General and Comparative Endocrinology 283 (2019) 113220

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

Endocrine regulation of regeneration: Linking global signals to local processes

Marietta R. Easterling[a,*], Kristin M. Engbrecht[a,b], Erica J. Crespi[a]

[a] Washington State University, School of Biological Sciences, Center for Reproductive Biology, Pullman, WA 99164, United States
[b] Pacific Northwest National Laboratory, Richland, WA 99352, United States

ARTICLE INFO

Keywords:
Hormones
Regeneration
Ecological factors

ABSTRACT

Regeneration in amphibians and reptiles has been explored since the early 18th century, giving us a working *in vivo* model to study epimorphic regeneration in vertebrates. Studies aiming to uncover primary mechanisms of regeneration have predominantly focused on genetic pathways regulating specific stages of the regeneration process: wound healing, blastema formation and growth, and pattern formation. However, studies across organisms show that environmental conditions and physiological state of the animal can affect the rate or quality of regeneration, and endocrine signals are likely the mediators of these effects. Endocrine signals working/acting directly on receptors expressed in the structure or via neuroendocrine pathways can affect regeneration by modulating immune response to injury, allocation of energetic resources, or by enhancing or inhibiting proliferation and differentiation pathways in regenerating tissue. This review discusses the cumulative knowledge known about endocrine regulation of regeneration and important future research directions of interest to both ecological and biomedical research.

1. Introduction

Research investigating epimorphic regeneration, the recapitulation of complex structures or organs after injury or amputation, largely focuses on elucidating the wound-healing factors, gene expression networks, and signaling pathways involved in the rebuilding of tissues and structures (Beck et al., 2009; Chang et al., 2017; Voss et al., 2015). In addition, endocrine signals that vary with nutrition, reproductive condition or level of environmental stress can broadly influence cellular processes at local tissue levels to optimize the allocation of resources for energy-dependent processes such as regeneration (Allan et al., 2001; Barabasi and Oltvai, 2004; Van Kleffens et al., 1998). Through the actions of their receptors, endocrine signals can interact with developmental pathways to change localized cellular process, which will determine the rate or quality of tissue regeneration (Fig. 1).

In this review, we will examine the role of endocrine signaling to regulate the molecular and cellular processes involved in regeneration. Although we refer to research describing environmental and endocrine effects on regeneration in invertebrates, (also see review by Das (2015), this review will focus on vertebrate model organisms exhibit epimorphic regeneration: teleosts (zebrafish) and urodele (newts, axolotl and salamanders) and anuran (*Xenopus*; frog model), as these models share similar endocrine systems and are more closely related to biomedical applications. Regenerative ability in *Xenopus*, *Ambystoma* and zebrafish are often studied because they are excellent *in vivo* models to advance the field of human regenerative medicine. Although limb patterning has been extensively studied in mouse and chick models, the use of *Xenopus, Ambystoma* and zebrafish are particularly suited to study epimorphic regeneration because of their external development. One can easily observe epimorphic regeneration *in vivo* and conduct manipulative experiments in the laboratory with many molecular tools that are easily available. Specifically, *Xenopus* and *Ambystoma* are emerging as great models for advancing cancer research as an inducible tumor model to study the pathogenesis of tumor progression and metastasis (Hardwick and Philpott, 2015; Roy and Gatien, 2008). Conserved genetic pathways between *Xenopus, Ambystoma,* zebrafish and mammals can give us insight to changes in cellular mechanisms such as metabolism and movement (Alvarado and Tsonis, 2006; Hardwick and Philpott, 2015). In amphibian models, there is no control on the lifespan of the progenitor cells and they have low incidence of spontaneous tumors, which lends to the hypothesis that their cell cycle is differently regulated (Hardwick and Philpott, 2015; Price and Allen, 2004). This is supported in metamorphed *Ambystoma,* in which cell function was altered, with a reduced number of blastema cells in the s-phase (Monaghan et al., 2014). These blastema cells loss their “stemness” and overall reduced regenerative ability (Monaghan et al., 2014), which

* Corresponding author.
E-mail address: marietta.easterling@wsu.edu (M.R. Easterling).

https://doi.org/10.1016/j.ygcen.2019.113220
Received 20 May 2019; Received in revised form 8 July 2019; Accepted 8 July 2019
Available online 13 July 2019
0016-6480/

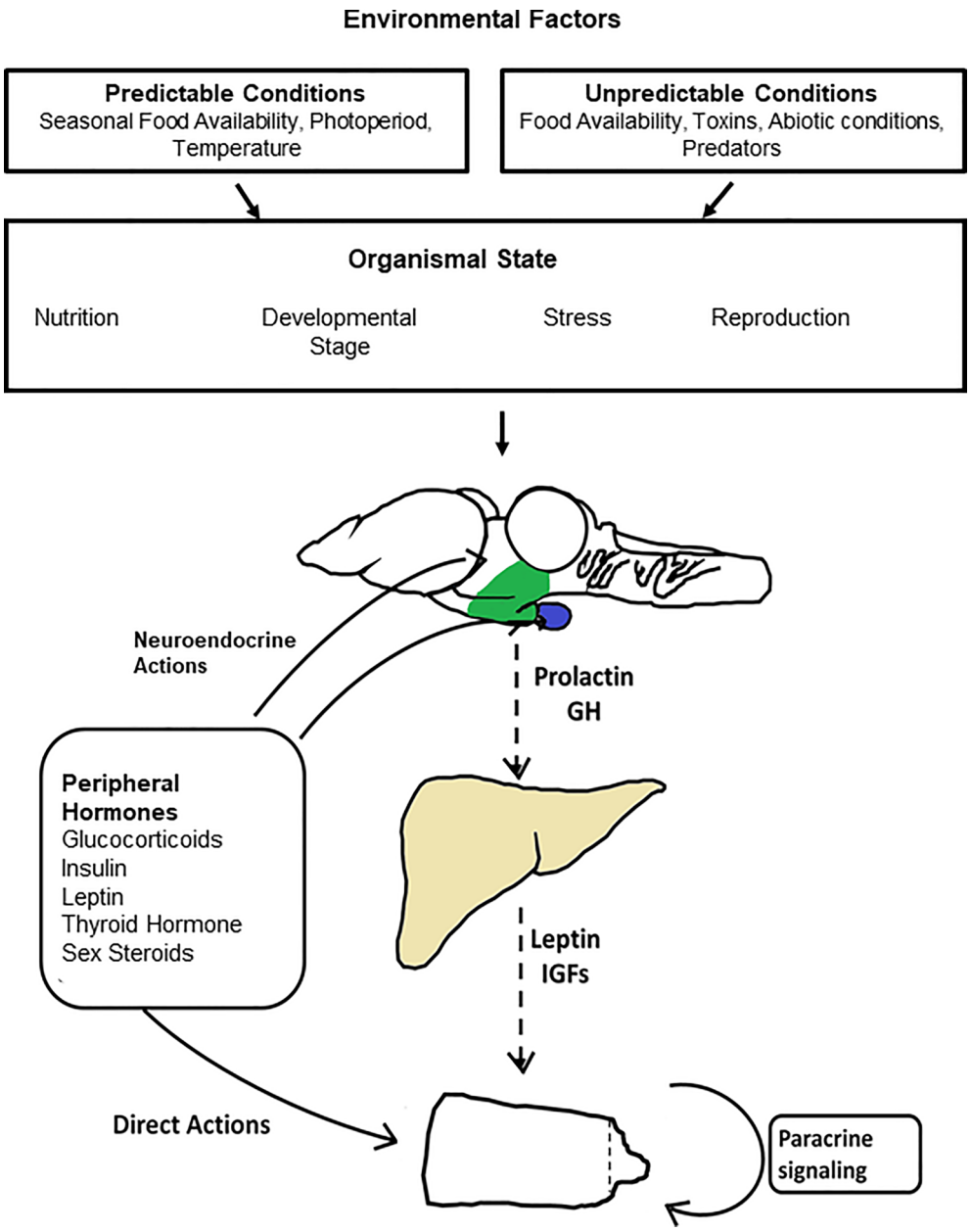
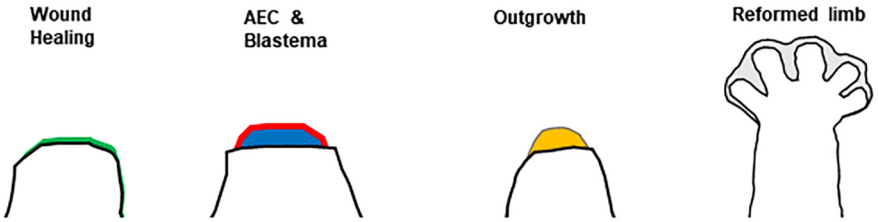


Fig. 1. Endocrine connections that transduce the effects extrinsic and intrinsic factors on epimorphic regeneration. The environment can vary by predictable or unpredictable conditions. Predictable changes involve biotic or abiotic factors that change with daily photoperiod or seasons, while unpredictable changes involve acute changes in biotic (food availability, predation) or abiotic (precipitation, oxygen availability, temperature) conditions or exposure to toxins or anthropogenic stressors. These conditions interact with an animal's organismal state, defined by level of nutrition, stress or life history stage that alter the animal's physiological milieu (intrinsic factors). The combination of extrinsic and intrinsic factors varies endocrine signals that can positively or negatively modulate local cellular processes involved in regeneration. These hormones are secreted in the periphery or the pituitary and can influence regeneration through direct (solid line) and indirect (dotted line) pathways. Direct pathways are when the hormone acts through its receptor(s) in at the site of injury (represented by a limb); indirect pathways are when the hormone acts on receptors in the brain or pituitary to stimulate neuroendocrine pathways that can enhance or inhibit regeneration. Often endocrine signals can be synthesized and secreted in skin or nearby tissues to also act as a paracrine factor regulating regeneration.

strongly suggests that cells are differentially regulated after metamorphosis through changes in hormone signaling. In the following sections, we first provide an overview of general features of epimorphic regeneration in vertebrates, then describe the extrinsic (environmental) and intrinsic (e.g., life history stage and physiological state) factors that have been shown to affect regeneration, with hypothesized roles of endocrine signaling that could be involved. We then review what is known about endocrine modulators of epimorphic regeneration and propose future research directions within this field that will yield novel insights into the fundamental mechanisms of regeneration and may result in applied use in regenerative medicine. A greater understanding of the endocrine regulation of regeneration will be exceedingly useful not only for understanding the basic mechanisms of regeneration, but also as a model of how global endocrine signals integrate with local molecular and cellular pathways during development, ultimately regulating the size and form of structures.

1.1. Overview of epimorphic regeneration in vertebrates

A diversity of animals can undergo epimorphic regeneration, a replacement of complex structures through mediation of blastema cells (Carlson, 2007), including hydra, planarians, insects, crustaceans, and echinoderms, but it is limited to amphibians and lizards in vertebrates (Bely and Nyberg, 2010; Das, 2015). Across organisms, the process is divided into the similar steps (Fig. 2, (Slack et al., 2004; Whited and Tabin, 2009). Wound healing occurs within a few hours after amputation the wound epidermis forms to help minimize blood loss and reduce the amount of apoptosis at the site of injury. Immune, angiogenic and neurotrophic factors are important for establishing the initial signaling cascades needed for wound healing (Bertolotti et al., 2013). They appear to be necessary for the formation of the apical epidermal cap (AEC), which forms from the wound epithelium instead of a thickened scar (King et al., 2012; Marshall et al., 2019). The AEC organizes cellular proliferation and outgrowth, cell motility and subsequent patterning of the regenerating limb/tail (see Fig. 2). As the cells begin to proliferate, and sometimes de-differentiate, under the AEC they form a



Cellular Processes	Motility, proliferation, Apoptosis, immune response	Motility, proliferation, dedifferentition	Motility, proliferation, Differentiations, pattern formation	Motility, proliferation, apoptosis
Developmental Gene networks	Wnt,Fgf 2,	Fgf 10, 8 Wnt 3α Sall4 MMP-2	Fgf 10, 8 Wnt 3α SHH, Notch, VEGF	SHH Notch VEGF
Growth Hormones &Insulin, IGF	+Yokoyama et al 2000	+ Sato and Inoue 1973 +Tassava 1984 +Fahmy and Sicard 1998 +Desborough 2000	+ Huang and Brown 2000 +Saera-Vila et al., 2018 +Vethamany-globus and +Liversage 1973 +Forty and Liversage 1993	+Han et al., 2008
Leptin	+Frank et al., 2000 +Stallmeyer 2001 +Marikovsky et al., 2002 +Murad et al., 2003 +Love et al., 2011, 2013 +Ponormareva et al., 2015 +Chang et al 2017	+Kang et al 2016	+Kang et al 2016	
Glucocorticoids	+Mathew et al., 2007 -King et al., 2012 +Godwin et al 2012 -Mescher 2017	-Mathew et al., 2007 -King et al., 2012	-Mathew et al., 2007 -King et al 2012	
Prolactin		+Light and Jones 1967 +Tassava and Kuenzli 1979 +Maier and Singer 1981 +Liversage et al., 1984 +Ndukuba and Ramachandran 1988	+Light and Jones 1967 +Tassava and Kuenzli 1979 +Maier and Singer 1981 +Liversage et al.,1984 +Ndukuba and Ramachandran 1988	
Thyroid Hormone	+/-Gibbs et al., 2011	-Monaghan et al., 2014 -Demircan et al., 2018	-Monaghan et al., 2014 -Demircan et al., 2018 -Marshall et al., 2019	
Sex Steroids	+Horng et al., 2017 -Gilliver et al., 2017			

Fig. 2. List of endocrine factors known to affect each step of epimorphic regeneration (following Whited and Tabin, 2009 with supporting citations. The wound epidermis (green) that forms immediately after injury becomes the apical epidermal cap (AEC, red); proliferating blastemal cells (blue) differentiate during pattern formation and the outgrowth phase (yellow), which is thought to recapitulate signals involved in the de novo development of structures. Positive or enhancing effects of hormones on each stage of regeneration (empirically demonstrated or hypothesized) are indicated by a + next to references, negative or antagonizing effects of hormones are indicated by a – next to the reference. A full review of the stages and developmental pathways involved in regeneration can be found atWhited and Tabin, 2009 and Slack et al. (2004).

group of proliferating undifferentiated cells known as the blastema. Through the interactions between AEC and the cells under it, the blastema elongates along a proximo-distal axis. Patterning and cell differentiation resumes recapitulate the structure.

Even within vertebrates, however, there is variation in specific mechanisms involved in regeneration. Teleost fish have large capacity to regenerate various tissues such a heart, spinal cord and fin (Marshall et al., 2019; Singh et al., 2015) through the process of dedifferentiation and transdifferentiation (Zhang et al., 2013). In urodeles, limbs and tails can fully regenerate throughout life (Sandoval-Guzmán et al., 2014; Yokoyama et al., 2011), at least in part because a population of stem cells kept active within Schwann cells located in the spinal cord is recruited to the site of injury to allow for regeneration through the adult stage (Sandoval-Guzmán et al., 2014). By contrast, in anurans hindlimbs and tails can regenerate fully during the larval period through a process of cellular dedifferentiation at the site of injury followed by redifferentiation (Yokoyama et al., 2011), but late-staged larvae and adults lose competence for complete limb regeneration (Tanaka et al., 2016). However, *Xenopus* retain the ability to regenerate the eye/retina through transdifferentiation in adults (Yoshii et al., 2007). Though there are several ways in which cells are repopulated, these organisms still undergo the same general steps and are organized by similar developmental pathways.

Much of the current research focuses on genetic pathways and paracrine signals involved in each step of the regeneration process, which we briefly summarize here (see reviews by Lien et al. (2006), Slack et al. (2004), Whited and Tabin (2009), Yoshinari et al. (2009) for more detail). Across vertebrates, the primary signaling factors involved with blastema formation are wnt, FGF-8, and FGF-10, like those involved with *de novo* limb outgrowth (Yokoyama et al., 2011). Wnt will activate FGF-8, which will in turn activate FGF-10 creating a positive feedback loop during the formation of the AEC to help with cellular proliferation and limb patterning in later stages (Singh et al., 2015; Yokoyama et al., 2011, 2000). In anurans, Sall4 is a gene that is

involved in the reprogramming of differentiated cells into dedifferentiated cells (Neff et al., 2005). The dedifferentiated cells are likely to be derived from the population of mesenchymal cells already present at the time of amputation (Neff et al., 2005). However, as stated above, in some species of urodeles, the new population of cells proliferate from satellite stem cells, which express PAX7, SOC3, and NANOG (VENTX in *Xenopus*), that migrate into the wound area (Scerbo et al., 2014, 2012; Tanaka et al., 2016). After the patterning gradient has been reestablished, the tissues of the regenerating limb will begin to differentiate and proliferate. Several cellular determination factors, such as VEGF (blood vessels) BMP (bone and cartilage) and MyoD (muscle), appear as the cells redifferentiate. As differentiation proceeds, patterning genes associated with *de novo* limb development are expressed, such as hedgehog at the posterior margin of the blastema to establish anterior-posterior axis formation of the limb (Tamura et al., 2010).

In the following sections, we aim to bridge the gap between our understanding of the molecular mechanisms involved with regeneration with environmental and endocrine regulation to form a cohesive, organismal understanding of epimorphic regeneration. Our hope is this review will stimulate interest in studying the endocrine factors involved in regeneration and increase collaborative work between the endocrinologists, ecological physiologists and cellular/development biologists to advance our knowledge of epimorphic regeneration.

2. Ecological factors and organismal state affect regeneration

Studies describing the ecological factors that influence wound healing (reviewed in Archie, 2013) and regeneration date back to the 1970s (Table 1). Both predictable (e.g., seasonal) and unpredictable changes (e.g., toxin exposure) in the environment that influence the energetic state have been shown to affect the rate and quality of regeneration. These include food availability, temperature and photoperiod, or exposure to environmental toxins or natural stressors (e.g., predators). In addition, regeneration ability can be affected by intrinsic factors associated with reproductive condition or development stage. We propose that variation in endocrine signaling associated with life history stage or environmental conditions modulate the cellular processes involved in regeneration to either enhance or inhibit their actions, ultimately regulating the quality and tempo of regeneration (Fig. 1). Below, we discuss a subset of the ecological factors that influence the organismal state of the animal and regeneration.

First, food availability is a strong regulator of regeneration in some animals, as expected due to the energetic resources needed for the regrowth of a structure. Nutritional status is positively associated with wound healing ability (reviewed in Archie, 2013), and studies in invertebrates for example in brittle starfish, *Ophiocoma echinata*, also show that regeneration of the arm is accelerated with nutrition (Lawrence et al., 1986; Pomory and Lawrence, 1999). In amphibians, axolotl larvae have shown that low nutritional states caused a reduction in size and timing of blastema formation (Tassava, 1983). However, in lizards and salamanders, tail regeneration occurs even in low food conditions. The redbacked salamander, will regenerate its tail even when food intake is limited during the brooding of eggs (Maiorana, 1977; Yurewicz and Wilbur, 2004). Similarly, juvenile leopard geckos (*Eublepharis macularius*), will continue to allocate resources to regenerate tails in low food conditions at the cost of growth (Lynn et al., 2013; Russell et al., 2015). This may be because their fat is stored in their tails and is required for long-term nutritional maintenance and predator avoidance; but, this also suggests that regeneration is occurring independently from nutritionally regulated hormones. In addition, Mexican cavefish, *Astyanax mexicanus*, change their metabolism to allow for long periods of food scarcity in the caves which have led to their loss regenerative ability (Stockdale et al., 2018). The cavefish are not able to regenerate heart tissue after injury, which is linked to a downregulation of mitochondrial and glycolytic pathways (Stockdale et al., 2018). The energetic trade-offs between regeneration and the allocation of resources selects towards traits and processes that promote survival (Bely and Nyberg, 2010; Stearns, 1992). These studies suggest that nutritionally regulated hormones, such as growth hormone, thyroid hormone, insulin or leptin may be influencing processes involved in regeneration.

Seasonal variation in environmental factors can also affect regeneration. Seasonal fluctuations in temperature and photoperiod have been shown to alter the rate of tail regeneration in several lizard and fish species (Poss et al., 2003; Raffel et al., 2006; Stancyk et al., 1994; Stockdale et al., 2018; Tattersall et al., 2012). Regeneration, specifically blastema formation, occurs twice as fast at warm temperatures and longer photoperiods compared to animals in lower temperatures (Tattersall et al., 2012). Seasonal shortening of day length can affect metabolic rate (Tattersall et al., 2012), which could be associated with reduced regenerative ability by reducing cellular metabolism, proliferation rates, blood flow, and suppress immune responses and wound healing ability (Archie, 2013). Hormones associated with changing photoperiod, such as prolactin or thyroid hormone, could therefore modulate multiple processes involved in regeneration.

Seasonal changes in reproductive condition can also affect regeneration rates in vertebrates and invertebrates (Table 1). In some animals there appears to be an energetic trade-off that favors reproduction over regeneration (reviewed in (Maginnis, 2006). For example, female lizards (*Uta stansburiana*) in a reproductive state take twice as long to heal wound (French et al., 2007), which could result in the delay or restrict regeneration (although this was not specifically tested). Likewise, in both males and females of the freshwater crab, (*Paratelphusa hydrodromous*) claw regeneration will be delayed or suppressed during reproductive season but will occur in the non-breeding season (Devi and Adiyodi, 2019; Suma Gupta et al., 1989). By contrast, some animals exhibit an energetic trade-off that favors regeneration over reproduction. Female plethodontid salamanders (*Plethodon cinereus*, *Batrachoseps attenuatus*) will regenerate tails while either brooding eggs or during the dry season when foraging is limited, at the cost of next year's ova production (Maiorana, 1977; Yurewicz and Wilbur, 2004) or failure to breed (males and females, Maiorana, 1977). These authors attributed this pattern of resource allocation in both salamanders and geckos to the fitness benefits of having tails—as an antipredator device (i.e. tail autotomy) and organ for fat storage (Maiorana, 1977). Alternatively, resource allocation decisions might be dependent on the lifespan, with shorter-lived animals favoring allocation to reproduction over regeneration (Maginnis, 2006). In sea stars, the effect of reproductive state is mixed since some reproduce through asexual replication (see review; (Bely and Nyberg, 2010). Finally, deer antlers, a model for mammalian regeneration, regrow seasonally when testosterone levels are shorter, and photoperiod is longer (Price and Allen, 2004). These studies suggest that the effect of reproductive hormones, such as estradiol or testosterone, could modulate processes involved in regeneration, but whether the actions of hormone signaling facilitates or suppresses energetic allocation towards regeneration depend on fitness trade-offs that are specific to the life history of the animal.

Lastly, unpredictable stressful environmental conditions can affect regeneration, however the effects depend on the context and duration of the stressors (Table 1). Studies in mammals show that acute stressors can accelerate wound healing (Dhabhar, 2009), and thus could have beneficial effects on early stages of regeneration. Acute stressors event such as predation, overcrowding, heat stock or hypoxia (Table 1) can cause changes in the immune response and its factors, by increasing the number of macrophages, and T-cells at the sight of the wound (Dhabhar, 2009, 2002) (see review in Archie, 2013). Activation of the hippocampus-pituitary-adrenal (HPA) axis (i.e., increased secretion of glucocorticoids), is known to increase the number of leukocytes and enhances delayed-type hypersensitivity, which decreases the timing of wound healing (reviewed in Dhabhar, 2009). However, the overall effect of acute stressors on regeneration is difficult to predict because

Table 1
Summary of environmental factors shown to affect regeneration ability in a variety of organisms. Exposure to certain environmental factors can cause increased regeneration (up arrow), decreased regeneration (down arrow), or both in different species in the same taxon. See text for more detailed descriptions of environmental conditions and responses. *Dichlorodiphenyltrichloroethane (DDT).

Environmental Factors	Taxon	Structure	Effects on Regeneration	Sources
Nutrition	Echinoderm: *Ophiocoma echinate, Luidia clathrate*	Arm	↓	Pomory and Lawrence, 1999; Lawrence et al., 1986
	Amphibians: *Batrachoseps attenuates, Plethodon cinereus,*	Tail	unaffected	Maiorana, 1977; Tassava, 1983; Yurewicz and Wilbur, 2004
	Lizards: *Eublepharis macularius*	Tail	unaffected	Lynn et al., 2013; Russell et al., 2015
Heavy metals	Planarians: *Dugesia etrusca*	Head, Whole body	↓	Calvero et al., 1998a,b
	Crustaceans: *Uca pugilator*	Limb	↓	Weis, 1976, 1977; Weis et al., 1992
	Fish: *Fundulus heteroclitus*	Fin	↓	Weis and Weis, 1976
Insecticides: DDT	Amphibian: *Rnan pipiens, R. catesbeiana* (tadpoles)	Tail	↓	Singer, 1952; Weis, 1975
	Crustaceans: *Uca pulitor*	Limb	↓	Weis and Mantel, 1976; Weis, 1977
Salinity	Echinoderm: *Ophiophragmus filograneusOphiothrix angulate*	Arm	↓	Donarchy and Watabe, 1986; Talbot and Lawrence, 2002
	Crustacean: *Uca pugnax, Uca pugilator*	Limb	↓	Shock et al., 2009; Weis, 1976
Seasonal variation	Deer	Antlers	↓	Price and Allen, 2004
	Echinoderm: *Paratelphusa hydrodromous*		↑	Suma Gupta et al., 1989
Seasonal variation-temperature	Echinoderm: *Microphiopholis gracillima*	Arm	↑	Stancyk et al., 1994
	Amphibian: *Notophthalmus viridescens*	Limb	↑	Raffel et al., 2006; Tattersall et al., 2012; Maier and Singer 1981.
Seasonal variation-Photoperiod	Lizard: *Anolis carolinensis, Hemidactylus flaviviridis*	Tail	↑	Ndukuba and Ramachandran, 1988
	Amphibians: *Notophthalamus viridescens*	Limb	↓	Connelly et al., 1968; Schauble, 1972; Schauble and Nentwig, 1974; Schauble and Tyler, 1972' Tassava and Kuenzli, 1979; Maier and Singer 1981
	Fish: Astyanax mexicanus	Tail	↓	Stockdale et al., 2018
Hypoxic conditions	Echinoderm: *Amphiurua filiformis*	Arm	↓	Nilsson et al., 2004
Turbulent Conditions	Echinoderms: *Hemipholis elongata*	Arm	↓	McAlister and Stancyk, 2003
Stress	Zebrafish: *Danio reo*	Tail	↓	Pauline and Anna, 2019

regeneration involves continued allocation of resources to the regrowth of structures (Tassava, 1983).

Furthermore, not all stressors increase glucocorticoid levels (e.g., acute predation exposure reduces glucocorticoids in amphibian tadpoles) (Fraker et al., 2009; Pauline and Anna, 2019), and this may cause different effects on regeneration. By contrast, chronic stressors, such as exposure to heavy metals, salinity, insecticides consistently have negative effects on wound healing and regeneration (Table 1), possibly through glucocorticoid-mediated inhibition of immune function, depletion of energetic resources, or HPA-independent mechanisms. Again, depending on the relationship between regeneration and fitness, this response could vary across organisms and could vary depending on the type of stressor, although these questions have largely been unexplored (Maginnis, 2006).

Organisms often have finite resources and depending on the relationship between fitness and physiological functions, energetic or physiological trade-offs determine where resources are directed (Stearns, 1992). These studies demonstrate that physiological states and environmental conditions can modulate the rate or quality of regeneration, both positively and negatively. Hormone actions often regulate such trade-offs, but relatively few studies have explored their direct role in regeneration. While this is a large gap in our understanding of how regeneration is regulated, there is ample evidence that endocrine regulation of regeneration is important.

3. Endocrine regulation of regeneration

Endocrine signaling has been shown to play a role in each step of epimorphic regeneration (Fig. 2). In this section, we review what is known about the roles of hormones associated with growth and energy balance, including those of the growth hormone (GH)-insulin-like growth factor (IGF) axis, insulin and leptin. We then review actions of glucocorticoids, which also alter energy balance as well as immune response, followed by prolactin, thyroid hormone, and sex steroids.

3.1. Nutritionally regulated hormones

3.1.1. GH, insulin and IGFs

Growth hormone (GH) is part of the cytokine superfamily of polypeptide regulators and is produced in the pituitary gland to regulate cellular differentiation and proliferation during development to regulate overall growth and body size in vertebrates (Cannata et al., 2010). Many of its actions work through stimulating insulin, a peptide hormone secreted from beta cells in the pancreas in response to elevated glucose levels and works through the IGF1/AKT pathway to increase several growth factors, which increase cellular proliferation, cellular protection and growth (Schiaffino and Mammucari, 2011). GH secretion varies with nutritional state and developmental stage of an organism to regulate growth in vertebrates (Sun et al., 2011). Additionally, insulin regulates metabolism and knockouts of insulin in mice leads to reduced body weight, size, infertility and later life diseases such as diabetes (Fürstenberger and Senn, 2002). Insulin has also been attributed to changes in body size and nutrition-dependent growth of horns in insects (for review see Lavine et al., 2015). GH stimulates IGF-I and II secretion in the brain and liver through endocrine, neuroendocrine, and paracrine factors to regulate body size and regeneration rate (Chablais and Jaźwińska, 2012; Tassava and Kuenzli, 1979). However, previous work has shown that insulin increases regeneration in adult newts by increasing the size of the blastema, through an unknown mechanism (Foty and Liversage, 1993; Vethamany-Globus and Liversage, 1973).

Although it has not been studied in the context of epimorphic regeneration, IGF signaling could be involved in regeneration based on its' roles in early development and cancer models in mammals. Research has shown that IGF stimulates cell proliferation and increases vascular endothelial growth factor (VEGF) a marker for angiogenesis

during limb outgrowth (Linkhart et al., 1996; Rabinovsky and Draghia-Akli, 2004) and IGF binding proteins (IGFBP) act as anti-apoptotic factors to help with digit formation in mice (Allan et al., 2001). Both IGFs and IGFBPs can act as a paracrine factor and endocrine factor in the *de novo* development of limbs (Allan et al., 2001), and it is possible that they could be regulating regeneration through both signaling pathways. However, it is unknown if IGFs and IGFBPs are directly increasing blood vessel and bone formation during regeneration. Work in mice has shown that IGF increases proliferation and differentiation of osteoblast precursors and neurogenesis in the brain (Åberg et al., 2006; Linkhart et al., 1996). In various obesity-related cancers, insulin signaling stimulates the development of the cancer tissue by increasing cellular processes such as proliferation, growth, protection, and metastasis through increasing angiogenesis around the cancer tissue (Samani et al., 2007). Finally, IGFBPs have shown to decrease apoptosis of cancer cells by interacting with the immune system (Fürstenberger and Senn, 2002). Testing some of these hypotheses may show insulin acts as a growth factor to enhance regeneration and the reformation of bone tissue and blood vessels.

There is evidence that signals regulated by GH, fibroblast growth factor (FGF), and epithelium growth factor (EGF), are critical for increased proliferation, motility and cellular protection during the blastema formation in zebrafish and *Ambystoma* (Fig. 2) (Desborough, 2000; Fahmy and Sicard, 1998; Sato and Inoue, 1973; Tassava, 1983). In *Xenopus*, FGF is involved with AEC formation, which is essential for the initiation of regeneration, distal growth and reorganization of the limb (Fig. 2) (Slack et al., 2007; Yokoyama et al., 2000). FGF signaling comes from the mesenchyme and up regulates other FGF factors and wnt signaling to enhance regeneration by increasing cellular proliferation (Yokoyama et al., 2000). A clear understanding of this interaction may explain why scar tissue is formed instead of regeneration when this signaling pathway is disrupted (Yokoyama et al., 2000).

GH's role in patterning of reforming structures such as neural, muscle and bone formation are not well defined. Research in GH's influence on bone formation is limited to fractures and development in early mice models (Han et al., 2008). However, using models that can regenerate at varying degrees such as zebrafish, *Ambystoma*, and *Xenopus* we can have a better understanding of growth hormone's role during later stage regeneration *in vivo* (Gospodarowicz and Mescher, 1980; Huang and Brown, 2000). For example, IGF is necessary for re-differentiation of reprogrammed myoblast and neural retina cells as well as promoting angiogenesis in zebrafish and *Xenopus* models (Lin et al., 2017; Saera-Vila et al., 2018; Weinstein et al., 2017) and in neural regeneration of *Xenopus* (Yoshii et al., 2007). However, there are areas of research that need to be defined such as if GH works directly or indirectly on regeneration, and we need to understand potential roles of IGF binding proteins in regeneration as they are also involved in cell proliferation, cellular metabolism, migration and angiogenesis (Bach, 2017).

3.1.2. Leptin

Another hormone that could mediate nutritional regulation of regeneration is leptin, a cytokine hormone that is involved with regulation of food intake and energy balance and mediates nutritional modulation of immune function and reproduction (Ahima and Osei, 2004; Londraville et al., 2014). In both amphibians and mammals, leptin mRNA is upregulated in cells at the site of injury or amputation (Chang et al., 2017; Love et al., 2011; Murad et al., 2003; Ponomareva et al., 2015). In mammals, administration of leptin protein accelerates wound healing (Frank et al., 2000; Stallmeyer et al., 2001), while reducing leptin signaling slows wound healing (reviewed in Poeggeler et al. (2010), Love et al. (2011). Leptin upregulation is thought to be stimulated by hypoxia in ischemic cells at the wound site, and actions of leptin include increasing blood vessel formation, keratinocyte proliferation, and recruitment of immune cells and cytokine production to the site of the wound (Kang et al., 2016; Love et al., 2013, 2011; Marikovsky et al., 2002; Poeggeler et al., 2010; Stallmeyer et al., 2001). Thus, leptin might play an important role in the wound-healing phase of regeneration and given that leptin treatment also accelerates wound healing in lizard (French et al., 2011), it could be an evolutionarily conserved wound healing factor in vertebrates.

While the upregulation leptin mRNA expression at the time of tail amputation has been associated with increased cell proliferation, production of reactive oxygen species, angiogenesis and neurogenesis, studies have not yet directly connected leptin signaling with specific processes involved in regenerating tail or limb. Leptin's effects on *de novo* limb development and known cellular responses to leptin-activated JAK/STAT signaling in other contexts suggest that leptin could be modulating other aspects of regeneration (Londraville et al., 2014). Leptin administration accelerates hind limb development in food restricted anuran larvae, and it acts directly on leptin receptors expressed in the developing limb to stimulate cell proliferation (Crespi and Denver, 2006), and therefore it might play a similar role in regenerating limbs since these mechanisms overlap (Keenan and Beck, 2016). For example, JAK/STAT signaling has been shown to activate the AKT/GSK3 and MTA/Wnt pathway especially during cellular differentiation, proliferation and migration (Poeggeler et al., 2010; Yan et al., 2012). Another hypothetical role of leptin in regeneration is on neurogenesis. In ob/ob, leptin knockout, mice were born with decreased body weight and brain weight (Udagawa et al., 2006). This decrease in brain size maybe due to decreased proliferation in the neurogenic regions of the brain. In both developing mice and *Xenopus*, leptin has been shown to increase proliferation, and cellular growth, of pre-neural cells in the neurogenic zones of the brain, specifically the hypothalamus (Bender et al., 2017; Udagawa et al., 2006). In *Xenopus*, leptin promotes spinal cord regeneration by stimulating neuroprotective genes, and this could be a hypothetical role of leptin in promoting regeneration (Fernández-Martos et al., 2012). The downstream factors of leptin that increase neurogenesis in the developing brain are unknown but the WNT/b-catenin pathway may be a target of leptin signaling (Bender et al., 2017). It is unknown if the JAK/STAT or MAPK/ERK pathway regulates WNT expression to control neurogenesis, more work needs to be done confirm this hypothesis.

However, in mammalian obesity-related cancers, JAK/STAT increase angiogenesis and MAPK/ERK may have a role in immune function and neurogenesis (Guo and Gonzalez-Perez, 2011; Yamagishi et al., 2003). Leptin signaling has been shown to increase angiogenesis by upregulating VEGF, increase cellular proliferation and protection through up-regulation of interleukins and Notch pathway (Guo and Gonzalez-Perez, 2011; Yamagishi et al., 2003). These processes are conserved and have been shown to regulate morphogenesis in developing limbs (Tanaka and Umesaki, 2008). Lastly, it also has been hypothesized that leptin signaling is associated with carbohydrate metabolism needed to provide energetic substrates for rapid cellular proliferation during regeneration (Li, 2016; Love et al., 2014). Future research is needed to test the hypothesis that paracrine leptin signaling has these pleiotropic actions in the regulation of wound healing and regeneration; but because circulating concentrations of leptin vary with nutritional condition, leptin might also act as an endocrine signal that mediates condition-dependent regeneration.

3.2. Hormones that vary with season, development, and environment

3.2.1. Glucocorticoids

Glucocorticoids (GCs) are important signals that regulate energy balance, mediate changes in resource allocation during times of stress, and modulate timing of life history transitions (Crespi et al., 2013; Sapolsky et al., 2000). Upregulation of GC signaling increases the production of glucose from stored fuels during times of stress and redirects energetic resources from processes that are not essential, like reproduction, growth or development, to those that are needed to ensure survival (Bonier et al., 2009; Sapolsky et al., 2000). Specifically, in

the case of injury in mammals, an up-regulation of GC signaling increases energetic resources that can be utilized to enhance immune response and expedite wound healing (Dhabhar, 2009). Additionally, GCs increase the movement of leukocytes out of the bloodstream and to the site of the wound, decreasing the timing of the wound closure and formation of the wound epidermis (Archie, 2013; Mescher and Neff, 2004).

In amphibians, newts and zebrafish, the transition from wound healing to regeneration depends on the reduction in pro-inflammatory factors upregulated immediately after injury (King et al., 2012; Mescher et al., 2017), and injury-induced GC signaling may play an important role in allowing for this progression of regeneration because of their anti-inflammatory actions. The inhibition of inflammation that typically occurs within 24 h after injury allows for the AEC to form by reducing scarification (Godwin et al., 2013), and prevention of inflammatory cytokines by suppressing phagocyte activity (Chedid et al., 1996; King et al., 2012; Mescher et al., 2017; Sapolsky et al., 2000). In support of this hypothesis, treatment with a GR agonist for the first 24 hr after limb amputation in *X. laevis* (Nieuwkoop-Faber stage 53) inhibited regeneration, presumably because it suppressed necessary pro-inflammatory actions during this time, but treatment after this time period did not suppress regeneration (King et al., 2012). Similarly, in zebrafish larvae and adults, activation of the glucocorticoid receptor (GR) during the wound healing/blastema formation stages also inhibits tail regeneration (Mathew et al., 2007).

Morpholino knockdown of GR in zebrafish larvae prevented GC-induced inhibition of tail, suggesting that stress-induced activation of this receptor during the initial 72hr after injury prevents regeneration (Mathew et al., 2007). However, it remains unclear which necessary mechanisms for regeneration are inhibited by GR signaling, how the immune system is affected, and whether these mechanisms are similar across zebrafish and amphibians (King et al., 2012).

The inhibitory effects of chronic stressors on regeneration (see Table 1) could be mediated by persistent elevations in glucocorticoids. Chronically elevated GCs result in slower wound healing, which could slow the advancement of processes associated with regenerating tissues (Archie, 2013; Sapolsky et al., 2000; Thomas and Woodley, 2015). Indeed, chronically elevated GCs for 7 days post amputation suppress hindlimb regeneration in *X. laevis* larvae (King et al., 2012; Mescher et al., 2017). However, actions of GCs in stages of regeneration after wound healing or its interactions with other hormones that could affect regeneration (i.e., thyroid hormone) have not been explored. As with assessment of the effects of any stressors, the timing and magnitude of the GC response after injury, and whether GCs are elevated prior to injury need to be considered when investigating the effects of GC signaling on regeneration. Much more research is needed across various types, durations, and combinations of stressors to understand mechanisms and generalities of GC effects on regeneration.

3.2.2. Prolactin

Prolactin is polypeptide hormone secreted by the pituitary gland, and is an important regulator of metabolism, immune function, and possibly regeneration. Prolactin is released in the presence of β-endorphins in response to stress and growth hormones (Rossier et al., 1980), but secretion also varies with life history stage and seasons. For example, in lizards, circulating prolactin levels are positively correlated with increase temperature and photoperiod length, which have shown to enhance blastema formation after tail loss during these conditions (Maier and Singer, 1981; Ndukuba and Ramachandran, 1988). Prolactin levels vary with season and nutrition in adult newts (*Notophthalmus viridescens*) (Liversage et al., 1984), both of which has been associated with regeneration capacity. Both circulating prolactin levels and regeneration ability were reduced during shorter photoperiods when fat stores are depleted in *N. viridescens* (Liversage et al., 1984; Maier and Singer, 1981), and intraperitoneal injection of prolactin enhanced regeneration of limbs by increasing cell de-differentiation, cell density and cellular growth (Liversage et al., 1984; Maier and Singer, 1981). Prolactin also has actions through the JAK/STAT pathway during blastema formation (Tassava and Kuenzli, 1979). Research in other biomedical contexts also suggests that prolactin could enhance regeneration, as prolactin signaling increases cellular proliferation and motility in cartilage and angiogenesis in arthritic mice (Moreno-Carranza et al., 2013). These studies suggest that further exploration in *Xenopus*, axolotl or zebrafish models will undoubtedly reveal the mechanisms through which prolactin signaling affects regeneration and increase the ability to ask how seasonal variation in prolactin is affecting regeneration in non-model, ecologically interesting species.

3.2.3. Thyroid hormone

Thyroid hormone (TH) is secreted from the thyroid gland and is a potent differentiation factor and morphogen during early development in vertebrates (Marshall et al., 2017; Monaghan et al., 2014). Because *X. laevis* larvae lose the ability to fully regenerate limbs, tail and heart though in some cases, *Xenopus* are able to regenerate cardiac tissue after metamorphosis, but the ability is still being debated (Marshall et al., 2017, 2019), when thyroid hormone levels increase during metamorphosis, and this ability is reduced even further after metamorphosis (Beck et al., 2009; Marshall et al., 2019; Monaghan et al., 2014; Yokoyama et al., 2011), it is an excellent comparative model for mammals to study why some mammals lose their regenerative ability as they age.

In all vertebrates, TH is an important morphogenic hormone during early development. In amphibians TH signaling drives morphogenic changes during metamorphosis (Fort et al., 2007), by, converting the non-bioactive form of TH, thyroxin (T4), to tri-iodo-thyronine (T3), which can activate its two nuclear receptors, TRα and TRβ, to cause changes in gene expression involved in cellular differentiation, bone ossification, apoptosis, and keratinization of skin (Buchholz et al., 2006). It is hypothesized that activation of these programs stimulate terminal differentiation might prevent cells from being able to de-differentiation into precursors that can recapitulate the signaling necessary for full regeneration (Marshall et al., 2017, 2019). Supporting this hypothesis, experimental induction of metamorphosis in axolotls with TH treatment reduces regenerative capacity by reducing the number of proliferating cells in the blastema and the ability to recapitulate limb patterning and sarcomeric structuring in the heart (Demircan et al., 2018; Monaghan et al., 2014). However, thyroid hormone signaling is very complex especially during metamorphosis. Researchers will have to be very careful about studying regulation of tissue specific regeneration based on the complexity of this system.

TH can also interact indirectly to regulate regeneration through the immune system, and production of reactive oxygen species (ROS). Studies show that in the process of metamorphosis, rapid increases in TH signaling synergizes with increased GCs to cause apoptosis of immune cells and down-regulate immune function (Bonett et al., 2010; Rollins-Smith, 1998). As described above, given that pro-inflammatory immune response is necessary for regeneration (King et al., 2012), increased TH signaling could affect the ability to regenerate. Additionally, thyroxin levels increase ROS signaling, which at low doses increases basal cellular metabolism, and at high doses increases apoptosis (Johnson et al., 2013). Recent studies show that ROS is very important for increasing immune response after amputation to have better wound healing for regeneration (Love et al., 2013; Romero et al., 2018). ROS has been shown to increase FGF and WNT expression, which as stated above, is very important in the formation of the AEC and blastema (Love et al., 2013; Romero et al., 2018).

Another mechanism through which TH signaling could inhibit competency for limb regeneration is via the specific effect of TH on nerve regeneration. Nerve regrowth is a major part of limb regeneration: nerves need to grow into the regenerated limb, and injured nerves secrete specific factors that direct multiple aspects of limb regeneration

(reviewed in Pirotte et al. (2016). If the motor neurons leading to the limbs are severed prior to amputation, limbs cannot fully regenerate because specific nerve derived signals are not released (Kumar and Brockes, 2012), and conversely, increasing innervation in limbs enhances patterning formation of regenerating limbs, leading to more successful regeneration (Mitogawa et al., 2018). Neurons are also involved in directing blood vessel formation in developing appendages (Mukouyama et al., 2002) and could play a similar role during regeneration (Love et al., 2011). Competence for spinal cord regeneration is also lost in *X. laevis* after metamorphosis, and TH treatment on larval spinal cord nerves prevents full regeneration (Gibbs et al., 2011). Therefore, if TH signaling causes a loss of competency of nerves to regenerate at the site of limb injury, then the entire limb might not be able to fully regenerate. However, TH stimulates neurogenesis in fetuses, and other studies show positive effects of TH signaling on post-injury peripheral and sensory nerve regeneration, especially when it is administered locally (reviewed in Barakat-Walter and Kraftsik (2018). As post-natal development continues there is a rise in TH expression and a decrease of cell proliferation especially in the CNS as it matures (Hadj-sahraoui et al., 2000). These changes in TH expression with peak expression after birth are similar to metamorphosis in *Xenopus*(Sachs and Buchholz, 2017). Thus, studying the TH actions on nerve regeneration in *Xenopus* could give us insights into mammal's loss of regeneration ability with age (Méndez-Olivos et al., 2017).

3.2.4. Sex steroids

To our knowledge, the effects of sex steroids on epimorphic regeneration has not been well studied, but there is evidence that these hormones affect wound healing (Horng et al., 2017). Estrogenic signaling generally has positive effects on wound healing by enhancing the production of pro-inflammatory cytokines and accelerating re-epithelization by increasing collagen production in the skin (Horng et al., 2017). By contrast, androgen signaling generally delays wound healing (French et al., 2007; Gilliver et al., 2007), although the effects of both of these hormones depend on context and species (e.g., chronic stress) (Bandeira et al., 2015; Price and Allen, 2004). Furthermore, sex steroids can influence the differentiation and behavior of several types of stem cells (Arvidson et al., 2011; Lee et al., 2016). In deer, testosterone is converted to estrogen at the tip and base of the antler (Price and Allen, 2004). Increase in testosterone levels decreases proliferation of multipotent cells and causes them to differentiate into osteoblasts (Price and Allen, 2004). However, progesterone has shown to be an enhancer of regeneration, in *Xenopus*, exogenous progesterone was shown to increase limb patterning in post-metamorphic frogs (Herrera-rincon et al., 2018). Given the differences in regeneration abilities when animals are in breeding vs. non-breeding condition described above, sex steroid signaling is likely mediating these differences to some degree. Future research could also determine whether there are sex differences in wound healing and regeneration abilities.

4. Conclusions and opportunities for research

The main goal that regenerative medicine is trying to achieve is complete epimorphic regeneration and while understanding molecular mechanisms involved in the process of regeneration is important, it does not explain the varying degrees of regeneration quality, timing, or differences in regenerative ability depending on extrinsic or intrinsic factors (Slack et al., 2004). We have discussed many examples of how the ability to regenerate structures varies with environmental conditions, both predictable (i.e., seasonal) and unpredictable (e.g., food availability, exposure to toxins), reproductive state or life history stage in diverse species, and presented links to endocrine mediators of this variation. However, in most cases specific mechanisms of action of endocrine signals have not been identified and relatively few endocrine signals have been studied in this context. Research that explores the endocrine regulation of regeneration in model organisms, such as *Xenopus*, *Ambystoma* and zebrafish, are essential for identifying mechanisms involved at each stage of the regeneration process, and future work in these systems is imperative to understand how regeneration occurs within the context of the living organism, where endocrine signals intersect with local cellular processes. For example, Zhang et al. (2018) characterized the importance of melanocortin receptor 4 signaling on *Xenopus* limb and mouse digit regeneration, implicating alpha-melanocyte-stimulating hormone (α-MSH) signaling in regeneration. In this case, local and neurotrophic actions of α-MSH were identified, showing that classic endocrine signals could play constitutive roles in regeneration as a paracrine factor, and this could be the case for many other hormones (e.g., leptin). However, it is also important to study how food intake or photoperiod affect or development stage alter endocrine α-MSH signaling when we think about how this factor regulates regeneration in physiological contexts.

There are multiple ways an understanding of the actions of endocrine signaling in regeneration can be applied to regenerative medicine. The use of hormones that enhance regenerative ability can be applied to improve protocols in which pluripotent stem cell (IPSC) lines are created, including IPSCs derived from progenitor cells to enhance regeneration (Chen et al., 2017). Given that less than 1% of the cells collected will be viable as IPSCs mostly due to cell apoptosis and a lack of proliferation (Medvedev et al., 2010), endocrine enhancers could greatly improve this rate and increase cost-efficiency. Also, given the pleiotropic nature of endocrine signaling, endocrine enhancers of regeneration, such as leptin or IGF-1, can be applied to the generation of therapies that promote regeneration in organs/structures containing heterogenous cell types, including blood vessels and neurons. For example, currently doctors use the abdominal pocket method to increase vascularization of injured digits prior to reanastomosis to enhance healing and functional outcome of digit tip replantation (Sawai et al., 2016). Knowledge of generalized factors that enhance vascularization found within these abdominal pockets, such as several endocrine factors described above, that could be topically applied might enhance replantation outcome while removing the risk of infections caused by abdominal surgery. Also, when considering the design for *in vivo* treatments in patients to promote regeneration, knowledge of endocrine factors that positively and negatively influence wound healing and regeneration that are specific to sex, age, season could inform therapies to optimize tissue repair and regrowth.

Study of the endocrine regulation of regeneration in both vertebrates and invertebrates can also address interesting questions in ecology and evolution. First, examining environmental effects on regeneration provides excellent opportunities to increase our understanding of endocrine-mediated energetic/physiological trade-offs (Das, 2015; French et al., 2011). As we describe, the priority of resource allocation to regeneration varies between life history stages when animals are faced with environmental stressors, and these trade-offs are ultimately determined by fitness consequences of these allocation decisions, or in the case of novel stressors, whether species have evolved adapted responses. Studies investigating the endocrine regulation of regeneration under different environmental conditions will increase our understanding the impact of anthropogenic stressors on the health and viability of animals with regenerative ability. By making inter-specific comparisons, we can resolve different endocrine mechanisms that allow one species to allocate resources regeneration when experiencing food restriction while other species do not. These studies can test proximate and ultimate hypotheses about why some animals can regenerate while others cannot (Bely and Nyberg, 2010) and will undoubtedly reveal novel mechanisms involved in regeneration that have yet to be described, and thus, contribute to biomedical applications as well.

Acknowledgements

We thank Lindsey Marshall, Robyn Reeve, and Grace Curtis for providing comments that have greatly improved this manuscript.

Competing interests

The authors declare no competing or financial interests.

Funding

This work was supported by a grant from Sigma Xi to MRE, KE, and a Washington State University Seed Grant award to EJC.

Author contributions statement

All authors contributed equally to the collection of papers and the formation of ideas presented in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygcen.2019.113220.

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