Annals of Anatomy 222 (2019) 114–119

Contents lists available at ScienceDirect

Annals of Anatomy

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

INVITED REVIEW

Organ regeneration evolved in fish and amphibians in relation to metamorphosis: Speculations on a post-embryonic developmental process lost in amniotes after the water to land transition

Lorenzo Alibardi[a,b,*]

[a] Comparative Histolab Padova, Italy
[b] Dept Biology Univ Bologna, Italy

ARTICLE INFO

Article history:
Received 26 November 2018
Received in revised form
10 December 2018
Accepted 11 December 2018

Keywords:
Fish
Amphibians
Amniotes
Metamorphosis
Organ regeneration
Scarring

ABSTRACT

Organ regeneration occurs in anamniotes (fish and amphibians) while is absent in amniotes (reptiles, birds and mammals). An evolutionary hypothesis is presented to explain the loss of organ regeneration in amniotes. The aquatic life in fish or the initial aquatic and later terrestrial life in amphibians requires complex life cycles after embryonic development. One or more larval stages that occupy different ecological niches are necessary in fish to reach the final adult stage, generally through metamorphosis. This is a post-embryonic process determined by genes that are constitutive of the genome of fish and amphibians, and that can also be re-utilized during adult life to regenerate injured or lost organs. During the adaptation to terrestrial niches, the larval stages disappeared and a direct development evolved with the formation of the amniote egg in reptiles and birds or the blastocysts in mammals. The genome for developing larvae and metamorphosis was therefore eliminated from the life cycle of amniotes. The loss of genes utilized for metamorphosis determined also the loss of the capability to regenerate organs in adults, especially of the neural organization of the nervous system. The cellular immune system that in anamniotes was operating in metamorphic destruction of larval tissues, in amniotes became no longer tolerant to embryonic-larval antigens. The loss of genes operating during metamorphosis and presence of intolerant immune cells determined the inability to regenerate organs in amniotes. Efforts of regenerative medicine must overcome these genetic and immune barriers to induce organ regeneration.

Contents

1. Introduction

It was known at least since the experiments of the Italian zoologist L. Spallanzani in 1765, that organ regeneration among vertebrates occurs in newts and salamanders (urodele amphibians) but not in other vertebrates (Okada, 1996; Tsonis, 2000; McCusker et al., 2015; Stocum, 2018). Other poorly known researches found that also fish can regenerate their appendages, in particular the caudal fin as discovered by the French naturalist M. Broussonet in 1786. In comparison to amphibians, studies on fish regeneration have been scanty but they indicated some ability to regenerate the amputated tail (Zanandrea, 1956; Maron, 1960; Bird, 1978; George, 1968). Recently, numerous studies have shown that some species of fish, in particular the teleost zebrafish, can also regenerate various tissues and organs, sometimes almost like those of salamanders (Wagner and Bernard, 1992; Santos-Ruiz et al., 2002; Nakatani

* Correspondence to: Department of Biology, University of Bologna, Bologna, Italy.
E-mail address: lorenzo.alibardi@unibo.it

https://doi.org/10.1016/j.aanat.2018.12.005
0940-9602/

et al., 2007; Bockelmann et al., 2009; Cuervo et al., 2012; Yoshinary and Kawakami, 2011; Nikiforova and Golikenchov, 2012; Davidson, 2014; Jazwinska and Sallin, 2015; Rasmussen and Sagasti, 2017). Among organs known to regenerate with different degrees in fish are the fins, scales, spinal cord, brain regions, optic nerve and eye parts, intestine, kidney, heart areas, skeleton parts, and others. A remarkable example of regeneration is seen in the transected spinal cord of the lamprey and some cartilaginous and bony fish: after the initial paralysis the fish slowly regains motor coordination and swimming ability (Maron, 1963; Bernstein, 1988; Lurie and Saltzer, 1991; Ferretti et al., 2003; Tanaka and Ferretti, 2009; Rasmussen and Sagasti 2016.). Therefore not only amphibians but also numerous fish, both anamniotes linked to an aquatic lifestyle, are capable to regenerate numerous organs nearly completely, recovering part or most of their original function (restitutive regeneration).

As opposed this remarkable regenerative capability is almost completely lost in amniotes, namely reptiles, birds and mammals, vertebrates variably adapted to a terrestrial life. The only parenchymal organs capable to regenerate in terrestrial vertebrates are the liver in most amniotes and the tail in lizards, while the seasonal regeneration of the bony horns of cervids appears an osteogenic specialization of localized periosteal cells that do not really form a blastema (Li et al., 2005; Alibardi, 2010, 2014, 2017a; Cordero-Espinoza and Hutch, 2018; Seifert and Muneoka, 2018). The adaptation of vertebrates to a terrestrial lifestyle with the evolution of the complexity of the nervous and immune systems somehow determined loss of organ regeneration that is replaced by scarring (Ferguson and O'Kane, 2004; Jazwinska and Sallin, 2015). The present hypothesis, based on the presence of larvae and metamorphosis in the lifecycle of anamniotes, provides a general biological explanation for the loss of developmental plasticity in amniotes. The present hypothesis may stimulate deep molecular studies on the genes involved in metamorphosis and in organ regeneration in vertebrates.

2. Life cycles of fish, growth and metamorphosis

Life in water, especially in low sea level where vertebrates evolved in the Cambrian or Ordovician, about 480 million years ago (MYA), is very different from life on land. In pre-vertebrate forms, the limited genome contained all the genes necessary for development and for building the larval forms before reaching the adult condition (Fig. 1A; Orton, 1953; Szarski, 1957; Lagler et al., 1962; McMenamin and Parichy, 2013). Larvae or intermediate developmental forms evolved because the dispersion of developing embryos in the aquatic environment after fertilization forces the hatchings to adapt to environments different from those of their adult condition. It is likely that also the first ostracoderm vertebrates possessed a larval form, as it is also testimonial by the ammocete larva present in the derived, extant cyclostomes (Fig. 1B). The numerous anatomical modifications of the lamprey larva during its life cycle include changes in the mouth, fins, brain, anal papilla and development of copulatory organs in males. It is also likely that larval forms for the ancient placoderms, achantodes, and cladoselacians of the Devonian Period, about 380 MYA, were also present in the initial phases of the life cycles of these first gnatostomes (Fig. 1B). In extant cartilaginous fish the larval form is relatively similar to the adult (Fig. 1B), although notable differences are seen in the snout, eyes, presence of filamentous gills, different shapes of the small scales and color pattern in embryos and juveniles in comparison to the adults. Primitive freshwater fish such as the bichir, a chondrostean affiliated to the ancient paleoniscoids of the Silurian Period, about 420 MYA, feature larvae with some organs that are different from those of the adult, such as external gills, presence of adhesive organs, immature digestive tube, initial symmetric fins and later development of asymmetric fins, changes in the shape and extension of the caudal fin etc. In another relatively primitive freshwater fish, the garfish *Lepisosteus* (holosteans), the larva initially develops, among others, adhesive organs, is devoid of scales, possess a temporary long dorsal caudal filament and a different pigmentation pattern from the adult.

After reproduction in numerous bony fish the fertilized eggs, either on the bottom or fluctuating in the sea or in streams of freshwater, are abandoned from their parents and they develop and hatch as tiny larvae that during the initial stages of post-embryonic life are very different from the adult parent, and occupy a diverse ecological and feeding niches (Szarski, 1957; Lagler et al., 1962; McMenamin and Parichy, 2013; Kipanyula and Maina, 2016). In some species, the larvae grow in size but also change shape and anatomy since their genome is programmed to give rise to different post-embryonic stages that grow with few anatomical traits different from the adults. This occurs in hagfish, trout, catfish, garfish, tuna, codfish, anchovy, etc. In other species such as lamprey, lungfish, bowfin, herring, carp, sucker, sunfish, goosefish, mole-fish, anglerfish, rockfish, eel, etc., the larva stage is so different from the adult stage to require one or more intense remodeling phases indicated as metamorphoses, in order to change dramatically shape and physiological adaptations. In some cases the tadpole (larva) changes not only internal organs but also the entire external look in successive periods, and at any change a true process of metamorphosis occurs (Fig. 1C; Szarski, 1957). Some larval and intermediate forms of fish are so different, like for the eels or tape-tail fish, that they were initially classified as different species or even families (Johnson et al., 2009). The skin in larvae is often devoid of scales and results smooth and, like the rest of the body features a watery consistency, similar to that of embryos, and the skeleton is only cartilaginous. This soft consistency of body tissues is also present in all the species that can regenerate organs, as will be reported later on.

Among bony fish some remarkable changes occur between post-hatched larvae and adults, and they require one or more periods of dramatic body and organ modifications, corresponding to multiple metamorphic phases (exemplified from the eel general cycle shown in Fig. 1C; Szarski, 1957). The case of salmons, where numerous anatomical and physiological changes occur from larvae to marine adults and during their return to freshwater, evidences another complex metamorphic life cycle (McMenamin and Parichy, 2013). These different developmental programs depend from the presence of a number of genes that determine the morphogenesis of some organs, their destruction during metamorphosis, and their following regeneration into modified organs or even new organs. For instance, in the case of eels the leaf-like shape, the transparency due to lack of pigmentation and hemoglobin, the larval teeth and internal organs are turned into a pigmented cylindrical body with fins, adult teeth and other organs. While thyroid and hypophyseal hormones determine metamorphosis (Szarski, 1957; Dufour and Rousseau, 2007; McMenamin and Parichy 2013) the molecular nature of the developmental genes activated or re-pressed by these hormones in fish are still largely unknown. This represents an important field of investigation in future studies.

Aside teleosts, other species showing larval forms very different from the adults are found among the primitive bowfish (*Amia* sp, holosteans) and the lungfish (*Neoceratodus*, *Protopterus*, *Lepidosiren,* sarcopterygian fish which ancestors date back to the Devonian period; Fig. 1B). These few examples indicate that the genomes in numerous species of fish, contain all the information for the development of these larvae and their specific organs, but also for the following destruction of larval organs with the replacement and/or regeneration of the definitive, adult organs. These metamorphic genes present in the genome allow the regeneration of the same organs in case of injury or loss in adults. Therefore

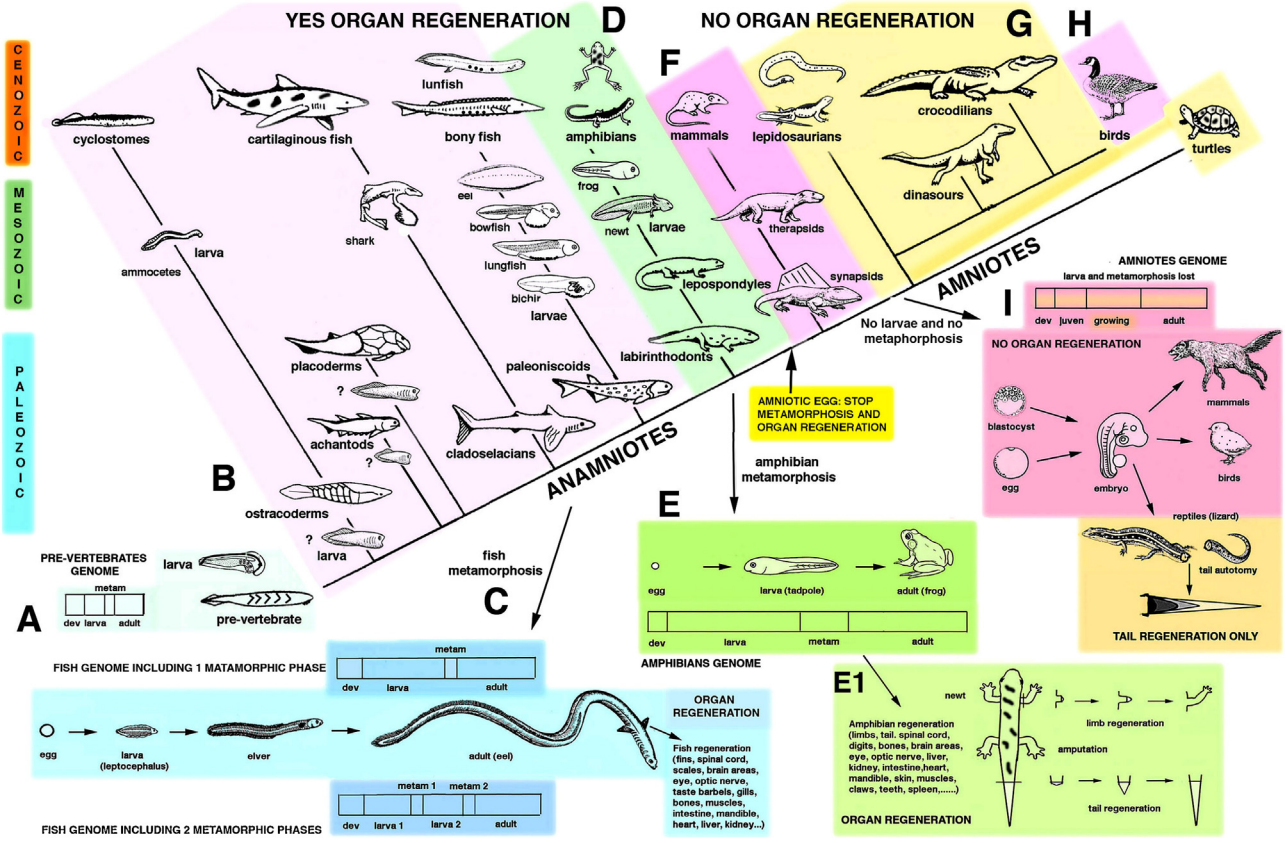

Fig. 1. Distribution of organ regeneration among vertebrates, subdivided according to their phylogenetic relationships. Organ regeneration is present in anamniotes that possess larvae while in amniotes no or rare cases of limited regeneration are observed. **A**, the relatively small genome of pre-vertebrate chordates is schematically represented by a thin rectangle (genome-bar) subdivided into the 4 phases of different length within the entire lifespan: development, larva, metamorphosis, and adult. The length of the different phases is only indicative. **B**, this area of the cladogram includes the main evolutive lineages of fish and some representative larvae stages are also shown. In extinct fish the likely presence of a larva (?) is indicated. **C**, shows three stages of metamorphosis in the eel as one of the best known examples of multiple metamorphic transitions among fish. The upper and lower genome-bars indicate two examples of fish genomes containing the 4 main phases within fish lifespan, one case comprising a single metamorphic phase (upper genome-bar) and another case with two metamorphic transitions and two distinct larval-juvenile stages (lower genome-bar). **D**, this area shows extant and extinct amphibians suggesting that they all possess/-ed larvae. **E**, illustrates the 3 main stages within the life-span of an amphibian and the corresponding phases regulated from their large genome. The length of the different phases within the long genome-bar, indicative of the high number of genes likely involved in the determination of these phases, is only indicative. Some amphibians (axolotl) may have a larval-metamorphosing phase that occupies mot of the lifespan, while frogs have a longer adult phase in comparison to the larval and metamorphic phases. **E1** points out that genes involved in larval development and metamorphosis are re-utilized in organ regeneration in adult urodeles. **G**–**H**, these areas show that no larvae are present in sauropsids (reptiles and birds) un-capable of regeneration. **I**, illustrates that the shorter genome bar of amniotes, compared with those of lungfishes and amphibians, has lost the larval and metamorphic phases present in anamniotes. A variable juvenile and growing phase, longer in reptiles but shorter in birds and mammals, remains but no organ regeneration. In lizards, following the evolution of autotomy and immune-evasion, a large but imperfect tail regenerates.

the process of metamorphosis appears as a pre-adaptation, a kind of anticipation of adult organ regeneration, a process known for some species of fish and in a limited number of organs, and in particular for the fin (Zanandrea, 1956; Maron, 1960; George, 1968; Wagner and Bernard, 1992; Nakatani et al., 2007; Yoshinary and Kawakami, 2011; Cuervo et al., 2012; Pfefferli and Jazwinska, 2015). The molecular discovery and characterization of these "metamorphic and regenerative genes" in future studies will allow to explain organ regeneration in fish, but also providing specific indications that explain the differences with amniotes.

3. Amphibian life cycles and metamorphosis in relation to the transition to land

The following group of vertebrates that evolved from piscine ancestors, the amphibians, represent the forms of passage from water to land, but they however needed an initial aquatic stage (tadpole) before a metamorphic process allowed them to become adapted to the land (Orton, 1953; Szarski, 1957; Laudet, 2011). Amphibians appeared during the end of the Devonian, about 350 MYA, from sarcopterigian fish ancestors that, like extant dipnoans, included larval forms that metamorphosed (Nogueira et al., 2016). The development of larvae or tadpoles was likely present also in ancient labirinthodont amphibians of the Carboniferous-Permian, 340-250 MYA, and this type of life cycles remained also in numerous species of extant lissamphibians, urodeles and anurans (Szarski, 1957; Fig. 1D). Sarcopterygian fish possess large genomes, probably also related to the number of genes utilized to develop larval forms and, in amphibians, that are needed in the transition from a complete aquatic life to a terrestrial life (Smith et al., 2009; Nogueira et al., 2016; Elewa et al., 2017). Amphibians therefore inherited large genomes and evolved in numerous forms during the Carboniferous Period, at 330-300 MYA.

Some aquatic species remained for the entire life cycle or most of it under a larval form capable of reproduction (neotenic) while others changed largely from their tadpole stage through a brief or long period of metamorphosis (Laudet, 2011; Fig. 1E). In some extant perennibranchiate urodeles such as the genus *Amphiuma*, *Proteus*, and *Necturus* the larvae grow to reach an adult and reproductive size but remain for the entire life cycle with a larval look, therefore neotenic. In *Ambystoma mexicanum* the tadpoles grow in size until they are capable to reproduce (neoteny; Szarski, 1957;

Grygorian, 2016). These neotenic form (axolotl) remains for most or the entire life cycle although metamorphosis can occur in special natural or laboratory conditions. In this case the shape changes, gills are resorbed, the tail become cylindrical, the mouth and intestine are modified, as well as the skin pattern and various internal organs including the skeleton (Brown and Cai, 2007; Laudet, 2011). This specie shows the highest phenomenon of organ regeneration, including the tail and limbs (McCusker et al., 2015; Stocum, 2018). Numerous other organs are also regenerated such as parts of the brains, spinal cord, liver, kidney, intestine, eyes, large skeletal elements, skin, etc., organs that are often destroyed and rebuilt during metamorphosis (Das et al., 2006; Brown and Kay, 2007).

Similar anatomical-physiological changes normally occur in more terrestrial adapted urodeles such as newts that undergo to a mild form of metamorphosis, whereas external gills disappear, the flat tail turns roundish without folds, the mouth and various internal organs change, and so forth. Newts broadly regenerate anatomical and functional organs, including limbs and tails (Fig. 1E1). The most terrestrial-adapted salamanders tend to loose the larva stage and broad metamorphic changes, their tissues become dryer than in aquatic urodeles, and various species show poor or no organ regeneration (Scadding, 1977, 1981). The best terrestrial-adapted amphibians, the anurans, initiate the life cycle as pisciform tadpoles that undergo the most dramatic metamorphosis (Fig. 1D, E). While regeneration is intense in early larvae, this capacity is rapidly lost approaching metamorphosis, and is almost completely gone in froglets after metamorphosis and in adults (Harty et al., 2003; Mescher et al., 2016). The passage from aquatic to terrestrial niches is somehow associated to the loss of regeneration, a condition that is typical for amniotes. Also the axolotl, after metamorphosis, lowers its regenerative ability (Monaghan et al., 2014). In plethodontids, urodeles that undergo to direct development and almost lack a larval form or that develop pedomorphic larvae (Beachy et al., 2017), regeneration is much slower than in other salamanders (Arenas-Gomez et al., 2017). Also in other evolutive lineages of amphibians the larval form has been lost, like in some anurans and in the limbless gymnophions (Szarski, 1957), and these amphibians do not or partially regenerate limbs or tails.

It is therefore likely that the large genomes of numerous amphibians contain genes utilized during metamorphosis that are later used for regeneration in case of injury or organ loss, a process that is indicated also from fossils of ancient labirinthodont amphibians, temnospondils and microsaurians of the Carboniferous-Permian, 340-250 MYA, (Szarski, 1957; Frobisch et al., 2014, 2015). Among other genes, those that are triggered by thyroid hormones, like in fish, appear implicated in metamorphosis after the interaction with thyroid hormone receptors (Das et al., 2006; Brown and Cai, 2007; Laudet, 2011). Among the genes up-regulated after hormonal stimulation are those coding for deiodinases (enzymes that inactivate thyroid hormones), caspase-3 (operating in apoptosis), some proteases for muscle and notochord degeneration, collagenases, matrix metallo-proteinases, fibroblast-activator factors, new keratins, and enzymes involved in the cell cycle controls. Some of these same genes are also activated during regeneration through thyroid hormone receptors, demonstrating the similarity between regeneration and metamorphosis.

The large genomes of urodeles and anurans appears not only associated to a more or less dramatic metamorphosis but also to their large regenerative power. One difference between urodeles and anurans is the genome involved in immunity, that especially in anurans become more efficient while remains weak in urodeles (Harty et al., 2003; Mescher et al., 2016; Alibardi, 2016). In anurans, T lymphocytes and effector macrophages become more effective to recognize antigens formed during embryonic and larval phases, and provide to eliminate the cells that expose these antigens by apoptosis and the following auto-lysis from lysosomes and heterolysis from macrophages (Nakai et al., 2017).

4. Loss of metamorphosis in amniotes and direct development

As it is suggested by anuran metamorphosis, the adaptation to the terrestrial life is correlated to the loss of organ regeneration (Harty et al., 2003; Mescher et al., 2016). We here hypothesize that the larva and metamorphic stages were lost in amniotes since their initial evolution in the mid-upper Carboniferous, with the origin of the reptilian egg and the definitive establishment of a direct development in basal amniotes (reptiles). Therefore all or part of the developmental genes operating in the stages of larva and metamorphosis disappeared from the genomes of amniotes, or were modified or could no longer integrate into developmental pathways capable to regenerate organs, in other words amniotes lost developmental plasticity. This hypothesis is sustained from recent researches that have detected loss of few genes in amniotes, genes that are implicated in the regeneration in anamniotes, such as genes of the Anterior gradient family 1 (*Agr1)* and some genes of the Rat sarcoma (*Ras*) such as *Ras-dva GTPase* (Ivanova et al., 2013, 2018). The *Agr1* expression is present in the *Xenopus* embryo and larva stages, but disappears approaching metamorphosis and in post-metamorphic stages. The expression of *Agr1* however increases during limb regeneration of young anuran larvae in the pre-metamorphic phase. The *Agr1* gene, essential for amphibian regeneration, is absent in amniote genomes and in humans (Ivanova et al., 2013). The *Ras-dva GTPase* expression also increases during the neurulation and early larval stages in the anuran *Xenopus laevis*, and also after limb/tail amputation in early *Xenopus* tadpoles or fin amputation in zebrafish, but this gene is lost in amniotes (Ivanova et al., 2018). These studies have suggested that even the elimination of few key genes can disrupt the entire signaling network of molecules sustaining appendage regeneration so that regeneration is no longer feasible.

In addition to loss of key regenerative genes, numerous organs in amniotes became more organized and specialized anatomically to perform complex functions in the terrestrial environment. Among these organs are the spinal cord and brain, and the progressive increase of size and performance of the telencephalon in amniotes, especially in mammals, has been correlated to the disappearing of *Agr* and *Ras-dva GTP* genes during evolution (Ivanova et al., 2013, 2018). These genes are also absent in lizard transcriptomes during tail regeneration (Alibardi, 2017a). In order to perform complex functions, the neuronal network sustaining higher memory and behavior activity must be fixed with only limited possibility to be disrupted and later regenerated. In amniotes, and especially in mammals, the stability of complex neural circuits became more important than plasticity and circuit regeneration, a deleterious process because memory and higher integrative and social behavior based on established and invariant nervous networks would disappear in case of continuous/frequent network remodeling or regeneration. Various inhibitory mechanisms have evolved to hamper regeneration plasticity and axonal sprouting in the mammalian (avian) nervous system (Ferretti et al., 2003; Tanaka and Ferretti, 2009; Rasmussen and Sagasti, 2016).

A way to eliminate regenerating cells, including the neuron-axons plasticity, was the improvement of immune cells in their ability to discriminate self and not-self antigens, maintaining only adult antigens when the immune tolerance is completed after birth (Simon et al., 2017). The late acquisition of immune-tolerance that occurs after birth in mammals, determines the selection of mature T-cells un-capable to recognize numerous early antigens (embryo-fetal antigens). The latter are present

during early embryonic stages but disappear as development progress. In order to regenerate an organ an initial accumulation of embryonic cells is necessary to form a blastema, but in adult bodies these cells are attached from immune cells, impeding regeneration (Alibardi, 2016). The only way to stop the immune antagonism was the evolution of mechanisms of immune-suppression. At least three major immune-suppression events occurred during amniote evolution: (1) immune-evasion of tumor cells (Gabrilovich et al., 2012), (2) blastema formation in the lizard tail (Alibardi, 2017a, 2017b, 2018a), and (3) placentation, especially in mammals (Trowsdale and Betz, 2009; Griffith et al., 2017).

In the case of lizards, a process of regeneration of the tail was present since the Permian-Triassic 280-220 MYA (Bellairs and Bryant, 1985; Alibardi, 2010, 2018b; LeBlanc et al., 2017). The tail is the largest organ that can regenerate in amniotes in relation to the body size, 1/6th-1/4th of the entire body mass. The regenerated tail contains large masses of integrated tissues, but also evidences several anatomical and functional limitations in comparison to the original tail, such as a segmental muscle organization, an axial cartilaginous cylinder replacing the vertebral column, and a simplified spinal cord without ganglia. The most likely explanation for justifying the regeneration of the tail in lizards is the evolution of a mechanism of self-amputation of the tail termed autotomy in ancient lizards, associated to a temporary immune-suppression (Alibardi, 2017b, 2018a, 2018b). The latter in particular allows the formation of a regenerative blastema that rapidly grows for a limited period, 1–2 months, however sufficient to give rise to a new tail with 60–90% of the original size, depending from the species (Bellairs and Bryant, 1985; Alibardi, 2010, 2017a, 2017b). This has suggested that, in general, organ regeneration requires a temporary mechanism of immunosuppression.

In conclusion, the present hypothesis suggests that only anamniotes with a more or less accentuated process of metamorphosis and organ plasticity are also able to re-activate the process in form of organ regeneration as adults because restructuring anatomical features is part of their life cycle. Restitutive regeneration therefore is only present in vertebrates that can still utilize developmental process normally operating during their life-cycle. Based on these biological premises, what is the real hope for organ regeneration in mammals if their entire evolution aimed to rapidly seal their wounds by scarring and blocking developmental plasticity? (Ferguson and O'Kane, 2004; Jazwinska and Sallin, 2015). It is clear that the dream to stimulate human organ regeneration has to face the real biological problems presented above. Although a perfect restitutive regeneration is not even present in salamanders, lower degrees of regeneration may be possible even in mammals. Attempts to induce organ regeneration in mammals should: (1) using comparative genomics, evaluate whether mammals still possess at least some of the genes that promote metamorphosis-regeneration in anamniotes, (2) induce the dedifferentiation of somatic cells for the formation of hydrated and plastic regenerative blastemas with the consistency of an embryonic organ, (3) find a way to immunosuppress especially T-cells during the regeneration of induced blastemas, maintaining under control infections and possible tumor formation, and finally (4) stimulate growth and morphogenesis of these blastemas by the induction of gradients of signally molecules such as Wnt, Shh, Notch, Hox etc, in order to regenerate the original organ. These enormous tasks presently appear still a long way to go, and it is likely that the much rapid development of prostheses for limbs or artificial organs will be the fate for regenerative medicine in the next decades (Laurencin and Nair, 2016).

Ackowledgments

The researches conducted over the years on the analysis of different aspects of organ regeneration in vertebrates have been mainly self-supported.

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