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REVIEW

A comparative perspective on lung and gill regeneration

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ABSTRACT

The ability to continuously grow and regenerate the gills throughout life is a remarkable property of fish and amphibians. Considering that gill regeneration was first described over one century ago, it is surprising that the underlying mechanisms of cell and tissue replacement in the gills remain poorly understood. By contrast, the mammalian lung is a largely quiescent organ in adults but is capable of facultative regeneration following injury. In the course of the past decade, it has been recognized that lungs contain a population of stem or progenitor cells with an extensive ability to restore tissue; however, despite recent advances in regenerative biology of the lung, the signaling pathways that underlie regeneration are poorly understood. In this Review, we discuss the common evolutionary and embryological origins shared by gills and mammalian lungs. These are evident in homologies in tissue structure, cell populations, cellular function and genetic pathways. An integration of the literature on gill and lung regeneration in vertebrates is presented using a comparative approach in order to outline the challenges that remain in these areas, and to highlight the importance of using aquatic vertebrates as model organisms. The study of gill regeneration in fish and amphibians, which have a high regenerative potential and for which genetic tools are widely available, represents a unique opportunity to uncover common signaling mechanisms that may be important for regeneration of respiratory organs in all vertebrates. This may lead to new advances in tissue repair following lung disease.

KEY WORDS: Regeneration, Lung, Gill, Blastema, Hypoxia, Zebrafish, Axolotl

Introduction

Molecular oxygen (O_2) is the final acceptor of electrons in the process of oxidative phosphorylation that drives the generation of energy in the form of adenosine triphosphate (ATP). Because O_2 plays an essential role in metabolism, vertebrate species have evolved efficient respiratory organs – such as gills and lungs – in order to mediate gas exchange and satisfy their O_2 requirements (Carvalho and Gonçalves, 2011; Maina, 2002). Different designs of gas exchangers are present across species, and these meet specific metabolic demands associated with factors such as body mass, habitat, sex, age or highly energetic lifestyles (e.g. flight) (Hsia et al., 2013; Longo et al., 2013; Maina, 2002; Torday et al., 2007). The origin or selective pressure driving the evolution of gas exchangers is controversial because these structures leave little trace in the fossil record; however, our current understanding of the evolutionary features of gills and lungs highlights the potential for common basic features.

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Lung diseases, such as chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension or lung cancer, represent some of the world's most common medical conditions and can lead to a loss of pulmonary mass (Barratt et al., 2018; Cao and Xiao, 2018; Farkas and Kolb, 2013; Turcios, 2020). In contrast to the previous belief that the regenerative potential of the lung is limited, in the past decade many studies have provided evidence of the extensive ability of the lungs to regenerate after injury (Basil and Morrisey, 2020; Beers and Morrisey, 2011; Kotton and Morrisey, 2014). This work has demonstrated the presence of resident populations of epithelial progenitor cells (see Glossary) in the lung (e.g. alveolar type II cells), which – together with bone marrow-derived endothelial progenitor cells – facilitate lung repair (McQualter, 2019; Rafat et al., 2013; Warburton et al., 2008). However, the identification of appropriate progenitor cells and signaling pathways essential for regeneration (see Glossary) of damaged lungs is largely unexplored. Furthermore, it remains to be discovered whether the interaction of the endogenous progenitor cells and signaling pathways can potentially be modified, which could provide novel therapeutic strategies. In this sense, the high capacity of some non-mammalian vertebrates to regenerate organs, including respiratory tissues, can shed light on the signaling molecules through which human lung tissue may be regenerated and recover normal function.

After amputation, gills in non-amniotes (fishes and amphibians) can be completely restored (Mierzwa et al., 2019; Saito et al., 2019; see Box 1 for a comparison of fish and amphibian gills). This requires a vascular niche and nerve supply in order to support the proliferation of new tissue (Saito et al., 2019; Mierzwa et al., 2019), as previously described for mammalian lung regeneration (Mammoto and Mammoto, 2019; Rafii et al., 2017). Interestingly, some of the molecular mechanisms involved in the regeneration of respiratory organs seem to be highly conserved across vertebrates (Saito et al., 2019). This makes non-amniotes an efficient model in respiratory regenerative research due to their low cost and easy genetic manipulation. One of the key factors regulating transcriptional responses for tissue repair is the master regulator, hypoxia-inducible factor (HIF) (Nauta et al., 2014; Novianti et al., 2019; Lokmic et al., 2012). HIF is activated by hypoxia and induces the expression of target genes needed for tissue regeneration (Lokmic et al., 2012; Nauta et al., 2014; Novianti et al., 2019). In fact, recent studies highlight hypoxia/HIF activation as a powerful tool for stimulating lung tissue regeneration (Vadivel et al., 2014; Xi et al., 2017).

This Review explores the historical and current state of our knowledge about gill and lung regeneration in non-amniotes. Regeneration in the mammalian lung has been recently reviewed elsewhere (Basil and Morrisey, 2020; McQualter, 2019; Rodríguez-Castillo et al., 2018), so is dealt with only briefly for comparison. We begin by discussing gill and lung evolution, and the homologies between gills and lungs, including ancestral embryological characters. We then consider the processes of gill and lung regeneration in fish and amphibians, and the conserved

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Glossary

Blastema
A heterogeneous group of undifferentiated and/or progenitor cells that are capable of regrowing and patterning a complex organ.

De-differentiation
A cellular process in which a differentiated cell loses its visible differentiated characteristics, or reverts to an earlier developmental stage.

Dense-cored vesicles
Membrane-bound organelles that store and release neuropeptides, hormones, monoamines or neurotrophic factors.

Oxygen-sensing chemoreceptors
Specialized cells that detect changes in the environment, such as a decrease in oxygen availability (i.e. hypoxia), and initiate physiological responses to restore homeostasis.

Pharyngeal arches
A series of bulges that emerge from the foregut of the embryo in vertebrates. They consist of an ectoderm that forms the pharyngeal clefts, an internal endoderm that forms the pharyngeal pouch and a mesenchyme (mesoderm and neural crest).

Progenitor cells
Cells that are able to differentiate, with their differentiation potential restricted to specific cell types.

Regeneration
An injury-mediated, tissue-specific reparative program. It can involve the formation of a blastema.

Stem cell
A cell type with the potential to reproduce itself and to generate differentiated progeny.

Transgenesis
Insertion of an exogenous gene into the genome of an organism using recombinant DNA techniques.

Box 1. Gill morphology in vertebrates

In vertebrates, two types of gills may be present: (1) external gills, which are freely exposed to the surrounding water; or (2) internal gills, which are covered by cutaneous modifications, such as an opercular flap (e.g. in teleosts) or a mesenchymal tissue mass (e.g. in elasmobranchs). Gills are present in most amphibians during the larval stage: external gills in larvae of Urodela (Caudata) and Apoda (Gymnophiona and caecilians), and internal gills in Anura (Salentia) larvae (Maina, 2019; Vitt and Caldwell, 2013). External gills are retained in adult stages of neotenic amphibians, such as *Necturus* and *Ambystoma*. Most fish possess internal gills, although external gills can be found in some adult lungfish or in larval stages of Polypteridae, Dipnoi (lungfishes) or bichirs (Maina, 2019; Perry et al., 2019; Stundl et al., 2019). The morphology of the external gills commonly consists of a single ramus that grows many gill filaments, which contain an extensive network of blood vessels used in gas exchange (Maina, 2019; Perry et al., 2019; Vitt and Caldwell, 2013). The number of ramus pairs varies between species; e.g. there are three pairs of external gills in salamanders (e.g. axolotl) and four pairs in lungfish (Maina, 2019; Stundl et al., 2019). The general morphology of the internal gills differs between amphibians and fish. In fish, gill arches support gill filaments that, in turn, give rise to secondary lamellae – the sites of gas exchange (Evans et al., 2005; Wilson and Laurent, 2002). In the internal gills of larval amphibians, gill arches give rise to a series of irregular gill 'tufts' that contain filament-like structures that divide several times and ultimately form respiratory terminal branches (Brunelli et al., 2009; Saltys et al., 2006).

molecular signaling pathways, before discussing the role of hypoxia in the regeneration of respiratory organs. Finally, we present an evolutionary hypothesis explaining why non-amniotes possess a higher capacity for organ regeneration than mammals.

Evolutionary perspectives

Origin of the respiratory system in vertebrates

There is little consensus about how and when respiratory structures underwent evolutionary modifications. Since the mid-20th century, it was believed that gills evolved separately in the ancient jawed (cartilaginous and bony fishes) and jawless (lampreys and hagfish) lineages based on their distinct embryonic origins: the gills of jawless vertebrates are derived from endoderm (Damas, 1944), whereas those of jawed vertebrates were thought to be derived from ectoderm (Kellicott, 1905). However, by using fluorescent labelling to stain cell membranes, a recent study demonstrated that the gill tissue in a jawed vertebrate (*Leucoraja erinacea*) develops from the endoderm, as it does in jawless vertebrates (Gillis and Tidswell, 2017). Thus, it seems that gills evolved before the last common ancestor of all vertebrates, facilitating a transition from immobile filter-feeder to actively swimming predator (Gillis and Tidswell, 2017) (Fig. 1).

The evolution of the lung also occurred early in vertebrate evolution, before the transition from aquatic to terrestrial life (Boucot and Janis, 1983). However, the timing and the initial selective pressure for the appearance of the lung is still enigmatic (Perry et al., 2019), and its evolutionary relationship with the fish swimbladder has long been debated. At the end of the 19th century, different theories were proposed regarding the issue of lung/swimbladder homology: Owen (1846) suggested that the tetrapod lung originated from fish swimbladder, whereas phylogenetic studies by Sagemehl (1885) indicated that lungs were transformed into a swimbladder; Goette (1875) further proposed that lungs developed from modified gill pouches in the posterior pharynx. Sagemehl's (1885) hypothesis was widely accepted during the 20th century, and several additional lines of evidence indicated the homologies of the swimbladder and the lungs: they both develop from posterior pharynx (Goodrich, 1930), they both regulate gas exchange with the environment (Liem, 1988), and they share similar histology (Graham, 1997) and surfactant proteins (Daniels et al., 2004). In contrast, later developmental studies proposed that lungs and swimbladders were not homologous, because lungs evaginate from the ventral side of the foregut endoderm, whereas swimbladders develop from the dorsal side (Field et al., 2003; Herriges and Morrisey, 2014; Hsia et al., 2013; Perry et al., 2001). Despite this, more recent genetic studies have supported the homology of lungs and swimbladders by studying the molecular mechanisms of lung development in primitive fishes. Tatsumi et al. (2016) found that the extant basal actinopterygian fish Senegal bichir (*Polypterus senegalus*) possesses orthologs of genes involved in tetrapod (sarcopterygian) lung formation (e.g. *fgf10*, *tbx4* and *tbx5*). This result supports the idea that lungs were present at least as early as the first bony fishes (Osteichthyes or Osteognathostomata), prior to the radiation of ray-finned (Actinopterygii) and lobe-finned (Sarcopterygii) fishes (Fig. 1). It seems that the descendants of bony fish inherited a lung that was either retained or underwent a transition to a swimbladder. Thus, in spite of more than one century of investigation, the origin of vertebrate respiratory structures is unclear. Amphibians provide a particularly interesting evolutionary case, as they may have lost lungs and gills (e.g. lungless salamanders), or inherited both organs during different life stages (e.g. anurans) or at a single life-stage (e.g. axolotl). Further comprehensive genetic and developmental analyses are required to elucidate the evolution of vertebrate respiratory systems.

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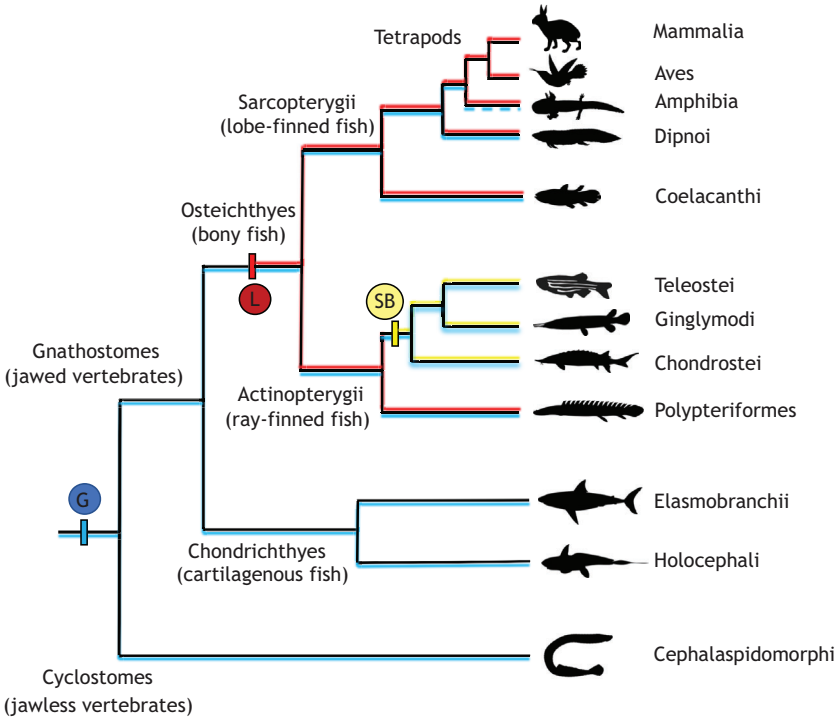

Fig. 1. The evolutionary history of gills, lungs and swimbladder in vertebrates. Gills (G) evolved prior to the divergence of cyclostomes (jawless vertebrates – lampreys and hagfish) and gnathostomes (jawed vertebrates – cartilaginous and bony fishes). Lungs (L) were present in the first bony fishes (Osteichthyes or Osteognathostomata) prior to the radiation of ray-finned (Actinopterygii) and lobe-finned (Sarcopterygii) fishes. Bony fish descendants either inherited a lung or the lung underwent transition to a swimbladder (SB). Blue line, gill possession; red line, lung possession; yellow line, swimbladder possession. Gills in amphibians can be present or absent, depending on the species (dashed blue line). Animal silhouettes courtesy of PhyloPic (http://phylopic.org/). Based on Hsia et al. (2013), Perry and Sander (2004) and Yamamoto et al. (2017).

Ancestral characteristics preserved in vertebrate respiratory organs: the pharyngeal arches

One of the most conserved embryonic structures in all vertebrates, both morphologically and genetically, are the pharyngeal arches (see Glossary) – a series of bulges that surround the foregut of the embryo (Frisdal and Trainor, 2014; Graham et al., 2005, 2019; Grevellec and Tucker, 2010). In all vertebrates, the pharyngeal arches consist of an ectoderm that forms the pharyngeal clefts, an internal endoderm that forms the pharyngeal pouch and a mesenchyme (mesoderm and neural crest) (Mork and Crump, 2015). Within the pharyngeal arches lie the aortic arches, which supply blood to the head region. The number of pharyngeal arches in vertebrates is species dependent, and it decreases with the evolution of tetrapods: there are 15 in hagfish (Oisi et al., 2015); nine in lampreys (Takio et al., 2007); seven in gnathostomes (e.g. chondrichthyans, actinopterygians and some basal sarcopterygians); six in amphibian; and five in amniotes, including humans (Frisdal and Trainor, 2014; Kardong, 2012). The first pharyngeal arch in all vertebrates forms the jaw, whereas the second forms the hyoid (Fraser et al., 2009; Graham et al., 2019). In non-amniotes, the 3rd to the 6th arches form the gills (Fig. 2) (Graham and Richardson, 2012; Jonz and Nurse, 2009; Schoch and Witzmann, 2011); although the bichir is an exception, where the gills are formed from the second (hyoid) arch (Stundl et al., 2019). In amniotes, including humans, the posterior arches no longer generate gills because the primary respiratory function is shifted to the lungs (Fig. 2). Instead, the posterior pharyngeal arches in amniotes are re-purposed to produce pharyngeal structures in the neck, and the vasculature is remodeled to support a pulmonary circulation that serves the lungs (Frisdal and Trainor, 2014). The epithelium of the lungs and gills derives from the endoderm of the posterior arches (Gillis and Tidswell, 2017; Hockman et al., 2017; Kotton and Morrisey, 2014). Furthermore, the most posterior arch of amniotes is considered to be homologous to the most posterior arch of non-amniotes due to the common expression of the *hox1* gene (Graham et al., 2019). These features highlight a common embryonic and genetic origin for gills and lungs, which could explain the fact that there are homologous cell types in both structures (see below).

Gill structure and cell populations: a comparison with the mammalian lung

Innervation and vasculature

Gills and lungs are innervated by both divisions (sympathetic and parasympathetic) of the autonomic nervous system (Hakim and Usmani, 2014; Jonz and Nurse, 2008; Jonz and Zaccone, 2009; Ochs and O'Brodovich, 2019; Sundin and Nilsson, 2002). In fish and larval amphibians, gills receive sympathetic innervation from spinal nerves and parasympathetic innervation from cranial nerves VII (facial), IX (glossopharyngeal) and X (vagus) (Jonz and Nurse, 2009; Jonz and Zaccone, 2009; Nilsson, 1984; Sundin and Nilsson, 2002; Zachar and Jonz, 2012). The sympathetic nerves that innervate the lungs arise from the upper thoracic and cervical ganglia of the sympathetic trunk, and the relevant parasympathetic nerves derive from the X (vagus) nerve (Gibbins, 2012; Rakovich et al., 2010).

In fish, oxygen-poor blood passes from the heart via the ventral aorta and enters the gills through afferent branchial arteries to be re-oxygenated at the secondary lamellae (Fig. 3). Blood is then collected by an efferent branchial artery and directed to the dorsal aorta for systemic distribution (Evans et al., 2005). In amphibian gills, there is no ventral aorta, and the arterial arches arise directly from the conus arteriosus, the interior of which is divided longitudinally by a spiral valve that controls the composition of blood reaching each arterial arch (Kolesová et al., 2007). Teleost fish also contain a secondary vascular system in the gill filaments (Olson, 2002).

In fish, gills are perfused by the entire cardiac output; however, during the phylogenic progression from amphibia and reptiles to birds and mammals there was a gradual separation of the pulmonary circulation from the systemic circulation (Monahan-earley et al., 2013; Wang et al., 2019; West, 2011). This evolutionary adaptation protects the blood–gas barrier from high vascular pressure (West,

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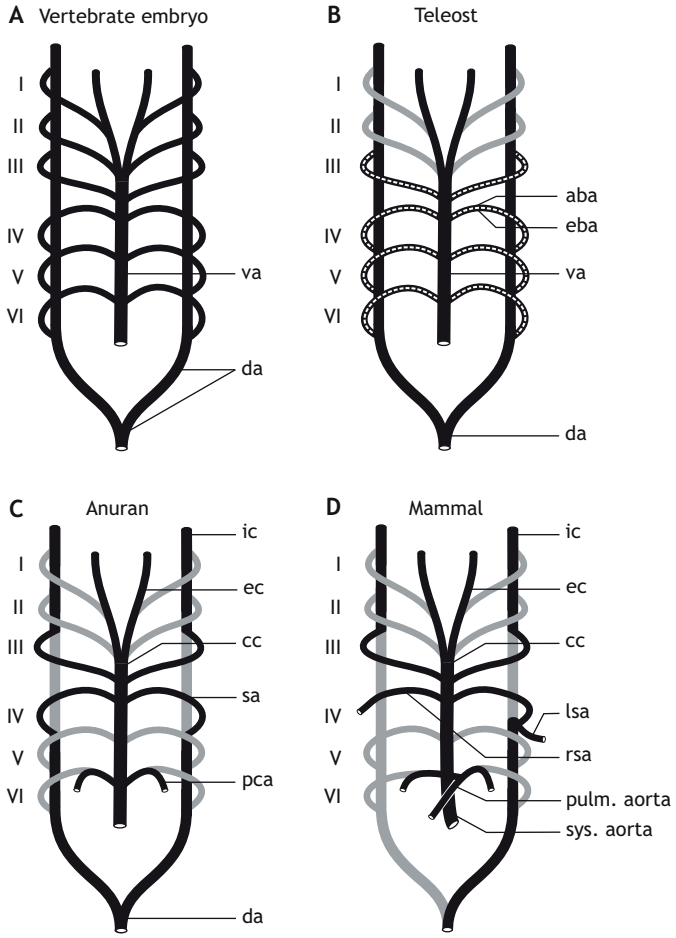

Fig. 2. Model for aortic arch organization in vertebrates. Aortic arches occupy the pharyngeal arches and are indicated from anterior to posterior by Roman numerals. Gray indicates arterial tissue that has disappeared during evolution. All diagrams are presented in ventral view. (A) Common disposition of aortic arches in vertebrate embryos. Arches I–VI link ventral and paired dorsal aortae. (B) Model for aortic arches in adult teleost fish, where arches I and II disappear during development and arches III–VI form the gills. The association of afferent and efferent branchial arteries via capillaries is indicated by dashed lines. (C) Model for aortic arches in adult anuran amphibians. During development, arches I and II disappear as in fish. Furthermore, arch V also disappears. The ventral aorta forms the carotid artery, which separates into the internal and external carotids (i.e. gill arch 1 and ventral aorta in fish). (D) Model for aortic arches in adult mammals. As in adult anuran amphibians, only arches III, IV and VI remain. Furthermore, the right dorsal aorta degenerates and the systemic aorta (aorta proper) remains on the left side. The first gill arch in fish (B) is homologous with the site of the internal carotid artery and carotid bifurcation in mammals (D). aba, afferent branchial artery; cc, common carotid artery; da, dorsal aorta; eba, efferent branchial artery; ec, external carotid artery; ic, internal carotid artery; lsa, left subclavian artery; pca, pulmocutaneous artery; pulm. aorta, pulmonary aorta; rsa, right subclavian artery; sa, systemic arch; sys. aorta, systemic aorta; va, ventral aorta. Based on Weichert (1967) and reproduced, with permission, from Jonz and Nurse (2009).

2011; Monahan-Earley et al., 2013; Wang et al., 2019). Interestingly, the trilaminar morphology of the blood–gas barrier (i.e. capillary endothelium, extracellular matrix and alveolar epithelium) has been conserved in gills and lungs from fishes to mammals (West, 2011). This is not surprising, given that all blood vessels are endothelial derivatives and the epithelial lining of the lungs and gills develops from the primitive pharyngeal arches (Gillis and Tidswell, 2017; Kotton and Morrisey, 2014; Schittny, 2017; West, 2011).

Cell types

Despite the fact that the morphologies of the gill and the lung differ widely, it is possible to identify some common cell types in both structures. The gill epithelium in the filament and lamellae is mostly covered by pavement cells, which increase the respiratory surface area and provide a platform that enhances adherence of a stable mucous layer (Brunelli et al., 2009; Carmona et al., 2004; Evans et al., 2005; Koppang et al., 2015). Pavement cells (i.e. alveolar epithelial cells type I, AEC1) are also present in the mammalian lung, and they play a similar role: covering the majority of the alveolar surface and forming the epithelial component of the thin air–blood barrier (Maynard and Downes, 2019). Pavement cells are structurally similar in gills and lungs: they are squamous cells with few mitochondria (Evans et al., 2005; Maynard and Downes, 2019) and they express genetic markers (e.g. *igfbp2* in the lungs and *igf1r* in the gills) that indicate insulin-like growth factor signaling (Lai et al., 2015; Wang et al., 2018). Goblet-type cells are also found in the gill and lung epithelium; they play a major role in secreting mucous components, such as glycoproteins or lipids, that protect the epithelial surface (McCauley and Guasch, 2015; Rogers, 1994; Wilson and Laurent, 2002).

One of the other primary cell types present in the gill epithelium of fish and amphibians are mitochondrion-rich cells (MRCs) that regulate ion uptake and excretion (Brunelli et al., 2009; Lewinson et al., 1987; Warburg et al., 1994; Wilson and Laurent, 2002). In marine teleost gills, MRCs control NaCl secretion via three major ion transporters: basolateral Na^+/K^+-ATPases and $Na^+/K^+/2Cl^-$ co-transporters (NKCCs), and apical Cl^- channels (Marshall, 2002; Silva et al., 1977). Interestingly, this mechanism of NaCl secretion is conserved in mammals, where the airway epithelium normally secretes a NaCl-rich fluid to aid mucus clearance from airways (Marshall, 2002). The NKCC transporter has been conserved in mammalian alveolar epithelial cells, and the pulmonary human cystic fibrosis transmembrane conductance regulator (CFTR) is considered to be homologous to the apical Cl^- channel in the gill (Londino and Matalon, 2013; Weidenfeld and Kuebler, 2017). Furthermore, the AECs express the gene *clcn2* (which encodes a chloride channel; Lamb et al., 2001), as do the MRCs in teleost gills (Guh et al., 2015; Lai et al., 2015).

The gill epithelium of fish and some amphibian larvae (e.g. *Xenopus laevis*) also contains oxygen-sensing chemoreceptors (see Glossary), called neuroepithelial cells (NECs; Jonz et al., 2004; Saltys et al., 2006), which detect changes in O_2 and CO_2/H^+ (Abdallah et al., 2014; Jonz et al., 2004; Qin et al., 2010). NECs in the gills are considered to be homologous to the airway chemoreceptors of the mammalian lungs (i.e. neuroepithelial bodies, NEBs). Both cell types are neurosecretory and contain cytoplasmic dense-cored vesicles (see Glossary) that carry neurotransmitters such as serotonin (5-hydroxytryptamine or 5-HT) (Fu et al., 2002; Jonz and Nurse, 2009; Saltys et al., 2006). Another defining feature of both NECs and NEBs is their complex innervation, which arises from multiple sources. NEBs receive innervation primarily from vagal afferents derived from the nodose ganglia, although additional sources of innervation – such as calcitonin gene-related peptide (CGRP)-immunopositive fibers derived from the spinal (dorsal root) ganglia and nitrergic fibers arising from the peribronchial ganglia – have been described in the rat (Adriaensen et al., 1998, 2003; Brouns et al., 2003; Cutz et al., 2013; Domnik and Cutz, 2011). In NECs, the innervation mainly arises from synapses with catecholaminergic nerve fibers from the cranial nerve ganglia and also from indolaminergic neurons intrinsic to the gill filaments (Bailly, 2009; Jonz and Nurse, 2003; Zachar and Jonz, 2012).

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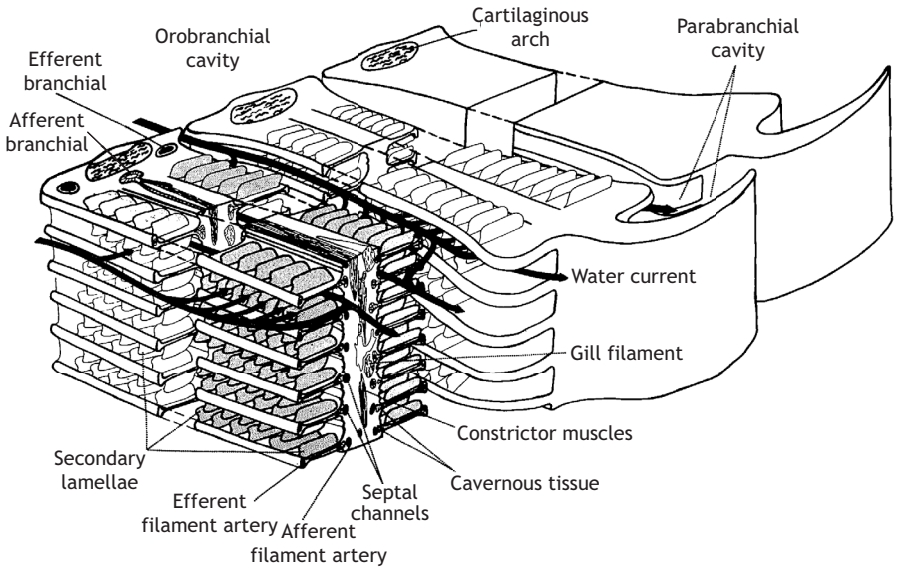

Fig. 3. Schematic of three gill arches in a dogfish. Different degrees of detail are given for each arch. The anterior-most arch shows secondary lamella and septum anatomy. The last arch shows the general anatomy of the filaments and the site in which the septa overlap the next posterior arch. Thick arrows show water flow between the secondary lamellae along the septal channels. Reproduced, with permission, from Hughes (1984).

Processes of gill and lung regeneration in non-mammalian vertebrates

The regeneration of the gills of fish and amphibians involves three major phases: (1) wound healing; (2) formation of the blastema (see Glossary); and (3) re-development, which includes the proliferation of blastema cells, their differentiation and tissue reconstruction (Saito et al., 2019; Mierzwa et al., 2019) (Figs 4 and 5A). Similar phases of regeneration occur in other tissues, such as the fish tail and amphibian limb (Münch et al., 2013; Nye et al., 2003; Poss et al., 2003; Stocum, 2017). Each of these phases is discussed in more detail below.

Wound healing

Although the early stages of wound healing following amputation are nearly identical among vertebrates (e.g. re-epithelialization or angiogenesis), there is a broad spectrum of wound healing outcomes. For example, in most mammals, injured tissues are repaired by scar formation, whereas other vertebrates, such as fish or amphibians, have the capacity to undergo scar-free wound healing that restores the original tissue structure (Ferguson and O'Kane, 2004; Gurtner et al., 2008; Jacyniak et al., 2017). In scar-free wound healing, epithelial cells start to migrate along the edges of the wound and the blastema forms after wound closure (Pfefferli and

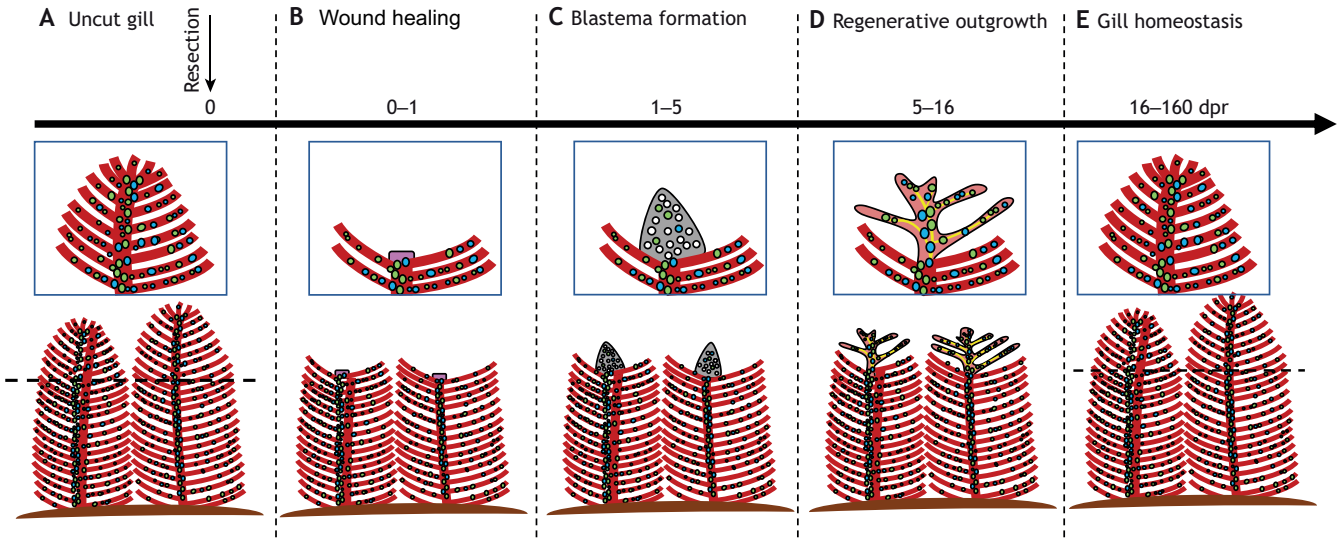

Fig. 4. Model for gill regeneration in zebrafish. (A) Uncut, the original zebrafish gill prior to amputation. The diagram shows the filament tip and lamellae, and exhibits cell populations, including neuroepithelial cells (NECs; green circles) and mitochondrion-rich cells (MRCs; blue circles). (B) From 0 to 1 dpr (days post-resection), tissue above the site of amputation consists of the wound epidermis (magenta) and a few blastemal cells (not shown). (C) At 1 dpr, a blastema (gray) is present, and proliferating cell nuclear antigen (PCNA)-positive cells (white circles) are first observed. These increase in density at 3–5 dpr. MRCs labelled with antibodies against the Na^+/K^+-ATPase are also present at 1 dpr (blue), whereas NECs are first observed at 2–3 dpr (green). (D) At 16 dpr, the redevelopment of new tissue (pink) extends rapidly; all NECs observed are associated with nerve fibers (yellow lines), and MRCs and NECs continue to increase in number as regeneration advances. (E) At 40 dpr, 50% of gill regeneration is complete; at 160 dpr, 85% of the gill reaches its original size and pattern. Regenerated gill tissue appears to have normal morphology, including a central gill filament that gives rise to numerous respiratory lamellae, and normal blood flow. Based on Mierzwa et al. (2019), and A. Mierzwa, F. Nguyen and M.G.J., unpublished observations.

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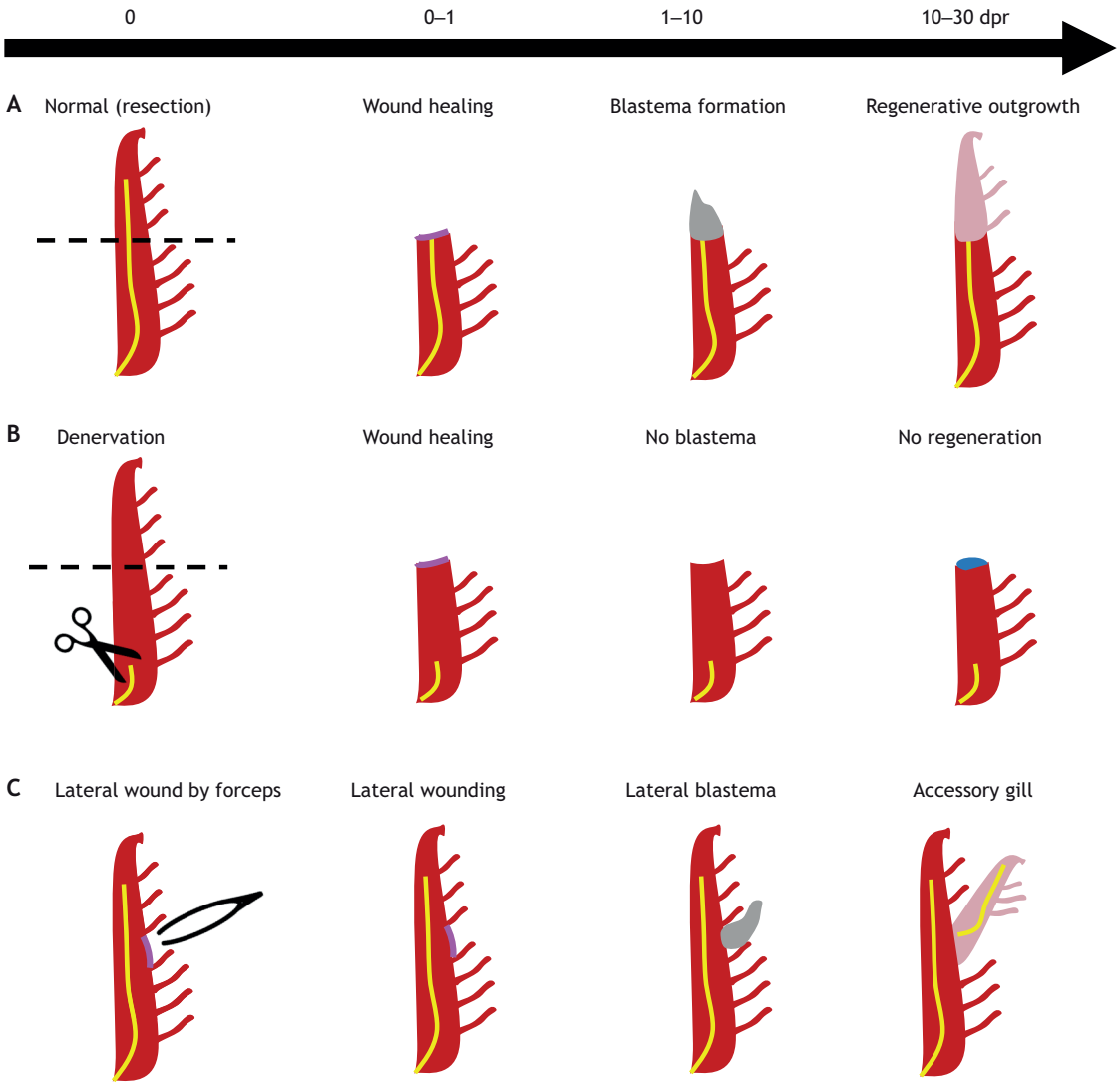

Fig. 5. Model for gill regeneration in axolotl. (A) Normal regeneration in innervated gills. From 0 to 1 dpr (days post-resection) there is a wound epidermis (purple) and, at 10 dpr, a blastema (gray) is present. The regenerated gills (pink) recover blood circulation within 15 dpr. At 20 dpr, most axolotl gill regeneration processes have taken place, including the formation of gill filaments (pink). (B) Gill regeneration is impaired after denervation. From 0 to 1 dpr, tissue above the amputation plane consists of the wound epidermis (purple) but no apparent blastema cell accumulation. At 20 dpr, there is no apparent blastema formation. At 25 dpr only a small growth from the stump is observed (blue). (C) Lateral wound healing is sufficient to induce the formation of an accessory gill without nerve rerouting. A lateral wound can be created using forceps in innervated gills. At 10 days after lateral wounding, a blastema is visible (gray). At 30 days after lateral wounding, the accessory gill shows well-developed gill filaments, blood vessels and nerve fibers. In A–C, the nerve is represented by a yellow line. In A and B, the dashed line indicates the resection site. Based on Saito et al. (2019).

Jaźwińska, 2015; Seifert and Muneoka, 2018; Sousa et al., 2011; Stocum, 2017).

Blastema formation

Although the presence of a blastema has been reported after gill amputation in fish and amphibians (Saito et al., 2019; Mierzwa et al., 2019; Figs 4 and 5A), there is no study to date that definitively addresses the origin of the blastema in the gills. One hypothesis is that the blastema in regenerating gills is a collection of undifferentiated and/or progenitor cells. Support for this idea comes from work in zebrafish, which display cells positive for the proliferating cell nuclear antigen (PCNA) in regenerating gill filaments (Mierzwa et al., 2019), and in which the presence of mitotic cells in growing gills after endurance exercise has been reported (Messerli et al., 2020). Both of these observations suggest active regions of cell division. In medaka (*Oryzias latipes*) gills, at least four types of fate-restricted stem cells (see Glossary) have been identified; these cells can divide and replace numerous diverse cell types during post-embryonic gill growth (Stolper et al., 2019).

A second hypothesis regarding the origin of blastema cells in the gill is that they are derived from mature cells near the injury site that re-enter the cell cycle (i.e. de-differentiation; see Glossary). De-differentiation is widely accepted to occur in urodele amphibians (Brockes and Kumar, 2002; Echeverri et al., 2001; Nechiporuk and Keating, 2002; Nye et al., 2003). Similarly, studies using transgenesis (see Glossary) and cell labeling in zebrafish have shown that the capacity for regrowth of amputated fins, and damaged heart and neural tissue depends on cellular de-differentiation (Poss et al., 2003; Singh et al., 2012; Tanaka and Reddien, 2011). The presence in zebrafish gills of *sall4* (Jackson et al., 2013), which encodes a zinc-finger transcription factor that governs the fate of stem cells (Yang et al., 2008; Zhang et al., 2006)

and is involved in the reprogramming of differentiated cells during amphibian limb regeneration (Neff et al., 2011), suggests that gills can be prompted into de-differentiation. We therefore cannot determine whether the blastema formed during the regeneration of fish and amphibian gills is derived from stem cells or cellular de-differentiation. Detailed tracing of cell lineage in the blastema cells will be required to differentiate between these two possibilities. For example, cell lineage tracing in the axolotl (*Ambystoma mexicanum*) can be carried out with transplanted cells (Kragl et al., 2009); in zebrafish cell lineage tracing can be achieved by tissue-specific *in vivo* recombination using the Cre-ER and lox system for long-term marking of specific cells (Hans et al., 2009). Interestingly, Kragl et al. (2009) showed that, during limb regeneration, stem cells do not become multipotent; e.g. muscle cell types are restricted to muscle lineage. This suggests that the blastema could be a heterogeneous pool of restricted progenitor cells, as previously reported for stem cell populations of the lung (Jensen et al., 2018 preprint; Kotton and Morrisey, 2014).

It is known that scar formation is rare after lung injury in mammals and axolotls; instead, lungs have remarkable reparative capacity due to the presence of stem/progenitor cells (Jensen et al., 2018 preprint; Kotton and Morrisey, 2014; Warburton et al., 2008). In axolotls, new proliferating cells can be detected after lung amputation, and these originate from epithelial cells that serve to replenish epithelial layers, as well as mesenchymal and ciliated cells that replenish local cells (Jensen et al., 2018 preprint). These findings indicate the absence of a specific stem cell niche, as in regeneration of the mammalian lung (Kotton and Morrisey, 2014) and axolotl limb (Kragl et al., 2009). In fact, it is difficult to imagine a single lung stem cell capable of generating all the different cell types in the complex respiratory system (Kotton and Morrisey, 2014). In mammals, multiple adult lung stem cells have been described to respond to injury [including basal cells, club cells and alveolar epithelial cells type 2 (AEC2; stem cells from the alveolus)], although lung epithelial cell lineages can also de-differentiate to re-enter the cell cycle and replace lost cells (El-Badrawy et al., 2016a; Kotton and Morrisey, 2014; Liu et al., 2006). Additionally, bone marrow provides progenitor cell populations that promote lung regeneration; these include haematopoietic stem cells, mesenchymal stem cells and fibrocytes, as well as mononuclear cells (El-Badrawy et al., 2016b; Sage et al., 2008).

Re-development

In gills, over a period of days to weeks after amputation, the blastema gives rise to new tissues (Saito et al., 2019; Mierzwa et al., 2019; Figs 4 and 5A). Blood vessels are present in newly amputated gills in axolotl (Saito et al., 2019), and the pigmented color of the regenerated gills in zebrafish suggests a normal blood flow (Mierzwa et al., 2019; Fig. 4). However, it remains unclear whether the re-establishment of the vascular network during gill regeneration starts in the blastema or begins at a later stage of regeneration. By comparison, the tail blastema in lizards grows rapidly and presents an early vascularization (Hutchins et al., 2014; Payne et al., 2017), whereas in mouse digit tips (Fernando et al., 2011; Simkin et al., 2015) and urodele limbs (Smith and Wolpert, 1975), the blastema is largely avascular. Vascular recruitment in the blastema is therefore dependent on how fast the tissue grows, and vascularization appears when oxygen diffusion cannot meet the metabolic demand of the cells (Payne et al., 2017). However, although vascularization is not strictly necessary to initiate blastema formation (Bayliss et al., 2006), it is essential for the continuation of blastema re-development, as demonstrated in fish, reptiles, amphibians and mammals (Payne et al., 2017; Pfefferli and Jaźwińska, 2015; Simkin et al., 2015; Stocum, 2017). In humans, by contrast, a vascular niche derived from pulmonary capillary endothelial cells is required to start the lung regeneration process (Rafii et al., 2015). After lung injury, pulmonary capillary endothelial cells produce the angiocrine factor matrix metalloproteinase 14 (MMP14), which liberates epidermal growth factor (EGF)-like ligands to induce proliferation of AEC2 (Mammoto and Mammoto, 2019; Rafii et al., 2015). Afterwards, the coordinated interaction between pulmonary capillary endothelial cells and alveolar progenitor cells expands the vascular plexus, forming new alveolar sacs and restoring the functional lung mass (Ackermann et al., 2014; Mammoto and Mammoto, 2019).

Vascularization is also an essential factor providing an optimal nutritional environment for nerve regeneration (Saffari et al., 2020). In fish and amphibians, wound healing does not need a nerve supply, but nerves are required for supporting the proliferation of blastemal cells (Farkas and Monaghan, 2017; Kumar and Brockes, 2012; Simões et al., 2014). Nearly 200 years ago, nerve-dependent blastema induction was discovered in the context of salamander limb regeneration (Todd, 1823); this was confirmed later in several studies in fish and amphibians (Kumar and Brockes, 2012; Simões et al., 2014). For example, denervated fins in zebrafish cannot form a blastema, which compromises successful regeneration (Simões et al., 2014); additionally, in urodeles, such as African clawed froglets (*Xenopus laevis*), growth and survival of blastema cells is also nerve dependent during limb regeneration (Suzuki et al., 2005). Given that gill regeneration is characterized by blastema formation, it is not surprising that gill denervation in axolotl results in complete loss of gill regeneration (Saito et al., 2019; Fig. 5B). Interestingly, a wound in the axolotl gill can also result in the formation of a lateral accessory gill without nerve deviation (re-routing) (Saito et al., 2019; Fig. 5C). According to the authors, this depends on the sensory axons present in axolotl gills (Saito et al., 2019). In zebrafish gills, nerve fibers are also present at the early stages of gill regeneration (3 days after resection) and, shortly afterwards, new innervated NECs appear, although the percentage of NECs that receives innervation increases significantly after 7 days post-resection (dpr) (Mierzwa et al., 2019; Fig. 4). This emphasizes the key role of innervation in cell outgrowth, which contributes to recovery of tissue homeostasis after gill injury. In mammalian lungs, NEBs also have the capacity to regenerate (Reynolds et al., 2000) and support a stem cell niche for club cell regeneration after lung damage (Hogan et al., 2014; Song et al., 2012), although the control of innervation in NEB homeostasis during lung regeneration remains unknown (Aven and Ai, 2013). There is a lack of information on lung re-innervation during the regeneration process, and even pulmonary re-innervation in the context of lung transplantation is not well understood (Studer, 2004). The presence of innervated cells, such as NEBs, after lung injury suggests that nerves contribute to lung regeneration in mammals, although further studies are necessary to corroborate this.

In addition to NECs, MRCs labelled with antibodies against the Na^+/K^+-ATPase are also present as early as 1 dpr in zebrafish gills (A. Mierzwa, F. Nguyen, M.G.J., unpublished observations; Fig. 4). The number of MRCs in fish gills has also been shown to increase in response to changing salinities in order to balance osmotic changes (Chasiotis et al., 2012; Utida et al., 1971). Future studies are required to elucidate whether ion and osmotic regulation in the gills are restored after amputation and regeneration. After mammalian lung injury, new AEC1s derive from AEC2s (Kotton and Morrisey,

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2014). The presence of AEC1s and AEC2s, both of which contain NKCCs and CFTR channels (Weidenfeld and Kuebler, 2017), would restore lung fluid balance during regeneration.

Molecular pathways underlying regeneration of respiratory tissues in non-mammals

To date, little research has investigated the molecular mechanisms of gill and lung regeneration in non-mammals. The capacity for gill regeneration was first identified in the early 20th century in aquatic salamander larvae (*Necturus*; Eycleshymer, 1906) and goldfish (*Carassius auratus*; Schäfer, 1936). However, it was not until more than one century later when the molecular mechanisms of gill regeneration were addressed for the first time (Saito et al., 2019). Saito et al. (2019) showed that treating axolotls with inhibitors of fibroblast growth factor (FGF) and bone morphogenetic protein (BMP) signaling delayed gill regeneration, suggesting the involvement of FGF and BMP signaling in this process (Saito et al., 2019; Fig. 6). BMP and FGF are well-known conserved pathways involved in tissue/organ repair across vertebrates. In mammalian lung, BMP signaling plays a crucial role in stem cell activation and differentiation after damage (Chung et al., 2018), whereas FGFs (e.g. FGF7 and/or FGF10) promote repair in different lung injury/disease animal models (Finch et al., 2013). Although the mechanisms of gill regeneration in fish remain to be defined, BMP signaling [along with signaling by other factors, such as peroxisome proliferator-activated receptor α (PPARA), Jun and GATA has also been shown to stimulate stem cell differentiation and reactivate developmental pathways in the gill in zebrafish (Zheng et al., 2010). BMP and FGF are also involved in blastema formation and proliferation during zebrafish fin regeneration (Poss et al., 2000; Shibata et al., 2016; Thorimbert et al., 2015), limb and tail regeneration in amphibians (Giampaoli et al., 2003; Liang et al., 2019; Satoh et al., 2016; Beck et al., 2006; Makanae et al., 2016), and digit regeneration in mammals (Takeo et al., 2013; Yu et al.,

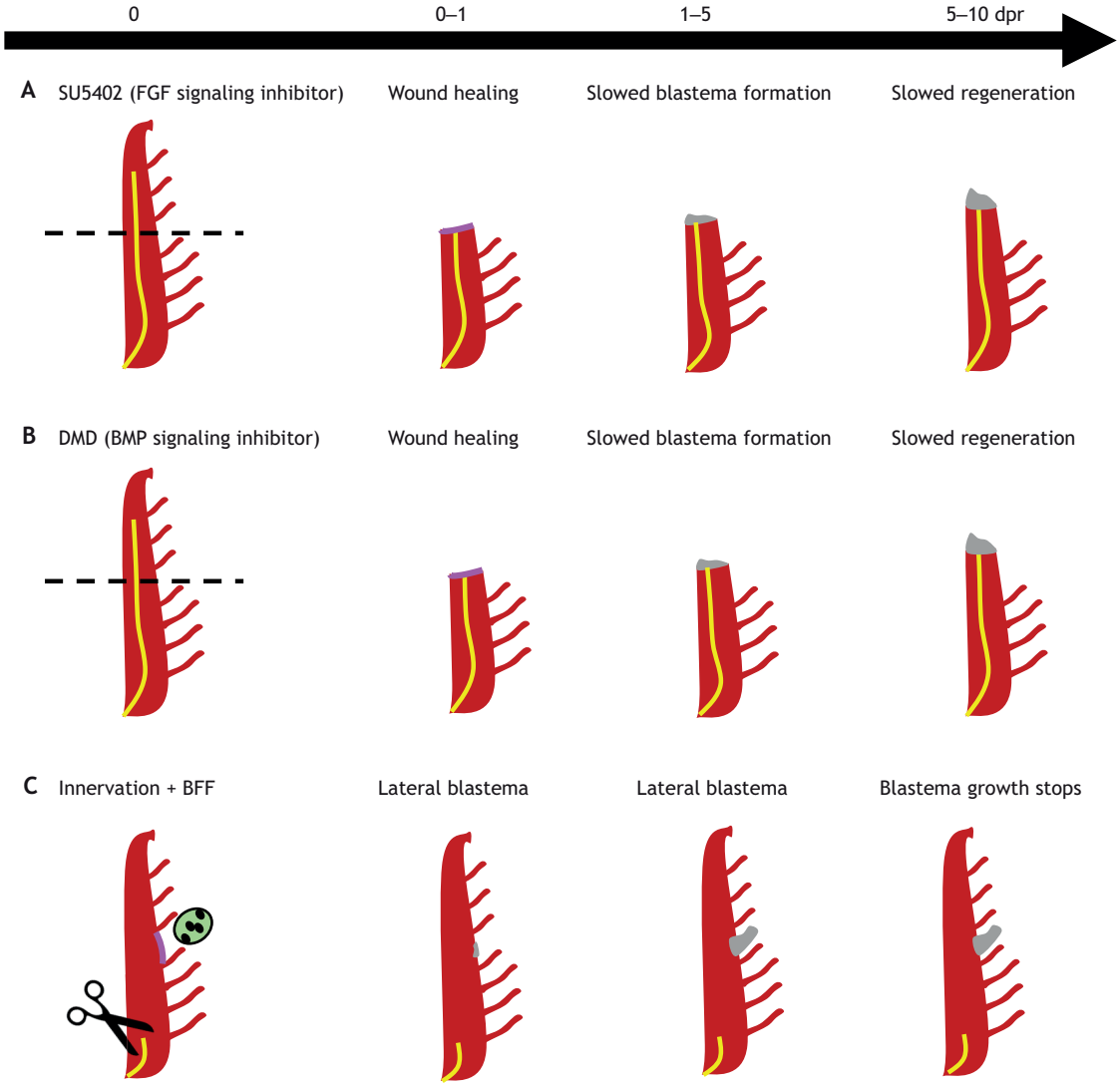

Fig. 6. FGF and BMP signaling in axolotl gill regeneration. (A) SU5402, an inhibitor of fibroblast growth factor (FGF) signaling, slows the pace of regeneration in innervated (yellow line) gills. From 0 to 1 dpr (days post-resection), normal gill regeneration results in a wound epidermis (purple). At 10 dpr, a small blastema (gray) is present. (B) DMD, an inhibitor of bone morphogenetic protein (BMP) signaling, also decreases the pace of regeneration in innervated gills. From 0 to 1 dpr, normal gill regeneration results in the wound epidermis. At 10 dpr, a small blastema (gray) is present. (C) A combination of proteins (BFF: Bmp7, Fgf2 and Fgf8; green oval) is applied to the wound in a denervated gill. At 5 dpr, a blastema is observable in the gills. Most of the BFF-induced blastemas cannot maintain their growth and are eventually resorbed. These results imply that BMP and FGF signaling are involved in the formation of a gill blastemal (gray). In A–C, the nerve is represented by a yellow line. In A and B, the dashed line indicates the resection site. Based on Saito et al. (2019).

2010), which highlights the fundamental role of these factors in regeneration across species and body structures.

To date, only one study addresses the mechanisms of lung regeneration in non-mammals; this study used axolotls (Jensen et al., 2018 preprint). The authors found a crucial role for the epidermal growth factor receptor family (ERBB) in lung regeneration in this species (Jensen et al., 2018 preprint). Specifically, during lung regeneration, there is a significant upregulation of receptors ERBB4 and EGFR and of the ligand neuregulin 1B (NRG1β), which are also known to play an important role in lung development and lung cell maturation and differentiation in mammals (Liu et al., 2009; Plopper et al., 1992; Purevdorj et al., 2008). In addition, Jensen et al. (2018) identified reduced cell proliferation in axolotl lungs after chemical inhibition of ERBB2, which is also known to be an important factor in the regeneration of mammalian tissues (Natarajan et al., 2007). These studies indicate that the axolotl is potentially a useful model for studying the molecular mechanisms underlying lung regeneration in vertebrates. Other amphibians, such as *Xenopus*, could also be attractive models, because these species possess a high ability to regenerate other tissues, such as the tail (in tadpoles), limb and eye (Beck et al., 2006; Blitz et al., 2006). It is likely that the well-conserved FGF and BMP pathways also play a key role in lung regeneration in *Xenopus*, because they are involved in *Xenopus* lung development (Rankin et al., 2015; Shifley et al., 2012). In reptiles, the capacity for lung regeneration has not been explored, even though it is known that lizards possess the ability to regenerate their tail (Jacyniak et al., 2017), and the leopard gecko can regenerate the heart (Jacyniak and Vickaryous, 2018). Studying these organisms with high regenerative potential could reveal new insights into lung regeneration in vertebrates.

Other key signaling molecules playing a major role in mammalian lung regeneration are Wnt (Kotton and Morrisey, 2014; Whyte et al., 2012), retinoic acid (Hind and Maden, 2004; Rodríguez-Castillo et al., 2018) and Notch, which controls NEB transdifferentiation following lung injury (Kiyokawa and Morimoto, 2020). Retinoic acid and Notch are also crucial factors for maintaining blastema cells in a proliferative state during zebrafish fin regeneration (Blum and Begemann, 2012; Grotek et al., 2013), whereas Wnt signaling plays an essential role during the early phases of limb regeneration in *Xenopus* (Yokoyama et al., 2007). Further studies of these factors, among others, could provide insight into the molecular mechanisms underlying gill regeneration in fish and amphibians.

These findings demonstrate that most of the signaling pathways that promote regeneration after injury have been conserved across evolution, and the same molecular mechanisms are involved in the regeneration of different structures, organs and tissues. If we are able to identify the conserved pathways underlying regeneration of respiratory tissues among vertebrates, this may lead to the discovery of new therapeutic approaches for human lung tissue repair and treatments for chronic lung diseases.

The role of hypoxia and HIFs in regeneration of respiratory organs

Hypoxia has been the focus of considerable regeneration research in recent years, increasing awareness of its biological and clinical significance (Darby and Hewitson, 2016; Jopling et al., 2012; Lokmic et al., 2012; Nakada et al., 2017; Rochette et al., 2017). One of the reasons for the intense interest is that hypoxia can be used in regenerative treatments to enhance tissue repair (Jopling et al., 2012; Nakada et al., 2017; Vadivel et al., 2014). However, the hypoxia 'dose' has to be adapted depending on several factors (e.g. species, age and physiological stage) in order to optimize the regeneration process while minimizing pathogenesis. Following injury, vascular function is impaired, leading to reductions in blood flow, which result in acute tissue hypoxia (Lokmic et al., 2012; Marsboom and Rehman, 2018). The hypoxic state can also be exacerbated by the high levels of oxygen consumption of cells from the wounded tissue, such as inflammatory and mesenchymal cells (Lokmic et al., 2012; Marsboom and Rehman, 2018). Cells can sense low oxygen levels and rapidly activate transcriptional and post-transcriptional mechanisms for adapting to hypoxia. Most of these responses occur through the upregulation of HIFs, master transcription factors that induce multiple target genes needed for repair of the damaged tissue (Lokmic et al., 2012; Nauta et al., 2014; Novianti et al., 2019). The role of hypoxia-induced regulatory events mediated by HIFs has also been the subject of lung regeneration research (Stenmark et al., 2006; Vadivel et al., 2014; Xi et al., 2017). During alveolar regeneration, hypoxia/HIF-1 activation drives Notch signaling, which promotes AEC2 differentiation from lineage-negative epithelial progenitors, thus enhancing the repair process (Xi et al., 2017). In newborn rats, HIF-1 enhances vessel growth and improves alveolarization by promoting the expression of a variety of angiogenic growth factors, such as vascular endothelial growth factor 1 (VEGF-1) (Vadivel et al., 2014). It is not surprising that HIFs play an active role in lung regeneration due to their important contribution to normal lung development in a hypoxic environment (Haworth and Hislop, 2003; Vogel et al., 2014).

Hypoxic activation of HIF-1 is also indispensable for successful blastema formation during regeneration of amphibian limbs (Payne et al., 2017; Rageh et al., 2002) and mammalian digits (Simkin et al., 2015) via the production of growth factors (e.g. VEGF). The effects of hypoxia on gill blastema formation remain unexplored, but hypoxia may play a positive role during branchial regeneration through activation of HIFs. In adult zebrafish, hypoxia positively regulates myocardial regeneration by stimulating the de-differentiation and proliferation of cardiomyocytes via HIF-1 (Jopling et al., 2012). In addition, caudal fin regeneration is enhanced by activation of the HIF-1 and VEGF pathways, which induce blood vessel development and tissue repair (Vivek and Malathi, 2017 preprint). In zebrafish gills, environmental hypoxia has been observed to stimulate the proliferation and growth of NECs (Jonz et al., 2004; Pan et al., 2020). Furthermore, fish gills contain active regions of cell division in order to maintain cell number during growth and regeneration (Laurent and Dunel, 1980; Mierzwa et al., 2019). Future research is now required to elucidate the role of hypoxia in regulating these populations of proliferative cells, and to investigate whether hypoxia can enhance gill regeneration by stem/progenitor cell activation.

Evolutionary hypotheses of regeneration

The issue of why ectothermic vertebrates (fish, amphibians and reptiles) have a higher regenerative capacity than birds and mammals remains unresolved. To date, a number of evolutionary hypotheses have been presented. One hypothesis suggests that, compared with mammals, the organs of adult fish and amphibians have a lower level of cellular complexity, which could facilitate cell proliferation and morphogenesis in damaged tissues (Jaźwińska and Sallin, 2016). For example, cardiomyocytes of zebrafish display a less complex cytoarchitecture than those of mammals and can undergo cell division, which mammalian cardiomyocytes are unable to do (Jaźwińska and Sallin, 2016). It has also been proposed that adult mammalian cells are maintained in a differentiated state, which restrains their de-differentiation and

transdifferentiation potentials (Zhao et al., 2016). The lower de-differentiation potential in mammals may be associated with cell cycle regulators; e.g. a barrier for muscle de-differentiation is the absence of retinoblastoma phosphorylation (Pajcini et al., 2010). Moreover, adult mammals have insufficient stem cells for tissue regeneration (Zhao et al., 2016).

A recent suggestion presented by Alibardi (2019) associates the complex life cycles of fish and amphibians with their high regenerative capacities. In amphibians, most of the tissues/organs are remodeled from larvae to adults; e.g. in some species, the tail and gill in larvae degenerate to adapt to terrestrial life (Ishizuya-Oka et al., 2010). Fish also undergo dramatic changes in shape and anatomy from larvae to adults, such as the development of swimbladder, gut, lateral line and adult fins (McMenamin and Parichy, 2013). According to Alibardi (2019), fish and amphibians that experience metamorphosis in early development could re-activate organ regeneration in adults because they have the genetic potential for restructuring anatomical features. However, this hypothesis would not explain the high capacity of reptiles to regenerate their tail (Jacyniak et al., 2017) and heart (Jacyniak and Vickaryous, 2018).

It has also been proposed that loss of regenerative potential in mammals could be directly related to the acquisition of endothermy (Hirose et al., 2019). It is thought that during evolution the loss of cardiac regenerative capacity was driven by increasing levels of circulating thyroid hormones in endothermic mammals with high metabolic rates (Hirose et al., 2019). Further studies are now required to clarify why the regenerative capacity is lower in mammals, which is a matter of the utmost importance in the field of regenerative biology.

Conclusions and future directions

The continued study of gill regeneration in non-amniotes has much to add to our understanding of tissue regeneration biology, including that of lung regeneration. As discussed in this Review, there are clear similarities in tissue structure, cell populations and genetic pathways in gills and lungs. These similarities support the idea that regenerating gills are an important source of insight into mammalian lung regeneration, just as urodele limbs have been used as a model for the regeneration of human appendages (Stocum, 2017). Much remains to be understood regarding the process of regeneration of respiratory organs in fish and amphibians, which highlights great potential for new discoveries in this field. Future research on gill regeneration will focus on understanding the source of the cells that form the blastema or defining the cellular and molecular mechanisms that modulate the regrowth of amputated gills. The genetic pathways that promote gill and lung regeneration seem to be highly conserved (Chung et al., 2018; Finch et al., 2013; Saito et al., 2019), and the genetic tools available in some model vertebrates, such as zebrafish, may lead to new developments in treating human lung disease. It is also of interest to examine the role of hypoxia and HIF-1 in gill regeneration, as hypoxia is an attractive therapy for lung regeneration in mammals (Vadivel et al., 2014; Xi et al., 2017). Following gill amputation, further characterization of new nerves and innervated cellular types, such as chemosensory NECs (homologous to mammalian NEBs), may help us to uncover the mechanisms of lung re-innervation during regeneration, a process that is poorly understood.

Currently, the incidence of lung diseases associated with a loss of pulmonary mass continues to increase, with a shortage of lungs available for transplantation. The creation of a bioengineered chimeric lung suitable for transplantation is still not feasible, and the recent discovery of de-differentiated/proliferative cells in the lung offers a unique opportunity to enhance lung repair. However, although progenitor cell availability is not a limiting factor in mammalian lung regeneration, this process is very restricted. How exactly lung stem/progenitor cell activation is controlled, and how outgrowth in lung tissue is stimulated by signaling molecules (e.g. FGF, BMP, Wnt, RA, Notch) are the focus of current and future investigations. Furthermore, a better understanding of cell growth regulation may also provide new perspectives on cancer prevention, because carcinogenesis shares common mechanisms with regeneration (Oviedo and Beane, 2009).

Why regenerative capacity is limited in mammals remains unknown, and it is not clear whether this ability was lost during mammalian evolution or is still present as a dormant ancestral characteristic. In this sense, the study of non-amniotes that possess the ability to regenerate, with the availability of powerful genetic tools, could provide insights that will uncover the molecular machinery regulating regeneration. Progress in our understanding of regeneration in the respiratory system in non-amniotes is important not only in the field of comparative physiology, but may also lead to advances in the fight against human lung disease.

Competing interests

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