Local problems need global solutions: The metabolic needs of regenerating organisms

Ines C. Kübler, MSc#1, Jenny Kretzschmar, MSc#2, Marko Brankatschk, PhD3, Tatiana Sandoval-Guzmán, PhD4,5
1Center for Regenerative Therapies Dresden, Technische Universität Dresden, Dresden, Germany
2MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Cambridge, UK
3Department of Molecular, Cell and Developmental Biology, Technische Universität Dresden, Dresden, Germany
4Department of Internal Medicine III, Center for Healthy Aging, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
5Paul Langerhans Institute Dresden of Helmholtz Centre Munich, University Clinic Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

# These authors contributed equally to this work.

Abstract

The vast majority of species that belong to the plant or animal kingdom evolved with two main strategies to counter tissue damage—scar formation and regeneration. Whereas scar formation provides a fast and cost-effective repair to exit life-threatening conditions, complete tissue regeneration is time-consuming and requires vast resources to reinstall functionality of affected organs or structures. Local environments in wound healing are widely studied and findings have provided important biomedical applications. Less well understood are organismic physiological parameters and signalling circuits essential to maintain effective tissue repair. Here, we review accumulated evidence that positions the interplay of local and systemic changes in metabolism as essential variables modulating the injury response. We particularly emphasise the role of lipids and lipid-like molecules as significant components long overlooked.

Keywords

insulin; lipids; metabolism; regeneration; systemic response

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Correspondence to: Marko Brankatschk; Tatiana Sandoval-Guzmán.

Correspondence: Tatiana Sandoval-Guzmán, Department of Internal Medicine III, Centre for Healthy Aging, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; tatiana.sandoval_guzman@tu-dresden.de; Marko Brankatschk, Department of Molecular, Cell and Developmental Biology, Technische Universität Dresden, Dresden, Germany; marko.brankatschk@tu-dresden.de.

Conflict of Interest

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1 Introduction

The functional restoration of damaged or lost tissues by trauma or disease is an integral component of life and widespread across species. Some animals, like salamanders, possess the unique ability to regenerate an entire limb in a few weeks. Other species like planarians and cnidarians even regenerate an entire body. In contrast, most vertebrates evolved to rapidly repair damages that expose the organism to external hazards. Such repair may result in non-functional tissue replacements and the formation of a fibrous matrix called a scar.¹

Regeneration in mammals is observed vastly in tissues with high proliferative potential and resident stem cell populations—the liver, blood or intestinal epithelium. Furthermore, decline or depletion of the resident stem cell pool (e.g., due to aging), affects cellular turnover and the regenerative potential.²

While the extent of regeneration and the timing differs from organ to species, there is a clear need for (1) new building blocks: amino acids, sugars, lipids and nucleic acids, (2) signals to orchestrate the process and (3) energetic fuel to accomplish it. Despite this, little is known on how a regenerating organism regulates its metabolism. Furthermore, and often overlooked, regeneration should not be seen as an isolated process, but rather influenced by the circumstances of the organism at a particular time and place. For example, a salamander that spends at least 6-9 weeks re-making a whole limb, should rebalance its metabolic homeostasis to adapt to this long-term energy demand. However, it remains a mystery how a local injury shifts the energy resources and how the organism modulates it.

Animal and vegetal species regenerate through different mechanisms (reviewed elsewhere,³–⁷) and this evolutionary diversity underlines regeneration as a basic biological property in living organisms. One common initial mechanism is re-epithelization of the wound, to seal the organisms from the external environment. Some organisms go further and form a specialised wound epidermis (WE).⁸ The WE is a multi-layered epithelium, functioning as an important signalling centre during subsequent steps like the formation of a temporal structure called the blastema. The blastema is a highly proliferative cell mass, containing the dedifferentiated cells, as well as recruited resident stem cells which can give rise to all cell types needed for regeneration of the missing body part. Planarians, teleost fish, salamanders, reptiles and mammals among others, regenerate lost body parts through a blastema. In models where the blastema is absent, persistent active migration and proliferation are crucial for the re-formation of the missing structure. However, the requirement of energy to regenerate tissues and complex structures is a common ground.

Although the regulation of blastema formation and pattern configuration is well studied, less is known about how other variables including environment and internal milieu affect the rate and quality of regeneration.⁹ Seasonal climate and food availability are important examples of external cues with a defining influence on the physiology of an organism. While internally, an organism balances energy to contend with age, reproduction status, nutrition and stress.¹⁰
In this review, we emphasise the—even less studied—interplay of regeneration and the recruitment of energy resources during a sustained repair. To use energy efficiently, an organism in need of a sudden high amount of energy to regenerate, will require a hierarchized process to maintain energy homeostasis. Understanding how this is done would help us understand how regeneration incompetent organisms could benefit from an adequate metabolism management.

2 Basic Systemic Regulation Of Metabolism

To maintain energy availability in all tissues, a vast network of regulatory checkpoints ensures homeostasis. Upon food ingestion, the main role of the digestive system is to obtain lipids, carbohydrates, proteins, minerals and vitamins. Although there is a significant interest in sugar and amino acid traffic, more recent work has re-started to look into lipids and uncovering novel roles in metabolism and signalling. \(^{11–13}\) First, the nutritional flow is regulated by intestinal cells after food ingestion. To obtain energy from the dietary components, complex dietary carbohydrates, protein and lipids, are broken down to ease their intestinal absorption, cellular transport and secretion into circulation. Nutritional flow continues with nutrient transport across barrier cells to reach cells of targeted tissues. In vertebrates, organs responsible for the regulation of metabolic homeostasis such as the liver, adipose tissue, pancreas and various glands, directly regulate the availability and use of nutrients and modulate anabolic or catabolic turnover. For the brain to exert control of homeostasis, integration of peripheral information is required. First, by direct innervation of these organs (e.g., direct innervation of the gut), the release of humoral factors into the bloodstream (e.g., leptin release by adipose tissue and insulin) and by the activity of dietary signal cues (e.g., glucose). \(^{10}\) Neural circuits sense and respond to the above-mentioned inputs, by commandeering adjustments that will keep a balance between energy intake and energy expenditure. In the arcuate and paraventricular nuclei of the hypothalamus, neurons sitting in a highly vascularized area, directly sense nutrients and circulating hormones. In turn, proopiomelanocortin neurons (POMC) inhibit food intake and increase energy expenditure, or neuropeptide Y neurons (NPY) will direct food intake and inhibit energy expenditure (reviewed in Myers et al., \(^{10}\)). In addition, anabolic or catabolic turnover in dedicated storage organs (e.g., adipose tissue and liver) buffer the systemic availability of all essential cues required to allow optimal cellular functionality. These organs can also be regulated centrally, for example, sympathetic neurons stimulate the activity of adipocytes amplifying catabolic turnover to free fatty acids (FAs) from stores. \(^{14}\) While the storage of glucose (in the form of glycogen) is limited to small quantities, most energy resources are stored as fat in lipid droplets. Lastly, energy balance is influenced by other physiological systems such as the reproductive and stress axis (reviewed elsewhere \(^{9}\)), and as proposed in this manuscript, by injury signals.

3 Metabolic Response And Adaptation In Injury

3.1 The injury message

The nervous, immune and circulatory systems convey and process information from the injury site. These systems are well studied independently, however, the interaction of
multiple systems and interorgan communication is gaining attention. The central nervous
system collects injury-related information via soluble factors, direct receptors that sense
mechanical, thermal or chemical damage, or by directly regulating ion channels in nerve
terminals. Specialised sensory neurons (nociceptors) detect stimuli that cause tissue damage
and convey the information via the afferent neurons through the spinal cord, and then to the
thalamus. The thalamus relays signals to the higher brain centres (the cerebral cortex), where
the information is processed and results in an action (withdrawal from the stimulus), pain
modulation and stress reaction (reviewed elsewhere).

Injury-induced release of reactive oxygen species (ROS), triggers the first immune response
recruiting inflammatory cells. Further immune system responds to damage-associated
molecular patterns (DAMPs), released by damaged or dying cells, to ensure asepsis of the
wound. Additionally, bacteria, pathogen-associated molecular patterns (PAMPs), metabolic
by-products and cytokines also trigger an inflammatory response necessary to mobilise
resources and restore homeostasis (reviewed elsewhere). However, when an exacerbated
response to a major injury is not controlled, secondary organ damage can occur even
in locations remote from the injury, known as injury-associated systemic inflammatory
response.

Other less explored elements are locally released factors (e.g., metabolites) that enter the
bloodstream. Together with DAMP signalling, such direct communication axes are able
to convey injury signals into a systemic response and allow bidirectional communication
between the site of injury and other body parts. Despite being well known that metabolites
act as efficient signalling molecules, only little is known about the role of those locally
released factors in wound repair and regeneration. However, it is likely that the interplay
between the injured tissue, the immune system and the nervous system, is at least influenced
by the various chemicals and metabolites produced locally.

### 3.2 Metabolic response to injury

Data from patients with severe trauma supports a significant metabolic re-adjustment. After
injury, the organism responds with a switch to a catabolic state and hypermetabolism
(elevated resting energy expenditure). In this situation, skeletal muscle is catabolised to
support protein synthesis and, interestingly, the administration of nutrients is not sufficient
to revert the catabolic state. In trauma patients with coma, hypermetabolism still
occurs, suggesting that movement or awareness of the patient is not the cause. Moreover,
metabolism after severe trauma is characterised by high cortisol, insulin resistance and
hyperglycemia. Prolonged hyperglycemia and hypermetabolism has adverse effects for
the healing process and could lead to further infections and even multiorgan failure. The
type of injury is unlikely to be a determinant for a metabolic systemic response. For
example, the resting metabolic rate is increased in patients with brain injury, burns and in
skeletal trauma.

### 3.3 Insulin

It is difficult to predict or compare the severity of the triggered hypermetabolism, as there is
no comprehensive study analysing different types of injury and normalising for the severity
of the trauma. A common denominator is however an acute insulin resistance, which seems to be unique to injury and likely to be the result of multiple factors. In patients with significant skin burns, the early phase post injury (hours) is characterised by high glucose levels and almost no response from the insulin signalling cascade. In a later phase (days and later) insulin levels rise, but blood glucose levels decrease only moderately, and heterotopic fat in various cell types including muscle and liver cells is observable. From the medical point of view, persistently high insulin reflects insulin resistance. In patients with brain trauma, metabolic dysfunction of brain cells adds to the damage, in the form of insulin resistance and decreased glucose uptake in undamaged brain areas, but also as a systemic effect. In a rat burn model, injury mimics the hyperglycemia and insulin resistance in patients. This response occurs as fast as 30-60 min after injury when trauma is combined with haemorrhage and helps to consolidate the response. In a rat model of surgical injury and haemorrhage, insulin signalling (IS) is affected in skeletal muscle as soon as 60 min post-surgery, reflected as a rapid decrease of AKT phosphorylation and insulin receptor function. Insulin resistance and hyperglycemia in turn, affect immune cells, favouring an inflammatory immune response. However, the interconnectivity and causation between insulin resistance, hyperglycemia and inflammation needs to be further investigated. In a tour de force study that mimics traumatic brain injury in Drosophila, Katzenberger et al., observe hyperglycemia in hemolymph and suggest that intestinal barrier dysfunction is a secondary trait triggered by injury.

As dysregulation of IS has a direct impact on the patient’s recovery, there is a need to control alternations of insulin signalling resulting from injuries. Furthermore, the effects of IS on cellular decisions are evident. Glucose levels and IS are essential for stem cell division rates of Drosophila intestinal stem cells. The intestinal stem cell niche is formed by different cell types including visceral muscle cells. These cells produce the Drosophila insulin-like peptide 3 (DILP3) in response to intestinal damage and the availability of a calorie-rich diet. DILP3 is sufficient to promote stem cell division and its localised reduction minimises regenerative activity. Finally, diseases affecting metabolism (such as Diabetes) complicate the healing process including non-metabolic organs like brain, bones.

### 3.4 Other humoral factors

Further evidence of a complex systemic response to injury is shown by Khallaf et al. The recovery of patients with traumatic brain injury (TBI), bone injury or concomitant TBI and bone injury was investigated. The group with combined injury showed accelerated bone healing, suggesting that humoral factors are involved. Indeed, an increase in growth hormone at 3 weeks after injury in the combined group is observed. In addition, an important systemic response to injury is the activation of the hypothalamic-pituitary-adrenal axis. Elevated corticosteroid levels were shown in patients of all groups. Moreover, within 24 h post injury in the group with the concomitant injury, a high concentration of the food intake and satiety regulator leptin was demonstrated. In support of a systemic effect, in a mouse model lacking leptin, the positive effect of the concomitant injury on bone healing is decreased.
Others have shown that traumatic head injury increases the release of insulin-like growth factor 1 (IGF-1)\textsuperscript{39} and parathyroid hormone\textsuperscript{40} in circulation that could further explain the accelerated healing of bone. In addition, human and animal injury models have confirmed the consistent increase in cortisol in response to injury.\textsuperscript{41}

Why these humoral factors are secreted is not fully understood, however, the consequences are various. For example, it has been proposed that insulin resistance and hyperglycemia are cortisol-induced. Although recent evidence shows that blocking the increase of cortisol in a rat injury model, does not prevent insulin resistance in the liver.\textsuperscript{25}

### 3.5 Cellular mTOR signalling

The target of rapamycin (mTOR) regulates cell growth and metabolism through phosphorylation of kinases such as protein kinase C (PKC) and protein kinase B (AKT), and interacting with other subunits, it forms two functional complexes, mTORC1 and mTORC2. In response to nutrient availability, mTOR is activated in different injured tissues\textsuperscript{42,43} The role of mTOR in skeletal muscle injury has been described as necessary. In the absence, or by blocking mTOR, muscle stem cells (satellite cells) fail to activate and proliferate.\textsuperscript{43,44} Rodgers et al. showed that mouse muscle injury on one side of the body triggers quiescent muscle stem cells on the contralateral side to enter an alert state, via mTOR.\textsuperscript{45} In addition, mTOR is required during tissue regeneration in planarian and zebrafish by regulating stem cell activation and blastema outgrowth.\textsuperscript{46,47} In salamanders, a subset of cells in the contralateral limb from an amputated animal, also express mTOR in response to limb regeneration.\textsuperscript{48}

One possibility to explain a systemic response via mTOR is the fact that mTOR is merged with insulin signalling via the AKT-Ser473. In fact, mTORC1 is an effector of the insulin/PI3K pathway that promotes lipid synthesis, glycolysis and nucleotide synthesis.\textsuperscript{49} Moreover, activated AKT promotes the localization of the glucose transporter GLUT1 at the plasma membrane, ushering the cellular uptake of the sugar.\textsuperscript{50} Enhanced GLUT1-mediated glucose uptake is one prominent example of growth factor induced nutritional flow untethering cells from the regulation of whole-body glucose homeostasis.\textsuperscript{51}

To fill local metabolic needs of healing tissues, a rather complex local and systemic regulatory network sets off to coordinate energy expenditure and availability. We are now starting to understand how a sustained healing, and highly proliferative process such as epimorphic regeneration, can maintain an active source of available fuel.

### 4 Bridge Keystones: Connecting Metabolic Regulators

#### 4.1 Epimorphic regeneration

Epimorphic regeneration is characterised by anabolic metabolism; it requires building blocks and local metabolic adaptations to regrow the lost appendage. The highly proliferative cells of the forming blastema are associated with a metabolic switch to a more embryonic-like metabolic state. In lizard and *Xenopus* tadpole tail regeneration, blastema cells increase glycolysis and hexose monophosphate pathways.\textsuperscript{52,53} Similarly, in zebrafish metabolic reprogramming to high glucose uptake and lactate production (known as Warburg effect)
is necessary for tail regeneration, and it is associated with the hexosamine biosynthetic pathway HBP and N-linked glycosylation.\textsuperscript{54}

Proteomic analysis has shown a decrease of several enzymes of the citric acid cycle and oxidative phosphorylation in both regenerating \textit{Xenopus} and axolotl.\textsuperscript{55} The regenerative environment is generally characterised by a local increase in reactive oxygen species (ROS) within hours post-amputation.\textsuperscript{53,54} ROS are produced as a byproduct of mitochondrial oxidative phosphorylation causing cell damage or by NADPH oxidases, particularly NOX2, enhancing immune defence and cell signalling functions.\textsuperscript{56} ROS are speculated to mediate glucose entry into glycolysis and the pentose phosphate pathway metabolism and to play a role in mammalian axonal regeneration through the NOX2-PI3K-p-AKT signalling pathway.\textsuperscript{53,57}

These findings are supported by an increase in hypoxia-inducible factor 1-alpha (HIF1\(\alpha\)) activity induced by high ROS levels.\textsuperscript{58} HIF1\(\alpha\) is a transcriptional master regulator that among many functions, induces the expression of VEGF, a key regulator of vasculogenesis and angiogenesis. In zebrafish and other vertebrates, vascularization of damaged heart tissue is one prerequisite to induce regeneration.\textsuperscript{59} This underlines how the vascular distribution, and thus oxygen and nutrient supply, during regeneration is intertwined with metabolism and stem cell function. Other less understood examples of ROS-induced tissue remodelling in response to wounding are reported in plants and flies. Plant leaves reconnect the wounded area shortly after tissue damage and an intense ROS production has been reported.\textsuperscript{60,61} Similarly, in the regenerating Drosophila gut, ROS induces vascular remodelling.\textsuperscript{62} Epimorphic regeneration also requires long-range factors like hormones that are locally upregulated. Notably, a local increase in the orexigen leptin and its receptor have been shown to enhance bone formation and healing of skin wounds.\textsuperscript{63–65} Although the role of circulating factors on leptin expression in the wound is not fully understood, there is evidence that cultured human fibroblasts secrete leptin in response to insulin.\textsuperscript{66} A further crosstalk with insulin signalling is observed intracellularly: leptin induces PI3K/AKT signalling, sharing the molecular cascade with the insulin receptor. At the injury site however, leptin is increased within early stages of \textit{Xenopus} tail blastema and axolotl limb regeneration.\textsuperscript{67,68} It remains to be defined how the locally secreted leptin impacts neighbouring tissues or systemic leptin function.

Earlier studies have shown that salamander blastema cell proliferation and survival in vitro and in vivo depend on the combined presence of several hormones, like insulin or growth hormone (GH).\textsuperscript{69,70} Insulin, proinsulin and insulin-like growth factor (IGF) are upregulated in tail regeneration and are required for blastema cell proliferation\textsuperscript{71} and heart regeneration in zebrafish.\textsuperscript{72} Insulin/IGF-1 signalling activates downstream pathways that enhance cell survival, proliferation and differentiation through MAPK signalling, and PI3K-AKT signalling. This leads to lower injury-induced hyperglycemia, protection against elevated ROS and angiogenesis.\textsuperscript{70} Thus, insulin/IGF axis not only regulates energy balance, it also plays an important local role activating growth, osteogenesis, angiogenesis and stem cell survival.
Alpha melanocyte stimulating hormone (α-MSH) and its receptor melanocortin receptor 4 (MC4R) impact epimorphic regeneration both locally and systemically. α-MSH, a cleaved peptide from the precursor POMC, is released into circulation from neurons in the hypothalamus. Recently, it was shown in *Xenopus* limb regeneration, that α-MSH/MC4R were increased in blastema in a nerve dependent manner, and blocking the signalling of MC4R impairs regeneration. Using a crude hypothalamic injury, the authors observe a similar impact on regeneration, arguing for a local and systemic role for MC4R. Local α-MSH/MC4R signalling regulates ROS levels, ensures mitochondrial stress balancing the rate of glucose metabolism and promotes neurotrophic functions within blastema cells. Furthermore, MC4R knockout mice fail to regenerate the digit tip, while systemic α-MSH administration rescues regeneration in heterozygous mice. When applied in a proximal and regeneration incompetent digit amputation, α-MSH stimulates regeneration.

Additional important factors linking metabolism and regeneration can be found in Table 1. Summarising, the local regenerative environment is characterised by changes in energy metabolism, in particular affecting glucose metabolism and IS. Evidence suggests that in addition, other systemic factors are crucial for epimorphic regeneration, likely induced by yet-unknown local key modifiers.

5 Lipids In Regeneration: The Unexplored Shore

5.1 Lipid circulation

In many animal species the bulk of endogenous lipids which enter circulation are produced by cells functionally analogous to intestinal cells, adipocytes or hepatocytes. All these cell types are able to secrete lipoprotein particles, systemic lipid carriers, or lipidated proteins destined to spread their lipid loads within the organism. The production of lipoprotein-lipid carriers is limited in type and location. Cells facilitate the uptake of lipoproteins or other lipid carriers initiating receptor mediated transport. These receptors belong to conserved protein families and their expression patterns are regulated by many factors including cell type, circadian rhythm and nutritional state. Stem cells are known to express different lipoprotein and albumin receptors (another major lipidated protein in circulation). It is likely that dividing cells in regenerating tissues require adequate lipids to facilitate their proliferation rates. Although most cell types are capable of producing lipid building blocks, such as FAs, to preserve time and energy lipids are absorbed from circulation. Animals absorb many dietary lipids; however, blood serum lipids represent a mixture of food lipids and endogenous lipids. The following sections are focused on bioactive lipids and lipid-like molecules of different origin.

5.2 Lipid and lipid-like cues in metabolism

Plants and some animal species rely on a steady nutritional flow to regenerate efficiently. However, plants are characterised by indeterminate post-embryonic development and the source for (re) generation of new organs are shoot or root stem cell niches—the so-called apical meristems. It is debated if these meristem cells are equivalent to stem cells in animals and if (re)growth of plants can be compared to animal regeneration. However, processes like the complete restoration of root-tips astonishingly mimic in many aspects the limb regeneration process in animals (reviewed...
in References 105,106). This highlights that despite mechanisms involved in regeneration between plants and animals that are likely to be different, the overall concepts and principles might be closely related and comparable. Remarkably, plants are able to absorb lipids from soil and are capable of long-range lipid transport, but it remains unclear to what extent and for which purpose plants possibly distribute lipids systematically.107,108

In the past years, metabolic research retook the focus on the metabolic activity of dietary lipid-like molecules and lipids. Lipid-like vitamins, such as A, D and E, are essential to many animals and their biochemical properties allow such compounds to integrate into cellular membranes (Figure 1). As such, these vitamins are in direct contact with membrane lipids capable of interacting with the latter.107 For instance, the antioxidant vitamins E and A are believed to scavenge free radicals and thus, to protect the functional integrity of cellular membranes as well as to promote plasma membrane repair.109–112 In plants, vitamins regulate systemic metabolism and growth6 and interestingly, most media used in plant organ regeneration are supplemented with a range of these bioactive compounds. Although the vitamins A and E are enriched in many plant species, virtually nothing is known about their contribution in plant regeneration. Animals need to absorb vitamin A and E, and these two vitamins have very different biological roles. Vitamin A often gets converted into retinoic acid (RA). RA has many targets including genes involved in mediating canonical antioxidant responses, or nuclear retinoid receptors involved in the regulation of many systemic parameters including the glucose-lipid homeostasis.113,114 Moreover, it is known that RA is essential for patterning during salamander limb regeneration115 mediating the proximodistal specification in salamander limb regeneration.116,117 Furthermore, antagonising the retinoic acid receptors disrupts skeletal patterning and skeletogenesis during regeneration.118 In zebrafish, RA regulates proliferation and is required for blastema formation,119 as well as in heart regeneration, where injury-triggered RA controls cardiomyocyte proliferation.120 Not surprisingly, blocking the rate-limiting enzyme Raldh2, inhibits regeneration in zebrafish.121 Vitamin E is an important antioxidant and protects polyunsaturated fatty acids (PUFAs) in cellular membranes from oxidative destruction.122 PUFAs reduce ROS species efficiently, limiting the range of such signalling.123 Hence, vitamin E indirectly modulates metabolic rates since membrane integrated PUFAs shift the signalling capacity of many signalling pathways and the local lipid composition likely modulates vascularization. Studies suggest an inhibitory effect of vitamin E on liver regeneration in rats by altering the lipid peroxidation in the cytosol and plasma membranes.124 In contrast, vitamin D promotes regeneration of zebrafish fin125 and heart126 tissues as well as human skeletal muscle repair, and is necessary for skeletal tissue integration in salamander limb regeneration.127 Dietary lipids are capable of modulating the metabolism of consumers.128 Essential fatty acids (EFAs) are precursors for the generation of endogenous complex lipids acting as signalling molecules (e.g., PIPs), or can directly induce metabolic signals.129 In humans, EFAs need to be absorbed from food. Most studies focus on plant derived n-3 and n-6 omega FAs with a carbon chain length of 18-20 atoms, such as alpha-linolenic acid or linoleic acid (Figure 1). In regenerating organisms, EFAs contribute in several instances, including inhibition of oxidative stress,130 analgesic and anti-inflammatory properties.131 For instance, n-3 PUFAs are known to promote regeneration of several tissues such as muscles,132 liver
cells, nervous system and endothelial cells. This list is by no means exhaustive, but demonstrates the broad target range of n-3 PUFAs. In contrast, n-6 PUFAs seem to inhibit the reparative potential of n-3 PUFAs. Nevertheless, some studies suggest that the chain length is another critical factor that modulates the bioactive potential of these lipids. For instance, in some plants very long FAs prevent the formation of regenerating tissue. Other examples are studies in rodents that report long EFAs promoting regeneration of various cell types and short saturated fatty acids (SSFAs) produced by intestinal microbes. Absorbed by host organisms, SSFAs are suggested to play many roles including regulating insulin signalling. The ratio between dietary SFAs/PUFAs changes the absorption rate of nutritional cues and metabolic rates, impacting on many parameters including lipid turnover (reviewed in References 140,141).

5.3 Endogenous signalling lipids linkup with the insulin signalling cascade

A less studied set of molecules in the context of repair are endogenous lipids regulating metabolic signalling cascades. However, what we currently know poses them as an important player. Starving organisms lower their metabolic rates and many enter dormancy-like states to endure long periods of food deprivation. Nevertheless, some species maintain their regenerative capacity despite none or insufficient food consumption. It appears that fasting or fasting mimicking diets can sensitise metabolic pathways and promote regeneration. For instance, in response to food deprivation, adipose tissues in mice produce and secrete lipid signalling cues named PAHSAs (Palmitic acid esters of hydroxystearic acid). Some PAHSA-lipid species promote insulin release into the blood system. However, dietary supplementation of these lipids had no effect on IS. Fasting also changes the activity of neuronal subsets wired with organs responsible for the redistribution of nutritional molecules. For example, free FAs that induce signalling in hypothalamic neurons or glia. Starving cells dismantle endogenous complex lipids to fill energy demands and produce free FAs fit for mitochondrial reduction. Free FAs activate neurons wired with hepatocytes and in response, the liver cells start to release hepatic glucose into the blood system, essential to maintain basic blood-glucose levels. Another factor important to facilitate IS are sterol levels, as the activity of the mammalian insulin receptor depends on membrane sterols. Extending the concept to sterol auxotrophs, dietary sterol yields could prove essential for IS and cell proliferation rates. Sterols are precursor molecules for the synthesis of many steroids and steroid hormones. Moreover, in plants, Drosophila and murine models it was shown that the activity of insulin producing cells is dependent on steroid hormones. In addition, steroids regulate the expression of insulin binding proteins that deactivate the hormone. In sterol auxotrophs, the quality of steroid hormones is defined by the identity of dietary sterols, however, steroids production is sex specific. Indeed, in humans, steroids are responsible to modulate sex-specific insulin sensitivity and regeneration potential in muscle.

Taken together, the role of endogenous lipid cues potentially reaches far beyond the conservation and distribution of energy. We propose that endogenous lipid cues produced in response to metabolic changes are important factors regulating IS during regeneration.
Therefore, we single out such lipid cues as rewarding targets to our understanding of systemic metabolism in the context of regeneration.

6 Outlook

6.1 Nutrition: Food and feeding behaviour

Absorbed dietary lipids can induce metabolic signalling, are structural units integrated into membranes which results in altered cellular bio-physical properties (Figure 1) and provide energy. Thus, the regenerative potential of tissues could profit from the quality and quantity of ingested lipids. In addition, dietary vitamins, sugars and proteins represent additional nutritional factors, especially since excess sugars are converted into lipids. However, the nutritional quality and flow are age dependent, as food preference, feeding frequency and energy management change with age. Nutritional changes potentially modulate the regeneration capability, as an example, salamanders, after a severe period of starvation can still form a blastema but fail to re-grow the limb (Figure 2).

The extraction of nutrients from ingested food is also dependent on the intestinal food transition time and on the activity of intestinal microbes. Many examples are known about intestinal microbes producing metabolites capable of modulating the metabolic rate of the host. Especially the microbial fermentation of dietary fibres results in the production of short fatty acids that regulate physiological values such as blood pressure, nutritional absorption, modulate behavioural variables and to change the host metabolic rates. All these parameters are important for adjusting screws directly or indirectly controlling the regenerative potential.

6.2 Regeneration: Systemic metabolic cues

We have provided relevant literature of multiple factors that circulate and reach areas distant to the injury site. This systemic response modulates cellular decisions with impactful consequences. While currently we lack the direct connections from the local response to the systemic response, it is possible to speculate that such signals are designed to craft a network of inter-organ communication and orchestrate a systemic adaptation.

Such messenger molecules can range from simple turnover metabolites, such as lactate, to specialised proteins produced specifically in response to tissue repair. Another possibility are factors that participate in homeostasis and then upon injury, acquire a transient role. One example of the latter category is leptin. It is certainly interesting to consider if leptin released by regenerating tissues hijacks the canonical leptin signalling and increases circulating lipid levels, while promoting healing locally.

6.3 Regeneration: Invasive microbes and microbiota

Tissue injury is often associated with microbial contamination and thus, an acceleration of the host immune-system activity is inevitable. The intensity of the immune response depends on many factors including the type of invading microbes, microbial products, infected area and wound closure. Interestingly, some elements produced by activated immune cells modulate systemic metabolic rates likely to redirect nutritional flows.
Hence, the immune response associated with extensive tissue damage could represent a critical metabolic switch, instructive in the decision to initiate tissue repair by regeneration or perhaps scar formation.

The immune and metabolic systems greatly benefit from the symbiosis of microbes in the homeostasis of organisms, and how they could have a remote effect on regeneration is a fascinating new aspect that is gaining deserved attention.\textsuperscript{170} In particular, microbiota could influence systemic inflammation and indirectly, insulin resistance in humans.\textsuperscript{171}

6.4 Regeneration: Biomedical implications

The modulation of the nutritional flow represents a plausible field to potentiate regenerative tissue repair. Therapeutic interventions at different levels focusing on bioactive dietary lipids and acute glucose homeostasis are imperative. Another therapeutic level to foster regeneration are strategies aiming at the physiology of affected organisms. More invasive methods are ideas involving targeted stimulation of organs key for metabolic controls (e.g., liver/adipose tissue) or microbial treatments aiming to optimise nutritional absorption, potentiate the immune response or provide microbial metabolites catalyzing metabolic signalling. In addition, ongoing research on insulin signalling and the metabolic shift of immune and stem cells close to tissue damage may result in therapeutic strategies including patients suffering from metabolic diseases like Diabetes.

6.5 Final remarks

In this review we have investigated the possibility that systemic metabolism is one key variable to promote regenerative tissue repair. We propose that regenerating cells do not simply rely on local signalling cues and sufficient nutritional provision, but actively influence other tissues responsible for the mobilisation of molecular building blocks, such as lipids. Future coordinated studies into the topic across different species will reveal conserved molecular mechanisms key to formulate biomedical strategies aiming to improve wound healing.

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References

1. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med. 2014; 6: 1–16.

2. Spehar K, Pan A, Beerman I. Restoring aged stem cell functionality: current progress and future directions. Stem Cells. 2020; 38: 1060–1077. [PubMed: 32473067]

3. Vogg MC, Galliot B, Tsiaris CD. Model systems for regeneration: Hydra. Development (Cambridge, England). 2019; 146 dev177212-10 [PubMed: 31676551]

4. Ivankovic M, Haneckova R, Thommen A, et al. Model systems for regeneration: planarians. Development. 2019; 146 dev167684-12 [PubMed: 31511248]

5. Marques II, Lupi E, Mercader N. Model systems for regeneration: zebrafish. Development. 2019; 146 dev167692-13 [PubMed: 31540899]

6. Tomar RS. Role of vitamins in plant growth and their impact on regeneration of plants under in vitro condition. Int J Res Appl Sci Eng Technology. 2018; 6: 423–426.

7. Birnbaum KD, Alvarado AS. Slicing across kingdoms: regeneration in plants and animals. Cell. 2008; 132: 697–710. [PubMed: 18295584]

8. Aztekin C. Tissues and cell types of appendage regeneration: a detailed Look at the wound epidermis and its specialized forms. Front Physiol. 2021; 12 771040 [PubMed: 34887777]

9. Easterling MR, Engbrecht KM, Crespi EJ. Endocrine regulation of epimorphic regeneration. Endocrinology. 2019; 160: 1–12. [PubMed: 30535329]

10. Myers MG, Affinati AH, Richardson N, Schwartz MW. Central nervous system regulation of organismal energy and glucose homeostasis. Nat Metab. 2021; 3: 737–750. [PubMed: 34158655]

11. Capolupo L, Khven I, Lederer AR, et al. Sphingolipids control dermal fibroblast heterogeneity. Science. 2022; 376 eabh1623 [PubMed: 35420948]

12. Zhu W, Zhang M, Chang L, et al. Characterizing the composition, metabolism and physiological functions of the fatty liver in Rana omeimontis tadpoles. Front Zool. 2019. 1–17. [PubMed: 30675174]

13. Mauricio T, Aveiro S, Guedes S, et al. Multi-omic profiling of macrophages treated with phospholipids containing Omega-3 and Omega-6 fatty acids reveals complex immunomodulatory adaptations at protein, lipid and metabolic levels. Int J Mol Sci. 2022; 23 2139 [PubMed: 35216253]

14. Bartness TJ, Liu Y, Shrestha YB, Ryu V. Neural innervation of white adipose tissue and the control of lipolysis. Front Neuroendocrinol. 2014; 35: 473–493. [PubMed: 24736043]

15. Choi S-I, Hwang SW. Depolarizing effectors of bradykinin signaling in nociceptor excitation in pain perception. Biomol Ther. 2018; 26: 255–267.

16. Yam MF, Loh YC, Tan CS, Adam SK, Manan NA, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018; 19 2164 [PubMed: 30042373]

17. Niethammer P, Grabher C, Look AT, Mitchison TJ. A tissue-scale gradient of hydrogen peroxide mediates rapid wound detection in zebrafish. Nature. 2009; 459: 996–999. [PubMed: 19494811]

18. Cooke JP. Inflammation and its role in regeneration and repair: a caution for novel anti-inflammatory therapies. Circ Res. 2019; 124: 1166–1168. [PubMed: 30973815]

19. Niethammer P. The early wound signals. Curr Opin Genet Dev. 2016; 40: 17–22. [PubMed: 27269791]

20. Frankenfield D. Energy expenditure and protein requirements after traumatic injury. Nutr Clin Pract. 2016; 21: 430–437.

21. Lord JM, Midwinter MJ, Chen Y-F, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. The Lancet. 2014; 384: 1455–1465.

22. Cuthbertson DP. Post-shock metabolic response. Lancet. 1942; 239: 433–437.

23. Mansoor O, Beafrere B, Boirie Y, et al. Increased mRNA levels for components of the lysosomal, Ca2+—activated, and ATP-ubiquitin-dependent proteolytic pathways in skeletal muscle from head trauma patients. Proc Natl Acad Sci USA. 1996; 93: 2714–2718. [PubMed: 8610106]
24. Li L, Messina JL. Acute insulin resistance following injury. Trends Endocrinol Metab. 2009; 20: 429–435. [PubMed: 19800814]
25. Li L, Thompson LH, Zhao L, Messina JL. Tissue-specific difference in the molecular mechanisms for the development of acute insulin resistance after injury. Endocrinology. 2009; 150: 24–32. [PubMed: 18801909]
26. Faisy C, Guerot E, Diehl J-L, Labrousse J, Fagon J-Y. Assessment of resting energy expenditure in mechanically ventilated patients. Am J Clin Nutr. 2003; 78: 241–249. [PubMed: 12885704]
27. Cree MG, Wolfe RR. Postburn trauma insulin resistance and fat metabolism. Am J Physiol-Endocrinol Metab. 2008; 294: E1–E9. [PubMed: 17957035]
28. Giza CC, Hovda DA. The neurometabolic cascade of concussion. J Athl Train. 2001; 3: 228–235.
29. Royes LFF, Gomez-Pinilla F. Making sense of gut feelings in the traumatic brain injury pathogenesis. Neurosci Biobehav Rev. 2019; 102: 345–361. [PubMed: 31102601]
30. Sugita H, Kaneki M, Sugita M, Yasukawa T, Yasuhara S, Martyn JAJ. Burn injury impairs insulin-stimulated Akt/PKB activation in skeletal muscle. Am J Physiol-Endocrinol Metab. 2005; 288: E585–E591. [PubMed: 15536206]
31. Thompson LH, Kim HT, Ma Y, Kokorina NA, Messina JL. Acute, muscle-type specific insulin resistance following injury. Mol Med. 2008; 14: 715–723. [PubMed: 19009015]
32. Leffler M, Hrach T, Stuerzl M, Horch RE, Herndon DN, Jeschke MG. Insulin attenuates apoptosis and exerts anti-inflammatory effects in endotoxemic human macrophages. J Surg Res. 2007; 143: 398–406. [PubMed: 17583747]
33. Aljada A, Ghanim H, Saadeh R, Dandona P. Insulin inhibits NFkappaB and MCP-1 expression in human aortic endothelial cells. J Clin Endocrinol Metab. 2001; 86: 450–453. [PubMed: 11232040]
34. Katzenberger RJ, Chitarbanova S, Rinkus SA, Fischer JA, Kaur G, Seppala JM, Swanson Swanson LC, Zajac JE, Ganetzky B, Wassarman DA. Death following traumatic brain injury in Drosophila is associated with intestinal barrier dysfunction. Elife. 2015; 4: 1–24.
35. O’Brien LE, Soliman SS, Li X, Bilder D. Altered modes of stem cell division drive adaptive intestinal growth. Cell. 2011; 147: 603–614. [PubMed: 22036568]
36. Napoli N, Conte C, Pedone C, et al. Effect of insulin resistance on BMD and fracture risk in older adults. J Clin Endocrinol Metab. 2019; 104: 3303–3310. [PubMed: 30802282]
37. Khallaf FG, Kehinde EO, Hussein S. Bone healing and hormonal bioassay in patients with Long-bone fractures and concomitant head injury. Med Princ Pract. 2016; 25: 336–342. [PubMed: 26954661]
38. Seemann R, Graef F, Garbe A, et al. Leptin-deficiency eradicates the positive effect of traumatic brain injury on bone healing: histological analyses in a combined trauma mouse model. J Musculoskelet Neuronal Interact. 2018; 18: 32–41. [PubMed: 29504576]
39. Mangiola A, Vigo V, Anile C, Bonis PD, Marziali G, Lofrese G. Role and importance of IGF-1 in traumatic brain injuries. Biomed Res Int. 2015; 2015 736104 [PubMed: 26417600]
40. Cadosch D, Gautschi OP, Thyer M, et al. Humoral factors enhance fracture-healing and callus formation in patients with traumatic brain injury. J Bone Jt Surg. 2009; 91: 282–288.
41. Xiu F, Stanojcic M, Diao L, Jeschke MG. Stress hyperglycemia, insulin treatment, and innate immune cells. Int J Endocrinol. 2014; 2014: 1–9.
42. He J, Chen J, Wei X, et al. Mammalian target of rapamycin complex 1 signaling is required for the dedifferentiation from biliary cell to Bipotential progenitor cell in zebrafish liver regeneration. Hepatology. 2019; 70: 2092–2106. [PubMed: 31136010]
43. Ge Y, Wu A-L, Warnes C, et al. mTOR regulates skeletal muscle regeneration in vivo through kinase-dependent and kinase-independent mechanisms. Am J Physiol-Cell Physiol. 2009; 297: C1434–C1444. [PubMed: 19794449]
44. Zhang P, Liang X, Shan T, et al. mTOR is necessary for proper satellite cell activity and skeletal muscle regeneration. Biochem Biophys Res Commun. 2015; 463: 102–108. [PubMed: 25998386]
45. Rodgers JT, King KY, Brett JO, et al. mTORC1 controls the adaptive transition of quiescent stem cells from G0 to GAlert. Nature. 2014; 510: 393–396. [PubMed: 24870234]
46. Hirose K, Payumo AY, Cutie S, et al. Evidence for hormonal control of heart regenerative capacity during endothermy acquisition. Science. 2019; 45 eaar2038-10
47. Tu KC, Pearson BJ, Alvarado AS. TORC1 is required to balance cell proliferation and cell death in planarians. Dev Biol. 2012; 365: 1–12. [PubMed: 22426104]

48. Johnson K, Bateman J, DiTommaso T, Wong AY, Whited JL. Systemic cell cycle activation is induced following complex tissue injury in axolotl. Dev Biol. 2018; 433: 461–472. [PubMed: 29111100]

49. Wei X, Luo L, Chen J. Roles of mTOR signaling in tissue regeneration. Cell. 2019; 8: 1075

50. Beg M, Abdullah N, Thowfeik FS, Altorki NK, McGraw TE. Distinct Akt phosphorylation states are required for insulin regulated Glut4 and Glut1-mediated glucose uptake. Elife. 2017; 6 e26896 [PubMed: 2859878]

51. Carvalho KC, Cunha IW, Rocha RM, et al. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. Clinics. 2011; 66: 965–972. [PubMed: 2180860]

52. Alibardi L. Histochemical, biochemical and cell biological aspects of tail regeneration in lizard, an amniote model for studies on tissue regeneration. Prog Histochem Cytochem. 2014; 48: 143–244. [PubMed: 2438787]

53. Love NR, Ziegler M, Chen Y, Amaya E. Carbohydrate metabolism during vertebrate appendage regeneration: what is its role? How is it regulated? Bioessays. 2013; 36: 27–33. [PubMed: 2426488]

54. Sinclair JW, Hoying DR, Bresciani E, et al. The Warburg effect is necessary to promote glycosylation in the blastema during zebrafish tail regeneration. npj Regen Med. 2021; 6: 55. [PubMed: 3451854]

55. Rao N, Jhamb D, Milner DJ, et al. Proteomic analysis of blastema formation in regenerating axolotl limbs. BMC Biol. 2009; 7: 83–25. [PubMed: 19948009]

56. Bishop TF, Beck CW. Bacterial lipopolysaccharides can initiate regeneration of the Xenopus tadpole tail. Iscience. 2021; 24 103281 [PubMed: 34765912]

57. Hervera A, Virgiliis FD, Palmisano I, et al. Reactive oxygen species regulate axonal regeneration through the release of exosomal NADPH oxidase 2 complexes into injured axons. Nat Cell Biol. 2018; 1-18: 1098.

58. Ryu JM, Lee HJ, Jung YH, Lee KH, Han HJ. Regulation of stem cell fate by ROS-mediated alteration of metabolism. Int J Stem Cells. 2015; 8: 24–35. [PubMed: 26019752]

59. Marín-Juez R, Marass M, Gauvrit S, et al. Fast revascularization of the injured area is essential to support zebrafish heart regeneration. Proc Natl Acad Sci USA. 2016; 113: 11237–11242. [PubMed: 27647901]

60. Soares NC, Wojtkowska J, Jackson PA. A proteomic analysis of the wound response in Medicago leaves reveals the early activation of a ROS-sensitive signal pathway. J Proteomics. 2011; 74: 1411–1420. [PubMed: 21440688]

61. Minibayeva F, Kolesnikov O, Chasov A, et al. Wound-induced apoplastic peroxidase activities: their roles in the production and detoxification of reactive oxygen species. Plant Cell Environ. 2009; 32: 497–508. [PubMed: 19183290]

62. Perochon J, Yu Y, Aughey GN, Medina AB, Southall TD, Cordero JB. Dynamic adult tracheal plasticity drives stem cell adaptation to changes in intestinal homeostasis in drosophila. Nat Cell Biol. 2021; 23: 485–496. [PubMed: 33972729]

63. Tadokoro S, Ide S, Tokuyama R, et al. Leptin promotes wound healing in the skin. PLoS One. 2015; 10 e0121242-e0121216 [PubMed: 25799398]

64. Zhou BO, Yue R, Murphy MM, Peyer JG, Morrison SJ. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. Stem Cell. 2014; 15: 154–168.

65. Stallmeyer B, Kämpfer H, Pfeilschifter J, Frank S, Podda M, Kaufmann R. A novel keratinocyte mitogen: regulation of leptin and its functional receptor in skin repair. J Invest Dermatol. 2001; 117: 98–105. [PubMed: 11442755]

66. Glasgow A, Kiess W, Anderegg U, Berthold A, Bottner A, Kratzsch J. Expression of leptin (Ob) and leptin receptor (Ob-R) in human fibroblasts: regulation of leptin secretion by insulin. J Clin Endocrinol Metab. 2001; 86: 4472–4479. [PubMed: 11549696]

67. Love NR, Chen Y, Bonev B, et al. Genome-wide analysis of gene expression during Xenopus tropicalis tadpole tail regeneration. BMC Dev Biol. 2011; 11: 70. [PubMed: 22085734]
68. Knapp D, Schulz H, Rascon CA, et al. Comparative transcriptional profiling of the axolotl limb identifies a tripartite regeneration-specific gene program. PLoS One. 2013; 8 e61352 [PubMed: 23658691]

69. Vethamany-Globus S, Liversage RA. Effects of insulin insufficiency on forelimb and tail regeneration in adult Diemictylus viridescens. J Embryol Exp Morphol. 1973; 30: 427–447. [PubMed: 4586766]

70. Vethamany-Globus S, Liversage RA. The relationship between the anterior pituitary gland and the pancreas in tail regeneration of the adult newt. J Embryol Exp Morphol. 1973; 1-12: 415–426.

71. Chablais F, Jazwinska A. IGF signaling between blastema and wound epidermis is required for fin regeneration. Development. 2010; 137: 871–879. [PubMed: 20179093]

72. Huang Y, Harrison MR, Osorio A, et al. Igf signaling is required for cardiomyocyte proliferation during zebrafish heart development and regeneration. PLoS One. 2013; 8 e67266 [PubMed: 23840646]

73. Zhang M, Chen Y, Xu H, et al. Melanocortin receptor 4 signaling regulates vertebrate limb regeneration. Dev Cell. 2018; 46: 397–409. e5 [PubMed: 30130530]

74. Xu H, Zhang H, Fang Y, et al. Activation of the Melanocortin-4 receptor signaling by α-MSH stimulates nerve-dependent mouse digit regeneration. Cell Regen. 2021; 10: 1–11. [PubMed: 33385259]

75. Thomson SE, Charalambous C, Smith C-A, et al. Microtopographical cues promote peripheral nerve regeneration via transient mTORC2 activation. Acta Biomater. 2017; 60: 220–231. [PubMed: 28754648]

76. Gauron C, Rampon C, Bouzaffour M, et al. Sustained production of ROS triggers compensatory proliferation and is required for regeneration to proceed. Sci Rep UK. 2013; 3 2084

77. Amcheslavsky A, Jiang J, Ip YT. Tissue damage-induced intestinal stem cell division in drosophila. Cell Stem Cell. 2009; 4: 49–61. [PubMed: 19128792]

78. Hsu H-J, Drummond-Barbosa D. Insulin levels control female germline stem cell maintenance via the niche in drosophila. Proc Natl Acad Sci USA. 2009; 106: 1117–1121. [PubMed: 19136634]

79. Magadum A, Ding Y, He L, et al. Live cell screening platform identifies PPARδ as a regulator of cardiomyocyte proliferation and cardiac repair. Cell Res. 2017; 27: 1002–1019. [PubMed: 28621328]

80. Anderson SP, Yoon L, Richard EB, Dunn CS, Cattley RC, Corton JC. Delayed liver regeneration in peroxisome proliferator-activated receptor-α-null mice. Hepatology. 2002; 36: 544–554. [PubMed: 12198646]

81. zu Reckendorf SM, Brand C, Pedro MT, Hegler J, Schilling CS, Lerner R, Bindila L, et al. Lipid metabolism adaptations are reduced in human compared to murine Schwann cells following injury. Nat Commun. 2020; 11: 2123. [PubMed: 32358558]

82. Fajardo VM, Feng I, Chen BY, et al. GLUT1 overexpression enhances glucose metabolism and promotes neonatal heart regeneration. Sci Rep UK. 2021; 11: 8669.

83. Chen F, Zhou J, Li Y, et al. YY 1 regulates skeletal muscle regeneration through controlling metabolic reprogramming of satellite cells. EMBO J. 2019; 38 e99727 [PubMed: 30979776]

84. Caldez MJ, Hui NV, Koh HWL, et al. Metabolic remodeling during liver regeneration. Dev Cell. 2018; 47: 425–438. e5 [PubMed: 30344111]

85. Chen Z, Downing S, Tzanakakis ES. Four decades after the discovery of regenerating islet-derived (Reg) proteins: current understanding and challenges. Front Cell Dev Biol. 2019; 7: 235. [PubMed: 31696115]

86. Xie G, Yin S, Zhang Z, et al. Hepatocyte peroxisome proliferator-activated receptor α enhances liver regeneration after partial hepatectomy in mice. Am J Pathol. 2019; 189: 272–282. [PubMed: 30448405]

87. Liu H-X, Fang Y, Hu Y, Gonzalez FJ, Fang J, Wan Y-JY. PPARβ regulates liver regeneration by modulating Akt and Erk signaling. PLoS One. 2013; 8 e65644 [PubMed: 23823620]

88. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes 1. Endocrinology. 1999; 140: 1630–1638. [PubMed: 10098497]
89. Wei Y, Wang L, Clark JCM, Dass CR, Choong PFM. Elevated leptin expression in a rat model of fracture and traumatic brain injury. J Pharm Pharmacol. 2008; 60: 1667–1672. [PubMed: 19000372]

90. Mazur E, Benková E, Friml J. Vascular cambium regeneration and vessel formation in wounded inflorescence stems of Arabidopsis. Sci Rep UK. 2016; 6: 33754

91. Kotsis T, Nastos C, Stamatis K, et al. Insulin metabolism and assessment of hepatic insulin extraction during liver regeneration. A study in a rat model. J Invest Surg. 2018; 33: 1–8. [PubMed: 29733751]

92. Jernås M, Olsson B, Sjöholm K, et al. Changes in adipose tissue gene expression and plasma levels of adipokines and acute-phase proteins in patients with critical illness. Metabolism. 2009; 58: 102–108. [PubMed: 19059537]

93. Starostová Z, Gvoždík L, Kratochvíl L. An energetic perspective on tissue regeneration: the costs of tail autotomy in growing geckos. Comp Biochem Physiol A Mol Integr Physiol. 2017; 206: 1–25. [PubMed: 28087330]

94. Ambrosi TH, Scialdone A, Graja A, et al. Adipocyte accumulation in the bone marrow during obesity and aging impairs stem cell-based hematopoietic and bone regeneration. Cell Stem Cell. 2017; 20: 771–784. e6 [PubMed: 28330582]

95. Sinha I, Sakhivvel D, Varon DE. Systemic regulators of skeletal muscle regeneration in obesity. Front Endocrinol. 2017; 8: 29.

96. Olsen AS, Sarras MP, Intine RV. Limb regeneration is impaired in an adult zebrafish model of diabetes mellitus: induced diabetes mellitus impairs limb regeneration. Wound Repair Regen. 2010; 18: 532–542. [PubMed: 20840523]

97. der Horst DJV, Roosendaal SD, Rodenburg KW. Circulatory lipid transport: lipoprotein assembly and function from an evolutionary perspective. Mol Cell Biochem. 2009; 326: 105–119. [PubMed: 19130182]

98. Weisiger R, Gollan J, Ockner R. Receptor for albumin on the liver cell surface may mediate uptake of fatty acids and other albumin-bound substances. Science. 1981; 211: 1048–1051. [PubMed: 6258226]

99. Kornilova ES. Receptor-mediated endocytosis and cytoskeleton. Biochemistry (Moscow). 2014; 79: 865–878. [PubMed: 25385015]

100. Palmisano BT, Zhu L, Eckel RH, Stafford JM. Sex differences in lipid and lipoprotein metabolism. Mol Metab. 2018; 15: 45–55. [PubMed: 29858147]

101. Zhang J, Nuebel E, Daley GQ, Koehler CM, Teitell MA. Metabolic regulation in pluripotent stem cells during reprogramming and self-renewal. Cell Stem Cell. 2012; 11: 589–595. [PubMed: 23122286]

102. Lindsay SM, Jackson JL, Forest DL. Morphology of anterior regeneration in two spionid polychaete species: implications for feeding efficiency. Invertebr Biol. 2008; 127: 65–79.

103. de Oliveira DN, Christoforetti RA, Barreto RE. Feeding behavior of a crab according to Cheliped number. PLoS One. 2015; 10 e0145121 [PubMed: 26682546]

104. Sena G, Wang X, Liu H-Y, Hofhuis H, Birnbaum KD. Organ regeneration does not require a functional stem cell niche in plants. Nature. 2009; 457: 1150–1153. [PubMed: 19182776]

105. Ikeuchi M, Favero DS, Sakamoto Y, et al. Molecular mechanisms of plant regeneration. Annu Rev Plant Biol. 2019; 70: 1–30. [PubMed: 31035825]

106. Laux T. The stem cell concept in plants. Cell. 2003; 113: 281–283. [PubMed: 12732137]

107. Guelette BS, Benning UF, Hoffmann-Benning S. Identification of lipids and lipid-binding proteins in phloem exudates from Arabidopsis thaliana. J Exp Bot. 2012; 63: 3603–3616. [PubMed: 22442409]

108. Benning UF, Tamot B, Guelette BS, Hoffmann-Benning S. New aspects of phloem-mediated long-distance lipid signaling in plants. Front Plant Sci. 2012; 3: 53. [PubMed: 22639651]

109. Atkinson J, Harrout T, Wassall SR, Stillwell W, Katsaras J. The location and behavior of α-tocopherol in membranes. Mol Nutr Food Res. 2010; 54: 641–651. [PubMed: 20166146]

110. Ulatowski L, Thakur V, Manor D, Parker R. Vitamin E protects against PUFA-induced behavioral and motor deficits (596.8). FASEB J. 2014; 28
111. Ciaccio M, Valenza M, Tesoriere L, Bongiorno A, Albiero R, Livrea MA. Vitamin a inhibits doxorubicin-induced membrane lipid peroxidation in rat tissues in vivo. Arch Biochem Biophys. 1993; 302: 103–108. [PubMed: 8470886]

112. Howard AC, McNeil AK, McNeil PL. Promotion of plasma membrane repair by vitamin E. Nat Commun. 2011; 2: 597. [PubMed: 22186893]

113. Blaner WS, Shmarakov IO, Traber MG. Vitamin a and vitamin E: will the real antioxidant please stand up? Annu Rev Nutr. 2021; 41: 1–27. [PubMed: 34115517]

114. Francis GA, Fayard E, Picard F, Auwerx J. Nuclear receptors and the control of metabolism. Annu Rev Physiol. 2003; 65: 261–311. [PubMed: 12518001]

115. Maden M. Vitamin-a and pattern-formation in the regenerating limb. Nature. 1982; 295: 672–675. [PubMed: 7057925]

116. Monaghan JR, Maden M. Visualization of retinoic acid signaling in transgenic axolotls during limb development and regeneration. Dev Biol. 2012; 368: 63–75. [PubMed: 22627291]

117. Crawford K, Stocum DL. Retinoic acid coordinately proximalizes regenerate pattern and blastema differential affinity in axolotl limbs. Development. 1988; 102: 687–698. [PubMed: 3168786]

118. Nguyen M, Singhal P, Piet JW, et al. Retinoic acid receptor regulation of epimorphic and homeostatic regeneration in the axolotl. Development. 2017; 144: 601–611. [PubMed: 28087637]

119. Blum N, Begemann G. Retinoic acid signaling controls the formation, proliferation and survival of the blastema during adult zebrafish fin regeneration. Development. 2012; 139: 107–116. [PubMed: 22096078]

120. Kikuchi K, Holdway JE, Major RJ, et al. Retinoic acid production by endocardium and epicardium is an injury response essential for zebrafish heart regeneration. Dev Cell. 2011; 20: 397–404. [PubMed: 21397850]

121. Mathew LK, Sengupta S, Franzosa JA, et al. Comparative expression profiling reveals an essential role for Raldh2 in Epimorphic regeneration. J Biol Chem. 2009; 284: 33642–33653. [PubMed: 19801676]

122. Raederstorff D, Wyss A, Calder PC, Weber P, Eggersdorfer M. Vitamin E function and requirements in relation to PUFA. Br J Nutr. 2015; 114: 1113–1122. [PubMed: 26291567]

123. Schöpf J, Wojtczak L. Fatty acids as modulators of the cellular production of reactive oxygen species. Free Radic Biol Med. 2008; 45: 231–241. [PubMed: 18482593]

124. Trejo-Solís C, de Sánchez VC, Aranda-Fraustro A, Sánchez-Sevilla L, Gomez-Ruíz C, Hernández-Muñoz R. Inhibitory effect of vitamin E administration on the progression of liver regeneration induced by partial hepaetectomy in rats. Lab Invest. 2003; 83: 1669–1679. [PubMed: 14615420]

125. Chen A, Han Y, Poss KD. Regulation of zebrafish fin regeneration by vitamin D signaling. Dev Dyn. 2021; 250: 1330–1339. [PubMed: 33064344]

126. Han Y, Chen A, Umansky K-B, et al. Vitamin D stimulates cardiomyocyte proliferation and controls organ size and regeneration in zebrafish. Dev Cell. 2019; 48: 853–863. e5 [PubMed: 30710373]

127. Vieira WA, Wells KM, Milgrom R, McCusker CD. Exogenous vitamin D signaling alters skeletal patterning, differentiation, and tissue integration during limb regeneration in the axolotl. Mech Dev. 2018; 153: 1–9. [PubMed: 30096415]

128. Brankatschk M, Dunst S, Nemetschke L, Eaton S. Delivery of circulating lipoproteins to specific neurons in the Drosophila brain regulates systemic insulin signaling. Elife. 2014; 3: 13–19.

129. Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an Omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell. 2010; 142: 687–698. [PubMed: 20813258]

130. Firat O, Makay O, Yeniay L, Gokce G, Yenisey C, Coker A. Omega-3 fatty acids inhibit oxidative stress in a rat model of liver regeneration. Ann Surg Treat Res. 2017; 93: 1–10. [PubMed: 28706885]

131. Silva RV, Oliveira JT, Santos BLR, et al. Long-chain Omega-3 fatty acids supplementation accelerates nerve regeneration and prevents neuropathic pain behavior in mice. Front Pharmacol. 2017; 8: 723. [PubMed: 29089890]
132. Tachtsis B, Camera D, Lacham-Kaplan O. Potential roles of n-3 PUFAs during skeletal muscle growth and regeneration. Nutrients. 2018; 10: 309. [PubMed: 29510597]

133. Yang Y, Shao C, Zhang W, et al. Omega-3 polyunsaturated fatty acids prevent progression of liver fibrosis and promote liver regeneration after partial hepatectomy in cirrhotic rats. Eur Rev Med Pharmacol. 2019; 23: 10151–10160.

134. Gladman SJ, Huang W, Lim S-N, et al. Improved outcome after peripheral nerve injury in mice with increased levels of endogenous α-3 polyunsaturated fatty acids. J Neurosci Off J Soc Neurosci. 2012; 32: 563–571.

135. Lee MYK, Cai Y, Wang Y, et al. Differential genomic changes caused by cholesterol- and PUFA-rich diets in regenerated porcine coronary endothelial cells. Physiol Genomics. 2012; 44: 551–561. [PubMed: 22454453]

136. Dyall SC. Interplay between n-3 and n-6 Long-Chain polyunsaturated fatty acids and the endocannabinoid system in brain protection and repair. Lipids. 2017; 52: 885–900. [PubMed: 28875399]

137. Shang B, Xu C, Zhang X, Cao H, Xin W, Hu Y. Very-long-chain fatty acids restrict regeneration capacity by confining pericycle competence for callus formation in Arabidopsis. Proc Natl Acad Sci USA. 2016; 113: 5101–5106. [PubMed: 27092001]

138. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016; 7: 189–200. [PubMed: 26963409]

139. Sanna S, Zuydam NR, Mahajan A, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019; 51: 600–605. [PubMed: 30778224]

140. Mensink RP, Temme EH, Hornstra G. Dietary saturated and trans fatty acids and lipoprotein metabolism. Ann Med. 1994; 26: 461–464. [PubMed: 7695873]

141. Legrand P, Rioux V. The complex and important cellular and metabolic functions of saturated fatty acids. Lipids. 2010; 45: 941–946. [PubMed: 20625935]

142. Gutierrez-Gutierrez O, Felix DA, Salvetti A, et al. Regeneration in starved planarians depends on TRiC/CCT subunits modulating the unfolded protein response. EMBO Rep. 2021; 22 e52905 [PubMed: 34190393]

143. Honeycutt NR, Pomory CM. Effects of salinity and feeding on arm regeneration in the starfish *Luidia clathrata* (Say, 1825) (Echinodermata: Asteroidea). Mar Freshw Behav Phys. 2019; 52: 1–15.

144. Cheng C-W, Villani V, Buono R, et al. Fasting-mimicking diet promotes Ngn3-driven β-cell regeneration to reverse diabetes. Cell. 2017; 168: 775–788. e12 [PubMed: 28235195]

145. Brandhorst S, Choi IY, Wei M, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and Healthspan. Cell Metab. 2015; 22: 86–99. [PubMed: 26094889]

146. Yore MM, Syed I, Moraes-Vieira PM, et al. Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. Cell. 2014; 159: 318–332. [PubMed: 25303528]

147. Pfimlin E, Bielohuby M, Korn M, et al. Acute and repeated treatment with 5-PAHSA or 9-PAHSA isomers does not improve glucose control in mice. Cell Metab. 2018; 28: 217–227. e13 [PubMed: 29937376]

148. Caron A, Lee S, Elmquist JK, Gautron L. Leptin and brain–adipose crosstalks. Nat Rev Neurosci. 2018; 19: 153–165. [PubMed: 29449715]

149. Wang R, Cruciani-Guglielmacci C, Migrenne S, Magnan C, Cotero VE, Routh VH. Effects of oleic acid on distinct populations of neurons in the hypothalamic arcuate nucleus are dependent on extracellular glucose levels. J Neurophysiol. 2006; 95: 1491–1498. [PubMed: 16306178]

150. Lam TKT, Pocai A, Gutierrez-Juarez R, et al. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. Nat Med. 2005; 11: 320–327. [PubMed: 15735652]

151. Bovi RJD, Kim J, Suresh P, London E, Miller WT. Sterol structure dependence of insulin receptor and insulin-like growth factor 1 receptor activation. Biochim Biophys Acta. 2019; 1861: 819–826.

152. Strilbyska OM, Semaniuk UV, Storey KB, Yurkevych IS, Lushchak O. Insulin signaling in intestinal stem and progenitor cells as an important determinant of physiological and metabolic traits in drosophila. Cell. 2020; 9: 803.
153. Hu Y, Bao F, Li J. Promotive effect of brassinosteroids on cell division involves a distinct CycD3-induction pathway in Arabidopsis. Plant J. 2000; 24: 693–701. [PubMed: 11123807]

154. Buhler K, Clements J, Winant M, Bolckmans L, Vulsteke V, Callaerts P. Growth control through regulation of insulin signalling by nutrition-activated steroid hormone in Drosophila. Development. 2018; 145 dev165654 [PubMed: 30266830]

155. Sekido T, Nishio S, Okubo Y, et al. Repression of insulin gene transcription by indirect genomic signaling via the estrogen receptor in pancreatic beta cells. In Vitro Cell Dev Biol Anim. 2019; 55: 226–236. [PubMed: 30790128]

156. Yamada T, Hironaka K, Habara O, Morishita Y, Nishimura T. A developmental checkpoint directs metabolic remodelling as a strategy against starvation in Drosophila. Nat Metab. 2020; 2: 1096–1112. [PubMed: 33046910]

157. Roed NK, Viola CM, Kristensen O, et al. Structures of insect Imp-L2 suggest an alternative strategy for regulating the bioavailability of insulin-like hormones. Nat Commun. 2018; 9 3860 [PubMed: 30242155]

158. Lavrynenko O, Rodenfels J, Carvalho M, et al. The eclysteroidome of Drosophila: influence of diet and development. Development (Cambridge England). 2015; 142: 3758–3768. [PubMed: 26395481]

159. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia. 2020; 63: 453–461. [PubMed: 31754750]

160. Velders M, Diel P. How sex hormones promote skeletal muscle regeneration. Sports Med. 2013; 43: 1089–1100. [PubMed: 23884322]

161. Wong R, Piper MDW, Wertheim B, Partridge L. Quantification of food intake in drosophila. PLoS One. 2009; 4 e6063 [PubMed: 19557170]

162. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci USA. 2014; 111: 16647–16653. [PubMed: 25043202]

163. Peng Z-L, Yin B-X, Ren R-M, Liao Y-L, Cai H, Wang H. Altered metabolic state impedes limb regeneration in salamanders. Zool Res. 2021; 42: 772–782. [PubMed: 34643071]

164. Pluznick JL. Microbial short-Chain fatty acids and blood pressure regulation. Curr Hypertens Rep. 2017; 19: 25. [PubMed: 28315048]

165. Ríos-Covián D, Ruas-Madiedo P, Margolles A, Gueimonde M, Reyes-Gavilán CG, Salazar N. Intestinal short chain fatty acids and their link with diet and human health. Front Microbiol. 2016; 7: 185. [PubMed: 26925050]

166. Dinan TG, Cryan JF. Microbes, immunity, and behavior: psychoneuroimmunology meets the microbiome. Neuropsychopharmacology. 2019; 42: 1–15.

167. LeBlanc JG, Chain F, Martín R, Bermúdez-Humarán LG, Courau S, Langella P. Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. Microb Cell Fact. 2017; 16: 79. [PubMed: 28482838]

168. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014; 157: 121–141. [PubMed: 24679531]

169. Dolezal T, Krejčová G, Bajgar A, Nedbalova P, Strasser P. Molecular regulations of metabolism during immune response in insects. Insect Biochem Mol. 2019; 109: 31–42.

170. Shavandi A, Saeedi P, Gérard P, Jalalvandi E, Cannella D, Bekhit AE. The role of microbiota in tissue repair and regeneration. J Tissue Eng Regen Med. 2020; 14: 539–555. [PubMed: 31845514]

171. Bandt J-PD, Waligora-Dupriet A-J, Butel M-J. Intestinal microbiota in inflammation and insulin resistance: relevance to humans. Curr Opin Clin Nutr Metab Care. 2011; 14: 334–340. [PubMed: 21587065]
Figure 1. Fatty Acids, Sterols and Lipid-like Vitamins in their Role as Signalling Molecules and Membrane Components.

Fatty acids (A) consist of a hydrophobic carbon chain with variable numbers of double bonds and a hydrophilic carboxyl (-COOH) group. The number of double bonds determines the degree of unsaturation. For example, (A) depicts the two times unsaturated fatty acid linoleic acid with a carbon chain length of 18. Fatty acids are usually not found in a free state but as phospholipids in membranes or in combination with glycerol as di- or triglycerides. In contrast, the lipid class of sterols (B) is characterised by a tetracyclic hydrophilic sterol unit and a hydrophobic carbon side chain. The main sterol in animals is cholesterol. Fatty acids and sterols are crucial structural components of all membranes and their proportion as well as degree of saturation results in altered cellular biophysical properties. Lipid-like vitamins, like vitamin E (C), can also influence membrane properties. Furthermore, lipids are important for energy storage, induce metabolic signalling and there is growing evidence on the role of lipids as signalling molecules in wound healing and regeneration.
Figure 2. Connection of Regeneration, Growth, Aging and Systemic Metabolism.
The regenerative potential varies greatly between species but tends to be lowest in vertebrates compared to plants and invertebrate species. The regenerative potential tends to decrease during aging and it has been shown that the nutritional quality and flow are age dependent. However, how the systemic metabolism impacts the regenerative abilities remains widely unexplored to date. Nevertheless, systemic metabolism and nutritional changes have the potential to be one key variable to promote regenerative tissue repair. Created with BioRender.com.
Table 1

Additional signals/processes linked to energy metabolism in repair and regeneration

| Signal/process | Effect | Species |
|----------------|--------|---------|
| Initiation of regenerative activity immediate after injury | mTOR signalling | Neurite regrowth. | Rat<sup>73</sup> |
| | Satellite cell activation. | | Mouse<sup>44</sup> |
| | Satellite cell activation. | | |
| | Satellite cell activation. | | |
| | Satellite cell activation. | | |
| | Satellite cell activation. | | |
| | Satellite cell activation. | | |
| Cell division rate/Growth | ROS | Apoptosis and JNK signalling promoting epidermal proliferation. | Zebrafish<sup>76</sup> |
| | Insulin | Regulation of division rates in intestinal and germline stem cells. | Drosophila<sup>77,78</sup> |
| | Leptin | Enhances proliferation, differentiation and migration of epidermal keratinocytes in wound healing. | Human<sup>63</sup> |
| | MC4R/α-MSH | Induces proliferation during the early regeneration phase. | Xenopus, Mouse<sup>74</sup> |
| | PPARα and β/δ | Regulates proliferation via induction of AKT signalling. | Zebrafish<sup>79</sup> Mouse/Rat<sup>80</sup> |
| Energy homeostasis adaptations | Peroxisome proliferator-activated receptor gamma (PPARγ) and sphingosine-1-phosphate (S1P) | Lipidome adaptations after resection/cell culture injury in Schwann cells. | Mouse<sup>81</sup> |
| | GLUT1 transporter | Switches to glucose metabolism after cryo-injury of the heart. | Mouse<sup>82</sup> |
| | Yin Yang1 (YY1) | Facilitates a metabolic reprogramming of satellite cells toward glycolysis. | Mouse<sup>83</sup> |
| | ROS | Reduces oxidative metabolism due to lower mitochondrial activity in liver regeneration. | Mouse<sup>84</sup> |
| | Regenerating Islet-Derived (Reg) proteins | Enhances liver and neuronal regeneration likely through insulin signalling downstream of the InR (AKT, pMAPK). | Conserved<sup>85</sup> |
| | MC4R/α-MSH | Regulates energy homeostasis/body weight and reduces mitochondrial stress during the early regeneration phase. | Xenopus<sup>73,74</sup> |
| | PPARα | Regulates lipid metabolism maintaining on-going FA oxidation. | Mouse<sup>86</sup> |
| | PPARβ | Regulates AKT/E2f mediated FA synthesis and glycolysis. | Mouse<sup>87</sup> |
| Cell differentiation/patterning | Leptin | Promotes osteogenesis. Increased leptin-induced osteogenesis via brain injury. | Human<sup>88</sup> Mouse<sup>89</sup> |
| | TGF-β | Promotes blastema formation via induction of epithelial to mesenchymal transition (EMT). | Zebrafish<sup>54</sup> |
| | Auxin | Polarisation signal that induces PIN1 auxin transporter-marked channel formation during (vascular) cambium regeneration and vasculature formation. | Arabidopsis<sup>30</sup> |
| | Vegfa | Promotes revascularization of the damaged heart, in its absence, proliferation is inhibited. | Zebrafish<sup>59</sup> |
| Resources allocation/storage sites | Insulin | Trophic effect of insulin in hepatic regeneration. | Rat<sup>91</sup> |
| | Adipose tissue | Secretion of adipokines may influence insulin resistance in critical illness. | Human<sup>92</sup> |
| | Lipid/energy storage sites | Unrestricted food can compensate for growth limitations of regenerating juveniles. | Gecko<sup>93</sup> |
| | Obesity | Ectopic adipocyte accumulation in bone marrow reduces haematopoietic regeneration. | Mouse<sup>94</sup> |
| | Obesity | Decreases regenerative potential of muscle cells. | Human<sup>95</sup> |
| | Hyperglycemia | Decreased fin regeneration. | Zebrafish<sup>96</sup> |