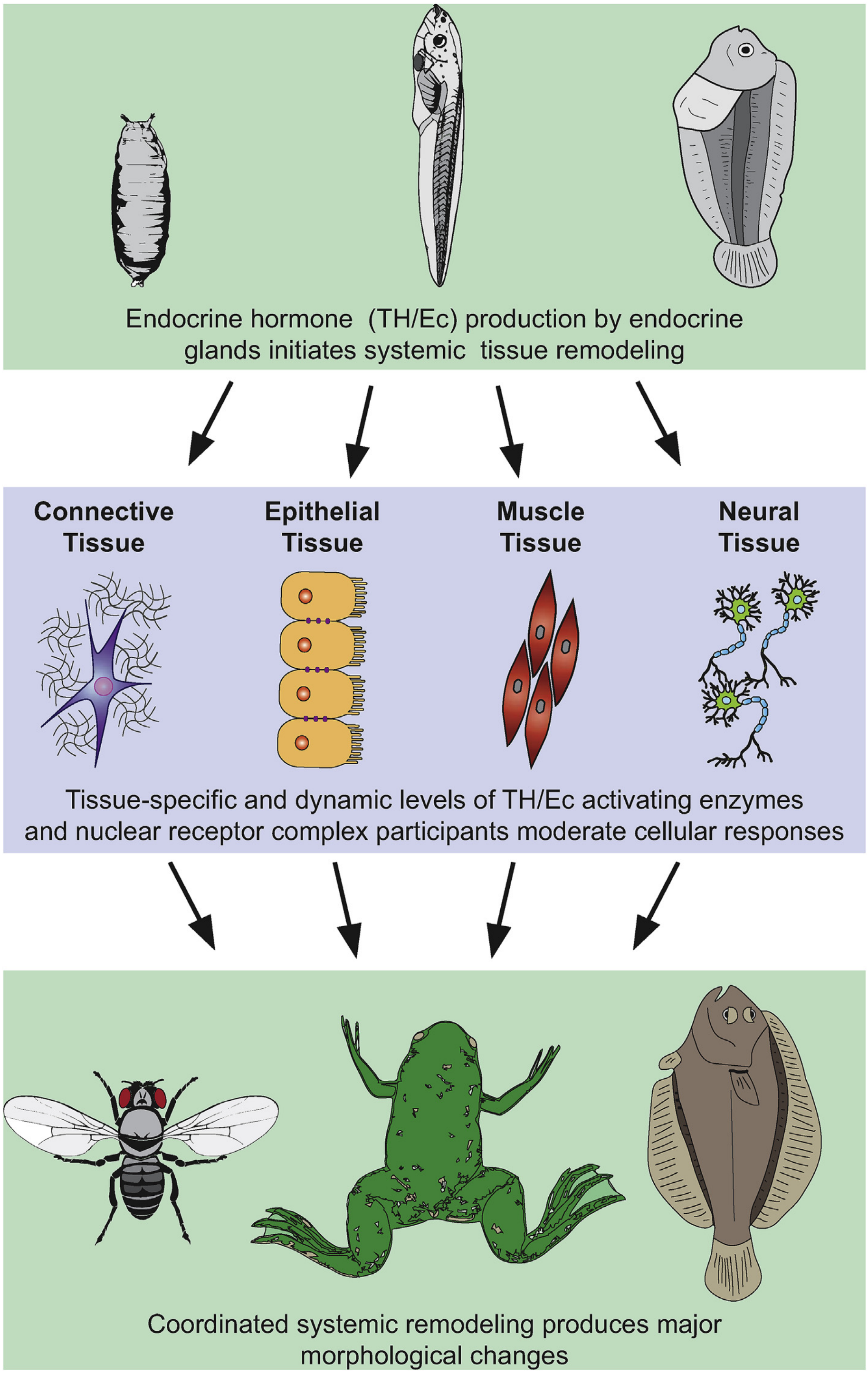

Fig. 4. Systemic endocrine signaling promotes metamorphic tissue remodeling in juvenile animals. Ecdysozoans and vertebrate animals that undergo metamorphosis (e.g., *Drosophila, Xenopus, and* Pleuronectiformes), rely on the systemic distribution of an endocrine hormone (e.g., ecdysone hormone [EC] or Thyroid hormone [TH]). The amount of biologically active forms of metamorphosis-inducing hormones, such as 20-hydroxyexdysone [ecdysterone] and triiodothyronine [T3] is tightly regulated and titrated across tissues. Furthermore, hormone signaling effects differ by cell/tissue type based on the presence of hormone nuclear receptors that moderate the ligand's effect on transcription. Thus, whole tissue, organ, and body morphology can be altered simultaneously. Tadpole and frog images modified from (P.D. Nieuwkoop and J. Faber, 1994).

evolved in order for the transcriptional response to be tissue specific. This regulation involves the conversion of the prohormones to biologically active forms, as well as a highly conserved nuclear receptor complex-dependent mechanism that controls the effect of the biologically active hormones on the transcription of downstream tissue remodeling genes.

3.2.1. Induction of metamorphosis in arthropods: ecdysterone and juvenile hormone

For Ecdysozoans, like *Drosophila melanogaster* and *Manduca sexta*, metamorphosis is triggered by increased production of the steroid hormone ecdysone and halted production of juvenile hormone (JH) (Hiruma and Kaneko, 2013; Ou and King-Jones, 2013). The prothoracic gland, an endocrine organ, produces and secretes the inactive form of ecdysone into the circulatory system. This inactive hormone is later converted into its active form, 20-hydroxyecdysone (a.k.a. ecdysterone) by a cytochrome P450 enzyme (Ou and King-Jones, 2013). The active form of ecdysone can then systematically trigger tissue and cell-type specific metamorphic response (Hiruma and Kaneko, 2013; Rewitz et al., 2013). Notably, full induction of metamorphosis by ecdysterone can only occur after JH production is halted by the corpora allata within the brain during the fifth and final larval instar (Hiruma and Kaneko, 2013; Kayukawa et al., 2017).

The tissue-specific effects on transcription by ecdysterone are moderated by the ecdysone receptor (EcR), which typically forms heterodimeric nuclear receptor complexes with retinoid X receptors (RXRs) (Holstein and Laudet, 2014). Remarkably, despite the evolutionary divergence in the specific hormones that induce metamorphosis amongst invertebrate and vertebrate animals, RXRs are conserved members of heterodimeric nuclear receptor complexes across several metazoan clades (Holstein and Laudet, 2014). Generally, invertebrates possess two or three ecdysone receptor isoforms: EcRA, EcRB1, and EcRB2; but only one RXR homolog, often referred to as ultraspiracle (USP) (Buchholz and Shi, 2018; Henrich, 2012). Therefore, there are a variety of complexes that can be formed between EcRs and RXRs. Furthermore, EcRs can form homodimers or heterodimerize with non-RXRs, such as the DHR38 nuclear receptor (Baker et al., 2003). The DNA binding sites of each nuclear receptor pair varies based on pair members and transcriptional co-factors, thus the different pairs preferentially or uniquely bind upstream of certain ecdysterone-inducible tissue remodeling genes (Beck et al., 2009).

Interestingly, some of the main tissue remodeling genes under the transcriptional control of ecdysone are MMPs and TIMPS (Jia et al., 2017; Kawasaki et al., 2018), the same class of proteins upregulated during metamorphosis and other remodeling events in vertebrate species. Thus, across invertebrates and chordates we see conservation in the transcriptional mechanisms utilized to carry out hormonal induction of metamorphosis and in the class of metamorphic hormone-regulated genes that ultimately execute the tissue remodeling.

3.2.2. Endocrine hormones also initiate tissue remodeling in non-metamorphic juvenile arthropods

As described above, changes in whole-body morphology experienced by juvenile metamorphic animals represent some of the most extreme examples of tissue remodeling observed in animals. However, tissue remodeling can also occur in non-metamorphic animals - albeit to a lesser degree. For example, it is well established that pulses of steroid hormones, like ecdysone and dafachronic acid (DA), regulate ecdysis (molting) in pre-metamorphic and non-metamorphic invertebrates, such as *Drosophila melanogaster*, *Manduca sexta,* and *Caenorhabditis elegans* (Aguilaniu et al., 2016; Ou and King-Jones, 2013). Additional hormones, such as insulin and serotonin, are important determinants of whether juvenile *C. elegans* undergo the tissue remodeling associated with an alternate life stage called the dauer diapause stage. Although *C. elegans* are not considered metamorphic invertebrates, under stress they can enter dauer diapause and remodel muscle and neural tissue in an attempt to endure the stressor (Androwski et al., 2017). This dauer stage is triggered by the down-regulation of insulin, serotonin, and dafachronic acid due to certain environmental influences, such as the lack of food or population-dependent pheromone concentrations (Aguilaniu et al., 2016; Fielenbach and Antebi, 2008). Furthermore, proper *C. elegans* dauer formation through tissue-specific remodeling has been shown to be moderated by ecdysterone hormone nuclear receptor orthologs, such as NHR-41 (NR2D1) and NHR-23 (NR1F4) (Aguilaniu et al., 2016; Gissendanner et al., 2004).

3.2.3. Induction of metamorphosis in chordates: thyroid hormone

Metamorphic chordates, such as *Xenopus laevis* and flatfish, use a different metamorphosis-triggering hormone than invertebrates; thyroid hormone (TH) (Furlow and Neff, 2006; Ishisuya-oka et al., 1998; Paris et al., 2008). In these animals, the thyroid stimulating hormone (TSH), generated by the pituitary gland, stimulates TH synthesis in thyroid gland cells by binding to TSH receptors (Denver, 2013). Two different forms of TH are produced by the thyroid gland and released into the circulatory system, thyroxine (T4) and triiodothyronine (T3). T3 is the more biologically active form, but T4 is generally the main TH produced by the thyroid gland. Consequently, T4 must be converted into T3 by deiodinase enzymes within various tissues in order for thyroid hormone signaling to be effective. Therefore, deiodinase enzymes serve a key regulatory role in TH-dependent tissue remodeling, because they control how much of the biologically active ligand is present within any given tissue.

Similar to ecdysterone in invertebrate animals, the TH effects on vertebrate tissue remodeling during metamorphosis are also tissue and cell specific (Schreiber, 2013; Veldhoen et al., 2014). However, in contrast to exposure to ecdysterone in invertebrates, premature TH exposure in these larval vertebrates is sufficient for the induction of precocious metamorphosis due to the absence of a vertebrate JH homolog that would prevent the activation of the TH metamorphic signaling pathway in pre-metamorphic larvae (Inui and Miwa, 1985; Tata, 1968). Thus, to achieve more precise control over TH-mediated transcription, TH signaling is moderated by numerous families of receptor proteins that help provide temporal and spatial specificity. For example, the thyroid hormone receptors (THRs) can form heterodimeric complexes with the retinoid X receptors (RXRs), retinoic acid receptors (RARs), or homodimerize (Lee and Privalsky, 2005; Li et al., 2002). In addition, most vertebrates have multiple thyroid hormone receptors (THRα and THRβ), RXRs (RXRα, RXRβ, and RXRγ), and RARs (RARα, RARβ, and RARγ) (Buchholz et al., 2006; Escriva et al., 2006; Holstein and Laudet, 2014), providing additional control of receptor function.

As an additional level of regulation, the various nuclear receptor pairs form complexes with coregulatory proteins that recognize and bind to specific DNA sequences known as thyroid hormone response elements (TREs) upstream of key metamorphic genes. Consequently, the effect that TH has on transcription varies greatly based on which, and how many, nuclear receptor pairs are present within the cells of tissues exposed to the hormone. For example, in *Xenopus,* THR alpha (THRα) and RXR alpha (RXRα) are constitutively expressed throughout pre-metamorphic stages, but the amount of these nuclear receptors is not ubiquitous across tissues (Fini et al., 2012; Lee and Privalsky, 2005). As a result, once TH production commences, the tissues with higher nuclear receptor expression (the tail and gut) show a greater sensitivity to the hormone and more extensive remodeling occurs. Prior to the initiation of TH-mediated tissue remodeling, THRα and RXRα form repressive complexes upstream of key metamorphic genes, like *THRβ*. However, once TH is present, it binds to THRα and the THRα/RXRα heterodimers shift from repressors to activators, resulting in the upregulation of *THRβ* transcription. Thus, remodeling processes are augmented in tissues containing higher concentrations of THRα/RXRα complexes. Once activated the THRβ/RXRα complexes bind to TH response elements present upstream of genes necessary for tissue remodeling including *BMPs, MMPs* and collagen genes(Nakajima et al., 2018; Veldhoen et al., 2014).

3.2.4. *Endocrine hormones also influence tissue remodeling and morphology in non-metamorphic juvenile vertebrates*

Clearly TH signaling has a drastic effect on the morphology of metamorphic vertebrates, what is less obvious is that TH signaling also induces tissue remodeling in non-metamorphic juvenile vertebrates in numerous species - ranging from zebrafish to humans. For example, *Danio rerio* (zebrafish) are not classified as animals that undergo complete metamorphosis, but they experience TH induced morphological changes to their fin and epithelial tissue during their juvenile life stage (McMenamin et al., 2014). These morphological changes include the establishment of the adult stripes, scale formation, reshaping of the caudal fin, and the development of various other fins along the body (Singleman and Holtzman, 2014). Even mice, rats, and humans show peaks in TH production anywhere from hours to weeks after birth that correlate with critical post-embryonic neural cell differentiation and myelination, cardiomyocyte proliferation, and bone ossification (Holzer and Laudet, 2013; Kenessey and Ojamaa, 2006; Li et al., 2014). In addition to thyroid hormone, endocrine signaling involving other hormones such as, parathyroid hormone, growth hormone, and prolactin have systematic effects on bone, adipose tissue, and mammary gland remodeling in post-embryonic vertebrates (Berryman et al., 2011; Cheung and Wong, 2008; Flint et al., 2006; Jung et al., 2004).

3.3. *Specialized regulatory mechanisms direct tissue remodeling in mature animals*

From a purely biological standpoint, adult animals have one goal: reproductive success. For that reason, mature animals (particularly those with relatively long lifespans) rely upon tissue remodeling-based adaptive plasticity to improve survival and optimize reproductive fitness throughout their lifespan. The regulatory mechanisms responsible for tissue remodeling events in adult animals vary greatly depending upon whether systemic or discrete tissue remodeling must occur.

3.3.1. *Systemic remodeling events in mature animals are regulated by evolutionarily divergent endocrine signaling*

On the extreme end of tissue remodeling events observed in mature animals, lies degrowth (or allometric re-sizing). Mature planaria and *Hydra* undergo whole-body degrowth in response to starvation (Chera et al., 2009; Felix et al., 2018). Like dauer formation in juvenile *C. elegans,* degrowth is an adaptive survival mechanism that involves the remodeling of epidermal, muscle, and neural tissue and alters the morphology of the entire body. Degrowth is dependent on increased cell death and autophagy (Chera et al., 2009; Felix et al., 2018; González-Estévez et al., 2007). Researchers speculate that endocrine signaling occurs in response to starvation and controls widespread apoptotic and autophagy cellular responses. The changes in mTOR, FGF, and JNK signaling seen in planaria and *Hydra* during whole-body remodeling after tissue amputation and regeneration further supports this hypothesis (Chera et al., 2009; Pellettieri et al., 2010).

Another intriguing systemic tissue remodeling event, functional sex change, is observed in several mature marine arthropods and chordates (e.g., *Crepidula fornicata*, *Thalassoma duperrey,* and *Lates calcarifer*). In these animals physical or social stimuli trigger differential regulation of sex hormones (i.e., estrogen and testosterone variants), which control the physiological transition from one sex to another (Broquet et al., 2015; Liu et al., 2017). Sequential hermaphroditism frequently involves the remodeling of differentiated sex organs as well as secondary sex characteristics. Whether the transition is male to female (protandry) or female to male (protogyny), the purpose of these tissue remodeling events is to optimize reproductive success. For example, in protandry wrasse fish species (*Thalassoma duperrey* and *Thalassoma bifasciatum*) the removal of the large, dominant, territorial male from a group will result in a large female transitioning into a male. During this transition, estradiol serum levels drop, 11-ketotestosterone serum levels increase, ovarian atresia occurs, and testes form (Liu et al., 2017). Furthermore, in *Thalassoma bifasciatum* (bluehead wrasse) sex change also entails transitioning from the external scale coloration and patterning of a female to that of a male. While the major stimuli and hormonal pathways behind functional sex change are well understood, the exact molecular and cellular mechanisms through which the sex-specific tissue morphology and function is altered must be investigated further.

Mature mammals also utilize systemic tissue remodeling to optimize their reproductive fitness, for instance various tissue remodeling processes are associated with pregnancy in mammals. During pregnancy, increased production of estrogen, progesterone, growth hormone, prolactin, and several other endocrine hormones induce uterine, mammary, and even heart tissue remodeling (Brisken and O'Malley, 2010; Chung et al., 2012; Jin et al., 2018; Li et al., 2012). These alterations impact reproductive fitness via their influence on offspring survival. For example, extensive mammary fat pad ECM degradation and increased epithelial branching are required for the induction of lactation (Kim and Nelson, 2012; Sternlicht et al., 2006). Once offspring are weaned and it is no longer beneficial to lactate, prolactin levels drop, triggering apoptosis in milk secreting cells and reversal of alveolar growth (Akhtar et al., 2016; Flint et al., 2006). For additional reviews on hormone-dependent remodeling and functional changes in mammary glands see Bonnans et al. (2014), Paine and Lewis (2017), or Sternlicht et al. (2006) (Bonnans et al., 2014; Paine and Lewis, 2017; Sternlicht et al., 2006).

3.3.2. *Discrete tissue-specific remodeling events in mature animals are regulated by paracrine and autocrine signaling*

Tissue plasticity and adaptive remodeling are essential to the optimization of fitness in adult animals. For example, most animals possess neural tissue and retain some level of neuroplasticity as adults. Generally, neural tissue is comprised of neurons, glial cells, ependymal cells, and neural ECMs. Developing synaptic connections and adhesion between the various cells and ECM of neural tissue clearly influence neuronal function in embryonic and juvenile animals, but for decades scientists worked under the assumption that the neural networks established during embryogenesis and juvenile life stages become unalterable upon maturation. In fact, the synaptic connection amongst neurons can be modified in mature animals under the right circumstances (De Luca and Papa, 2017; Pizzorusso et al., 2002; Wlodarczyk et al., 2011).

For example, in murine hippocampal cultures, serotonin signaling has been shown to activate MMP9 cleavage of the ECM-hyaluronan receptor (CD44), which via CDC42 action encourages synaptic remodeling in neural cells (Bijata et al., 2017). Therefore, it seems that serotonin signaling amongst neural cells, through synapsis or other mechanisms, can induce tissue remodeling. Furthermore, rodent and porcine neural tissue culture studies in which the ECM density and composition is actively modified demonstrate that neural matrixes stabilize synaptic connections and the degradation of these matrixes promotes synaptic restructuring (Bikbaev et al., 2015; Sood et al., 2016). Such studies support the hypothesis that the modification of neural ECM by cells within neural tissue can either sustain, promote, or retard the potentiation of neurons in adult animals via the modulation of synaptic plasticity. The exact role and importance of tissue remodeling with regards to neuroplasticity has yet to be thoroughly investigated. Nevertheless, the remodeling of neural tissue in animals has significant implications with regards to sensory information processing, learning, and cognitive behavior. For further discussion of neural ECM remodeling and synaptic plasticity see (Song and Dityatev, 2018; Wlodarczyk et al., 2011).

Induction of tissue remodeling via mechanotransduction, paracrine, and autocrine signaling is another common mechanism applied across several species to adaptively modify tissue morphology and function. This is particularly true for muscle and connective tissues in adult animals. For example, the hearts of animals that experience exercise or pregnancy undergo physiological remodeling of cardiac muscle tissue that results in temporary, non-pathological, hypertrophy (Chung and Leinwand, 2014; Pandey et al., 2018). Physiological cardiac tissue remodeling compensates for increased mechanical stress on cardiac muscle caused by the increased blood volume and pressure during intensive exercise regimens (or pregnancy) (Chung and Leinwand, 2014; Varga et al., 2017). This increase in mechanical stress triggers a PI3k/Akt signaling cascade in cardiomyocytes. PI3k/Akt signaling can then induce transcription of adaptive genes (i.e. IGF1 and GH), effect protein synthesis, and alter cellular energy metabolism (Chung et al., 2012; DeBosch et al., 2006; Maillet et al., 2012). Intracellular TH, insulin, GH, and IGF1 signaling can also promote physiological hypertrophy independent of, or in concert with, increased cardiac muscle strain (Kenessey and Ojamaa, 2006; Kim et al., 2008). For more in-depth reviews of physiological heart remodeling and growth see Li et al. (2012), Maillet et al. (2012), or Varga et al. (2017) (Li et al., 2012; Maillet et al., 2012; Varga et al., 2017).

Another example of adaptive, yet discrete, tissue remodeling is functional bone remodeling in mature chondrocytes. Unlike bone homeostasis, which has been shown in mice and humans to maintain bone tissue density and morphology through the sequential activation of osteoclasts and osteoblasts, functional bone adaptation alters tissue density and morphology (Hadjidakis and Androulakis, 2006; Sanchez-Fernandez et al., 2008; Sims and Martin, 2015; Tang et al., 2009). Bone functional adaptation is a remodeling process that occurs in response to prolonged changes in mechanical stress, as detected by osteocytes embedded within the bone. When osteocytes sense mechanical load-initiated changes in interstitial fluid flow, through an as-yet-undefined mechanism, it promotes the rapid influx of calcium and efflux of ATP, nitric oxide (NO), and prostaglandin E_2 (PGE_2) (Hadjidakis and Androulakis, 2006; Kamioka et al., 1995; Tan et al., 2008). Osteocytes also upregulate insulin-like growth factor I (IGFI), c-fos, cytokines, and Wnt/β-catenin within an hour of experiencing mechanical stress (Govey et al., 2014; Kamel et al., 2010; Lean et al., 1996). ATP, NO, and PGE_2 all serve as autocrine and paracrine signals; they induce mesenchymal stem cell differentiation into osteoblasts, promote osteoblast bone deposition, inhibit osteoclast bone resorption, and prevent osteocyte apoptosis (Kamioka et al., 1995; Tan et al., 2008). Hence bone tissue actively responds to mechanical stress and optimizes an animal's fitness by increasing bone density and strength. Additionally, as one would expect, in the absence of mechanical stress bone deposition by osteoclasts becomes prevalent. This occurs because the lack of mechanical loading for an extended period results in osteocyte apoptosis and removes the autocrine signals that inhibit osteoclast action (Gu et al., 2005).

4. Conclusions and future research directions

Physiological tissue remodeling is a crucial factor in the establishment and maintenance of tissue shape, structure, and function in animals. Valuable scientific insights can be ascertained through the comparison of species-specific molecular mechanisms that initiate and direct tissue remodeling. For instance, by simply examining our current knowledge of the physiological tissue remodeling events that occur across several animal phyla, three things have become clear: (1) animal tissue remodeling is nearly always associated with ECM remodeling, (2) systematic tissue remodeling relies on endocrine hormone signaling, and (3) discrete tissue remodeling takes advantage of localized paracrine and autocrine signaling. However, we still lack enough knowledge of physiological tissue remodeling events to develop precise models for how tissue morphology and function are controlled in any animal. Attaining a deeper understanding of the molecular, cellular, and biophysical processes involved in establishing and maintaining tissue structure and function will require the continued study of tissue remodeling in a variety of animal models, from mammals to nematodes.

For example, researchers have known for several decades that adult snapping shrimps (*Alpheus heterochelis*) can experience the structural and morphological transformation of a small pincer claw into a large snapping claw after losing their snapping claw, through a sexually dimorphic process involving the remodeling of nerve and muscle tissues within the pincer claw across one or two molts (Govind et al., 1988; Mearow and Govind, 1986; Mellon Jr and Stephens, 1978; Read and Govind, 1997; Young et al., 1996). Yet this impressive tissue remodeling event has not, to our knowledge, been further studied in the past 20 years and the molecular mechanisms responsible for this remodeling event remain unknown. Given that we now have innumerable molecular and analytical tools available to us (e.g., next-generation sequencing, gene editing, and two-photon excitation microscopy), we see no reason why tissue remodeling processes like these should remain a mystery. The primary benefit of studying and deciphering these natural tissue remodeling processes is that they provide us with an insight of how tissue morphology and function can be manipulated and controlled.

Furthermore, the development of tissue-remodeling based medical treatments will depend on the precise and explicit manipulation of tissue structure, function, and morphology. To do this, researchers will have to continue to study the natural tissue remodeling processes that occur in model animals. Since there is significant tissue remodeling occurring throughout the life span of all animals, there is ample opportunity to asses and affect the mechanisms that drive remodeling. Devoting more time and energy towards understanding how to reform tissues provides a realistic and applicable solution to health issues that cannot be resolved by purely regenerative medicines, such as brain anomalies, obesity, abnormal bone growths, and other morphological defects. Therefore, researchers should also work towards an alternate and arguably more readily attainable tissue remodeling-focused research aim: to develop approaches that allow us to manipulate the remodeling of tissues and thus direct the morphology of post-embryonic tissues, organs, or whole organisms. If tissue remodeling based therapeutic medicines are developed, they will certainly synergize well with current and future advances in the sister field of regenerative research.

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