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Ecological and Medicinal Importance of Lampreys (Cyclostomata: Petromyzontiformes: Petromyzontidae)

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Abstract: For Pacific lampreys, life is not just about moving from freshwater to saltwater when they reach maturity, these ancient fish have to return to the same river environment where they were born. Going from a saltwater creature to a freshwater creature is not easy, however, and several modifications in appearance and physiology are necessary to survive the dramatic change in salinity. Their return to freshwater is not random, based on chemical signals left by the migration of lamprey larvae to return to rivers They can return to the same place they came from, but, unlike Pacific salmon, this precision is not always guaranteed, however, this transformation and the mapping of rivers require a lot of energy, and the animals resort to parasitization to survive. Lamprey swimming is among the most efficient in the world, as its movements generate zones of low pressure around the body, pulling the body through the water rather than pushing. The objective of this article was to characterize lampreys (Cyclostomata; Petromyzontiformes; Petromyzontidae) regarding their ecological and medicinal importance. The methodological analysis included studies of a particular topic. In its construction process, it is necessary to go through six essential stages: Identification of the theme and selection of the hypothesis or research question; establishment of criteria for inclusion and exclusion of studies/sampling or literature search; definition information to be extracted from selected studies/categorization of studies; evaluation of included studies; interpretation of results; and presentation of knowledge review/synthesis To carry out the study, a search for scientific articles was carried out through Virtual Health Library, in the SCIELO, LILACS, and PUMED databases, using the terminologies registered in the Health Sciences descriptors. Regarding the inclusion criteria, the following were used: Full articles, in Portuguese, and English.

Keywords: Biology, Freshwater, Life Cycle, Morphology, Mucus.

Research Paper

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1. INTRODUCTION

Lamprey is the name given to animals belonging to the Phylum: Chordata; Subphylum; Vertebrates; Infraphylum: Agnatha; Class: Cephalaspidomorphi; Subclass: Hyperoartia; Clade Cyclostomata; Order: Petromyzontiformes; Family: Petromyzontidae; Subfamilies: Geotriinae, Mordaciinae and Petromyzontinae. There are around 40 species of lampreys, which inhabit marine environments and also freshwater regions. In general, lampreys are around 30 cm long, but the species *Petromyzon marinus* Linnaeus, 1758 can reach 1.20m (Figure 1) (Araújo, 2006; Almeida, 2021).

Its body is elongated and resembles an eel. They have a disc-shaped mouth and a tongue full of keratin teeth, used to penetrate the skin of their prey and extract blood, body fluids, and tissues. The lamprey is a fish belonging to the Agnata group, which means it does not have true jaws or paired fins. It has a round mouth, with numerous small teeth and a sucker. In Portugal, there are three species of lamprey are marine, river, and stream. The sea lamprey is the best-known, and much appreciated in gastronomy (Araújo, 2006; Diogo and Ziermann, 2015; Almeida, 2021).

Figure 1: *Petromyzon marinus* Linnaeus, 1758
Source: https://simrbase.stowers.org/sealamprey

1.1. Morphology

They are characterized by a disc-shaped, jawless mouth lined with a series of teeth called odontoids. This mouthpart is used in most species to parasitize other fish and, in this way, feed in adulthood. The ammocotes of the river lamprey are morphologically indistinguishable, but in the adult form the two species present characteristics that easily diagnose them, namely the body size, the river lamprey has much larger dimensions, and the river odontoids have pointed odontoids while the brook lamprey does not (Figure 2) (Mano and Yoshitaka, 2007; Diogo and Ziermann, 2015; Almeida, 2021; Pedro, 2021; Mallatt, 2023).

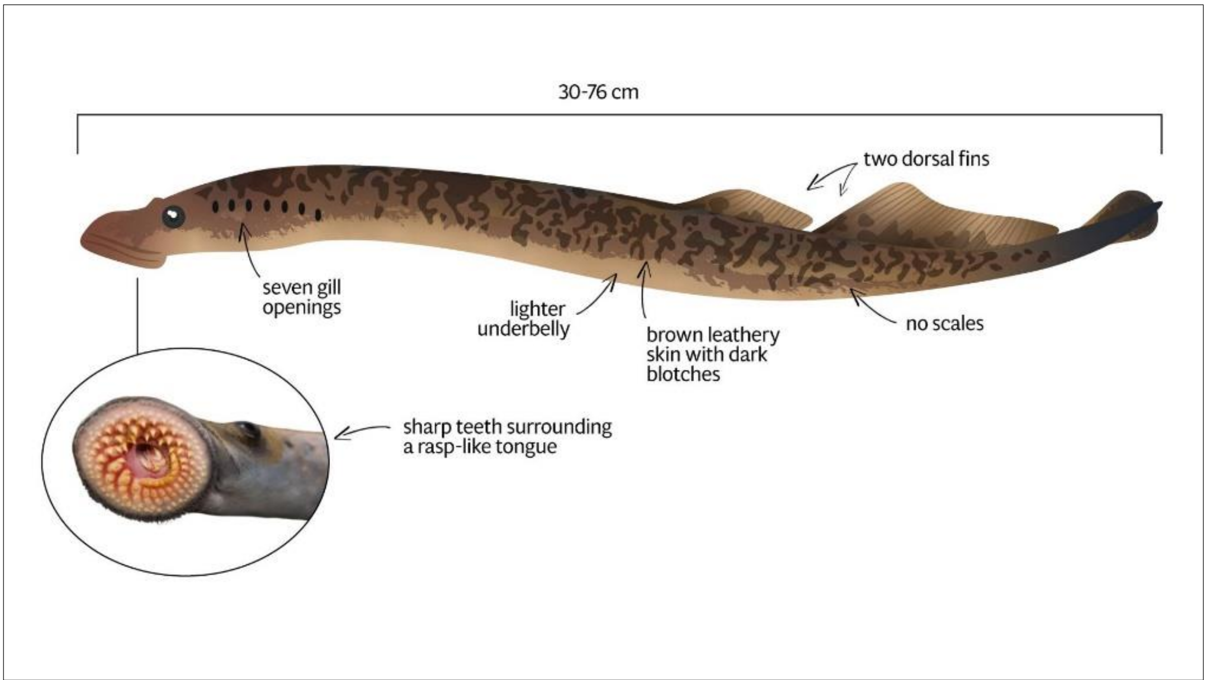

Figure 2: **External morphology of the lamprey**
Source: https://www.invasivespeciescentre.ca/invasive-species/meet-the-species/fish-and-invertebrates/sea-lamprey/

They have lateral eyes and only one nasal opening on the top of the head. On each side of the head, there are seven approximately circular gill slits, which are not protected by an operculum. Below the dorsal fin, the cloaca is located. When adults, feed, they attach their round mouths to the flank of vertebrates, generally large fish. They then use their rough mouth and tongue with keratin teeth to penetrate the prey's skin to remove food from its body (Figures 3-4) (Lafferty and Kuris, 2002; Araújo, 2006; Diogo and Ziermann; 2015; Almeida, 2021; Pedro, 2021).

Figure 3: These images show adult sea lampreys (top and left) and a developing sea lamprey embryo
Source: Image credit: Stowers Institute for Medical Research

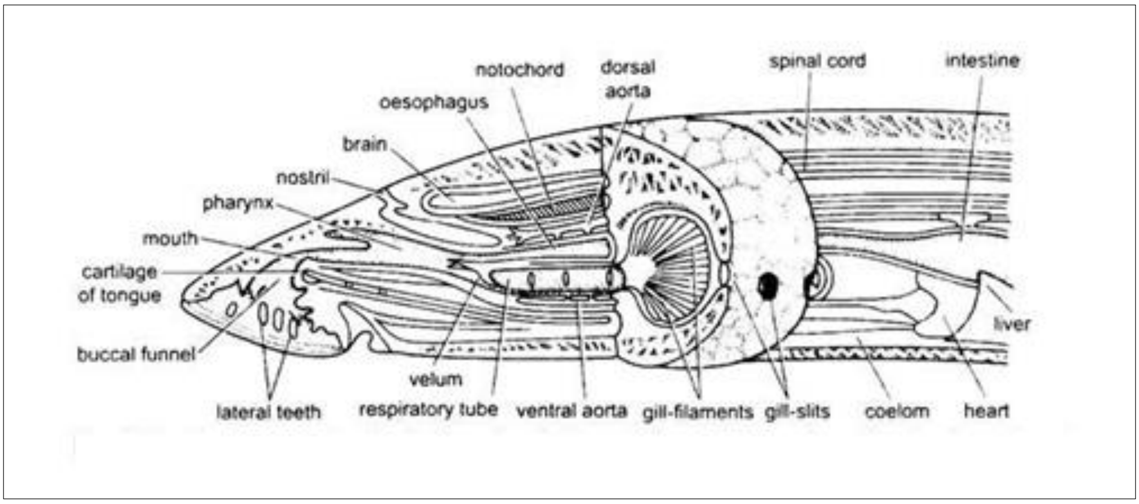

Figure 4: ***Petromizon*** **Linnaeus, 1758, longitudinal sectional view of the anterior portion showing the internal structure. A portion of the body is kept intact to show the position of a gill slit**
Source: After Storer and Using

The distribution area of the river lamprey is confined to the European Continent. It is distributed from the coastal waters and rivers of Northern Europe, along the North and Baltic Seas coasts, to the Iberian Peninsula in the south in the Tagus River basin. The species uses suction through its spherical, jawless mouth, creating a vacuum where its pointed protuberances help bite and hold the bodies of fish and aquatic mammals for food. In doing so, they suck blood and bodily fluids, leaving a spherical wound, but without killing the host (Reinhardt *et al.,* 2008; Potter, 2014; Almeida, 2021; Mallatt, 2023).

1.2. Life Cycle

Anadromous, demersal, and euryhaline species' life cycle is summarized as follows: They are born in rivers, descend to the sea to reach maturity, and return to the river to reproduce. The marine phase of the species has great unknowns. After 2-3 years at sea, it reaches maturity and its reproductive instinct takes it to the river. At the breeding site, they attach themselves to rocks with the help of their mouth disc, which at sea allows them to cling to prey to feed on its blood, and the male digs a hole in the sand, where they are deposited by the female, between 60,000 and 300,000 eggs measuring around 1 mm in diameter. After preparing the nest, the female trapped in a rock allows the male to attach himself to her head and fertilize the eggs (Figure 5) (Renaud *et al.*, 2009; Silva *et al.*, 2013b; Renaud and Cochran, 2019; Saints, 2024; Santos, and Morelli, 2024).

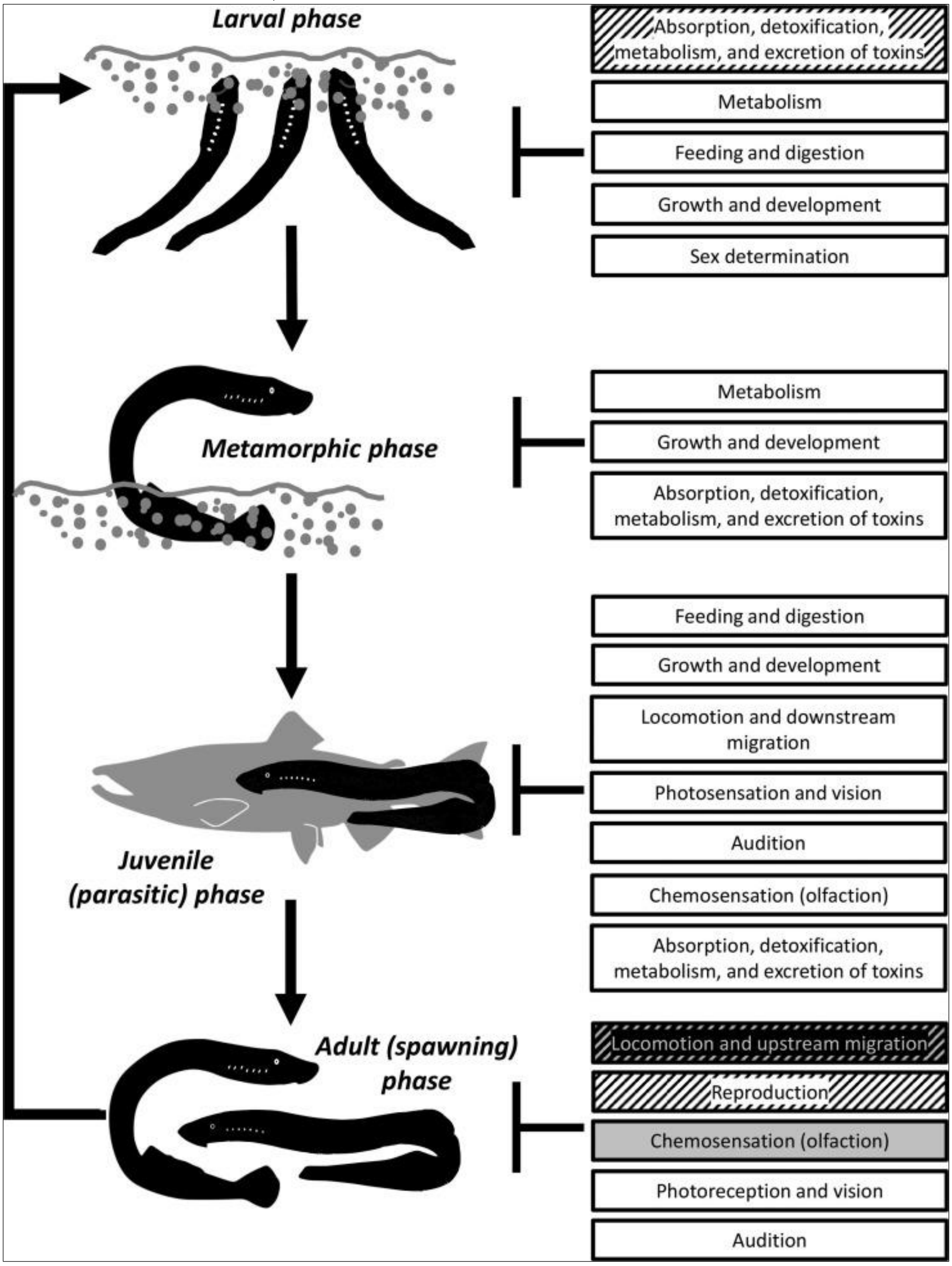

Figure 5: Features of lampreys relevant to control and conservation are divided into current or field-tested methods (black), methods currently under investigation (gray), and proposed or potential methods (white). Methods of control either target the indicated life stage directly (e.g., lampricides) or prevent that life stage from being successful (e.g., traps and barriers that prevent mature lamprey from entering the spawning stage). Features that fit into multiple categories are identified with hatched boxes representing each category
Source: https://doi.org/10.1016/j.jglr.2021.10.015

Ammocete larvae live in freshwater for an estimated period of between 3 and 5 years, feeding on debris and microorganisms, and have no teeth and rudimentary eyes. After metamorphosis, they descend the river to the sea between January and March, living parasitically, feeding on the blood of fish such as salmon, trout, and shad, among others. They frequently appear, at this stage of their life cycle, in fisheries (Diogo and Ziermann, 2015; Almeida, 2021).

1.3. Bioecology

For Pacific lampreys, life is not just about moving from freshwater to saltwater when they reach maturity, these ancient fish have to return to the same river environment where they were born. Going from a saltwater creature to a freshwater creature is not easy, however, and several modifications in appearance and physiology are necessary to survive the dramatic change in salinity. Their return to freshwater is not random, based on chemical signals left by the migration of lamprey larvae to return to rivers They can return to the same place they came from, but, unlike Pacific salmon, this precision is not always guaranteed, however, this transformation and the mapping of rivers require a lot of energy, and the animals resort to parasitization to survive. Lamprey swimming is among the most efficient in the world, as its movements generate zones of low pressure around the body, pulling the body through the water rather than pushing (Figure 6) (Reinhardt *et al.*, 2008; Almeida, 2013; Potter, 2014; Diogo and Ziermann, 2015; Elena, 2015; Renaud and Cochran, 2019; Mallatt, 2023; Saints, 2024).

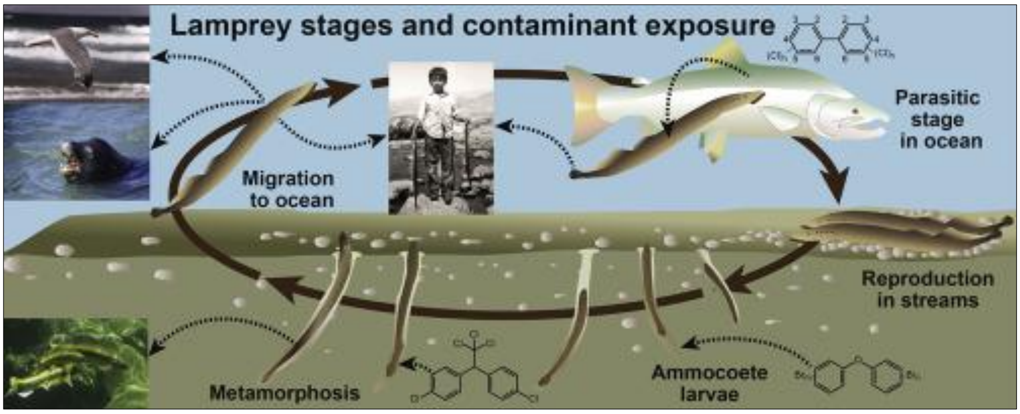

Figure 6: In 2011, 30 paired samples 15 larval lamprey/15 sediment samples were collected at 15 sites from the Umatilla River Basin, Deschutes River Basin, Fifteen mile Creek, Mill Creek, Hood River, and Willamette River Basin
Source: https://doi.org/10.1016/j.envpol.2015.03.003

In Portugal, it was not yet known exactly what time of year this species migrated. With this work, it was possible to identify a relatively short migratory season that runs from February to March. In the rest of Europe, reproductive migration varies between Summer/Autumn in the most northern countries and Autumn/Winter in the most southern countries and can last until spring. Nest construction and breeding sites are normally located in the middle (Renaud *et al.*, 2009; Santos, 2009; Silva *et al.*, 2013b; Silva *et al.*, 2013c).

Pacific lampreys *Entosphenus tridentatus* (Richardson, 1836), also known as vampire fish, females lay up to 200,000 eggs in nests, incubated in fresh water for three to four weeks. After hatching, the larvae burrow into the sediment and remain there for up to a decade. This species usually migrates downstream to the ocean to feed and only returns to freshwater habitats years later to reproduce. During adulthood, they can travel hundreds of miles inland in search of the perfect place to spawn and breed (Figure 7) (Rubinson, 1990; Potter and Gill, 2003; Renaud *et al.*, 2009; Santos, 2009; Silva *et al.*, 2013a).

Figure 7: A composite image showing different phases of the lamprey life cycle. The picture of the embryo (left) is stained by in situ hybridization for a gene marking migratory neural crest cells
Source: https://thenode.biologists.com/a-day-in-the-life-of-a-lamprey-lab/lablife/

Reaching up to 84 centimeters in length, lampreys are prey for many species of birds, mammals, and even other fish due to their extremely fatty meat, which can contain three to five times more calories per weight than salmon (Silva *et al.,* 2013c; Santos, 2024).

1.4. OBJECTIVE

The objective of this article was to characterize lampreys (Cyclostomata; Petromyzontiformes) regarding their ecological and medicinal importance.

2. METHODS

The methodological analysis included studies of a particular topic. In its construction process, it is necessary to go through six essential stages: Identification of the identification of the theme and selection of the hypothesis or research question; establishment of criteria for inclusion and exclusion of studies/sampling or literature search; definition information to be extracted from selected studies/categorization of studies; evaluation of included studies; interpretation of results; and presentation of knowledge review/synthesis To carry out the study, a search for scientific articles was carried out through Virtual Health Library, in the SCIELO, LILACS, and PUBMED databases, using the terminologies registered in the Health Sciences descriptors. Regarding the inclusion criteria, the following were used: Full articles, in Portuguese, and English.

3.0. SELECTED STUDIES

3.1. Ecological and Medicinal Importance

Ecologists know that lampreys are responsible for maintaining the health of rivers. Doctors study them to understand their incredible ability to regenerate even after severe damage a healing factor that may offer a way to regenerate spinal injuries in humans. These fish are extremely useful for the ecosystem. They transport nutrients from lakes to rivers and their larvae filter the plankton (John Hume-University of Michigan). There is also its contribution to medicine: Proteins in fish saliva act as anticoagulants and dilate blood vessels (Figures 7-9) (Macey *et al.*, 1998; Wong *et al.,* 2012; Smith, 2018; Suzuki and Grillner, 2018; Yokoyama, 2021; Oliver *et al.,* 2022).

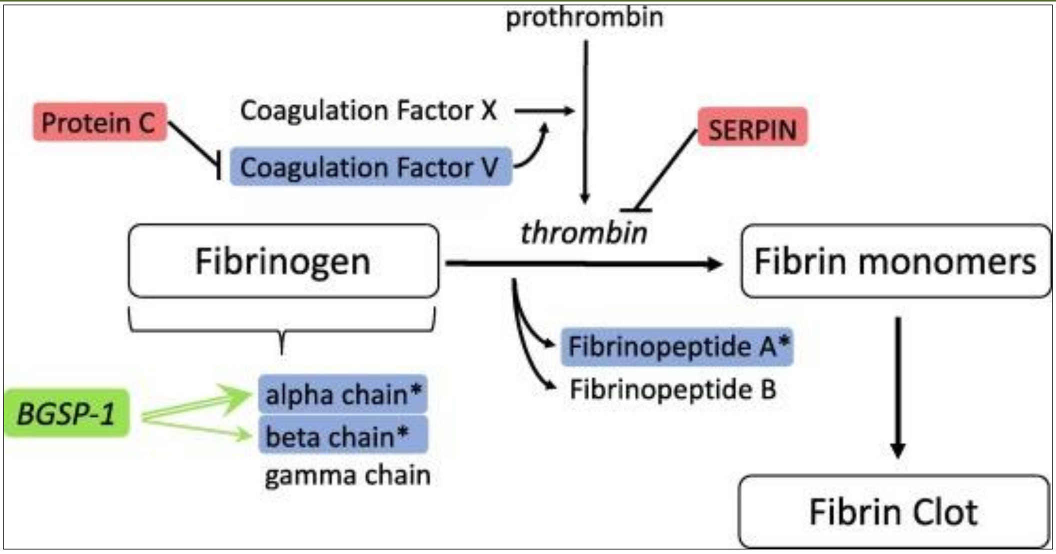

Figure 7: Schematic depicting a simplified pathway of fibrin clot formation in vertebrates to demonstrate the impacts of sea lamprey parasitism on this process in Lake Charr plasma. Thrombin initiates clot formation by cleaving fibrinopeptides A and B from the alpha and beta chains of fibrinogen, respectively. The resulting free fibrin monomers can then polymerize into a fibrin clot. Thrombin is activated from prothrombin by coagulation factor X and its cofactor, coagulation factor V. Inhibition of blood clot formation is mediated in part by a serine protease inhibitor (SERPIN) that acts on thrombin, and protein C acting on coagulation factor V. Proteins highlighted in red were elevated in parasitized fish, while proteins highlighted in blue were lower in parasitized fish relative to non-parasitized controls. An asterisk indicates a protein that was not fully recovered to control levels 7 months after the parasitism event. Buccal gland secretory protein 1 (BGSP-1; green) is a fibrinogenolytic component of lamphredin secreted by parasitic lampreys during feeding. Green arrows show known specific targets of BGSP-1, with size indicating relative specificity

Source: https://doi.org/10.1016/j.jglr.2021.11.005

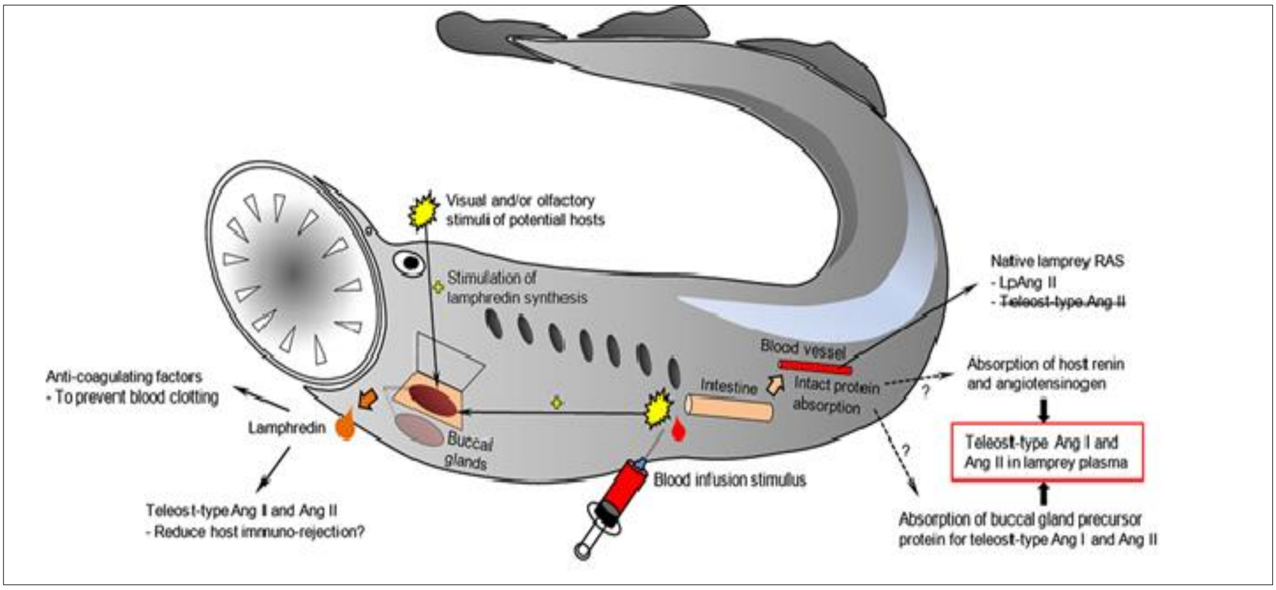

Figure 8: Schematic diagram of the localization of teleost-type angiotensin components in lampreys. Teleost-type Ang I and Ang II are produced in the buccal gland but they are largely absent in the systemic circulation. Instead, lampreys possess a different form of angiotensin (LpAng II) in their plasma, which is biologically active. Visual and/or olfactory stimuli by the presence of potential host and blood infusion into the intestine enhance the production of teleost-type Ang II in the buccal gland. Besides anti-coagulating effects, lamphredin may also contain host-specific hormones (e.g. Angiotensins) to evade host immune rejection, as part of the endocrine mimicry strategy. The source of teleosttype angiotensin components in lamprey plasma is still unclear. Previous isolation of teleost-type angiotensin components may originate from intact protein absorption of buccal gland

precursor proteins of teleost-type Ang I and Ang II produced by the buccal gland. Alternatively, intact absorption of host renin and angiotensinogen may also generate teleost-type angiotensin components in lamprey plasm
Source: https://doi:10.1016/j.biochi.2011.09.015.

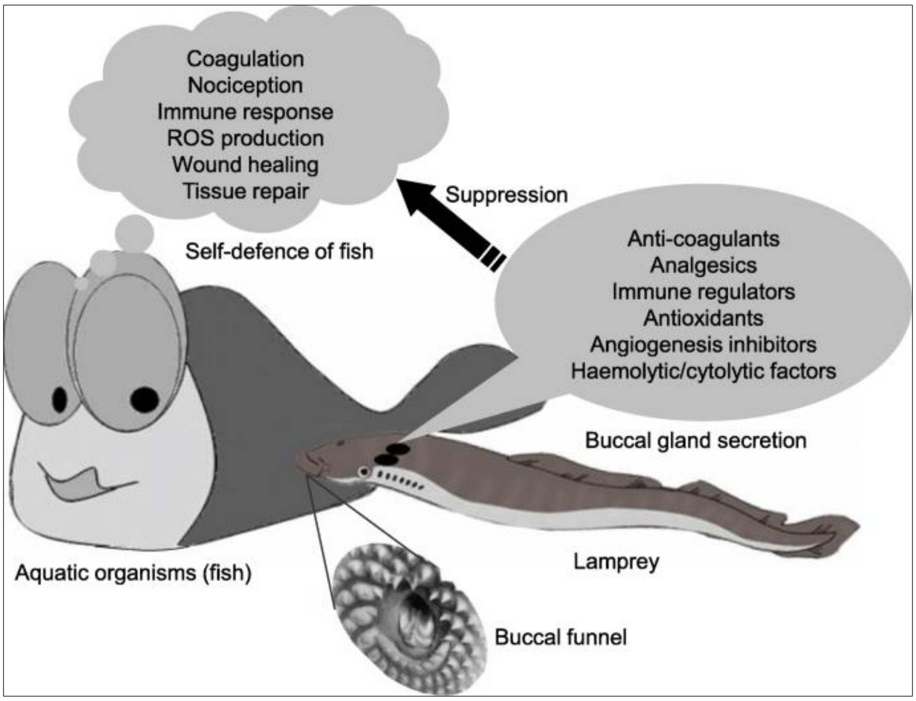

Figure 9: Lampreys have to evolve various strategies to subvert the adverse responses generated by host fishes. When lampreys feed on host fishes, novel proteins related to anticoagulation, analgesia, immune regulation, antioxidantion, anti-angiogenesis, and cytolysis emerge in their buccal glands to suppress the adverse responses generated by host fishes
Source: https://doi. org/10.1186/s12953-018-0137-5

They also have a high iron tolerance, which could be useful to researchers studying cures for hemochromatosis, a condition that affects people who are unable to control the amount of iron they absorb from food and which can result in a range of illnesses, including cirrhosis and erectile dysfunction. Finally, there is the incredible regeneration capacity of these fish, which can practically completely recover from total injuries to their spinal cord. Something humans can currently only dream (Figure 10) (Silva *et al.*, 2013b; Silva *et al.*, 2013c; Tulenko, 2013; Smith, 2018; Yokoyama, 2021).

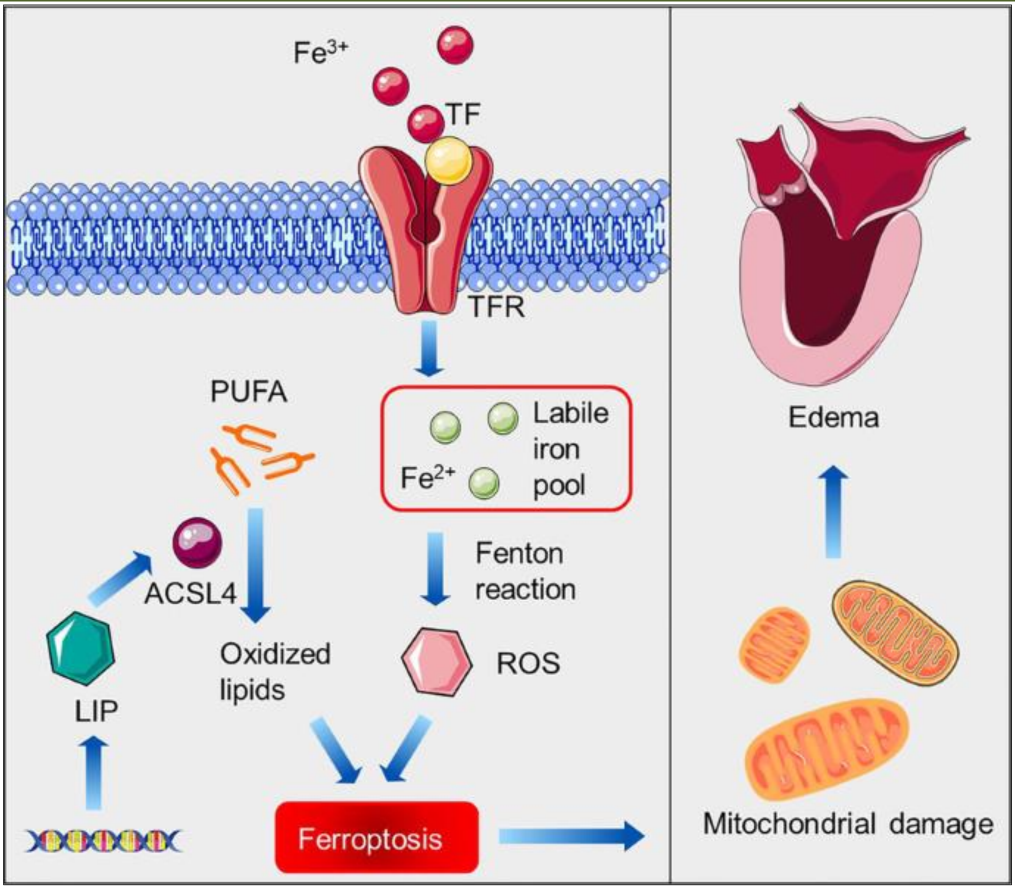

Figure 10: Network visualization of key signaling and lipid regulatory modules implicated in ferroptosis. The gene regulatory network comprises the following circuits (in chronological order of execution): 1. Iron overload; 2. Lipid peroxidation 3. Ferroptosis and 4. Mitochondrial damage and pericardial edema. Full protein names of the nodes in this network are as follows: TF: transferrin, TFR: transferrin receptor, ACSL4: acyl-CoA synthetase long-chain family member 4

Source: https://doi.org/10.1186/s12964-022- 00933-0

New research suggests that these aquatic dwellers may provide an adaptable vehicle for drugs that treat the biological effects of conditions or health events affecting the brain. A recent study, conducted by a team of scientists from the University of Wisconsin-Madison and the University of Texas at Austin, has looked at a type of molecule from the immune system of lampreys, called variable lymphocyte receptors (Smith, 2018; Suzuki and Grillner, 2018; Yokoyama, 2021).

The researchers explain that what makes VLRs interesting is their ability to target the extracellular matrix, a network of macromolecules that provide structure to the cells they surround. This network makes up a large part of the central nervous system, so the research team believes that VLRs can help carry drugs to the brain, boosting the effectiveness of treatments for brain cancer, brain trauma, or stroke (Tulenko, 2013; Suzuki and Grillner, 2018; Yokoyama, 2021).

In the current research, the investigators were interested in testing the effectiveness of VLRs, taking advantage of the disruption of the brain-blood barrier in the case of glioblastoma, an aggressive form of brain cancer. Molecules like this [VLRs] normally couldn't ferry cargo into the brain, but anywhere there's a blood-brain barrier disruption, they can deliver drugs right to the site of pathology (Shusta) (Figure 11) (Green and Bronner, 2014; BBC News, 2015; Cohut and Eric, 2019; Barany *et al.*, 2020; Aurangzeb, 2021; Brittney, 2021).

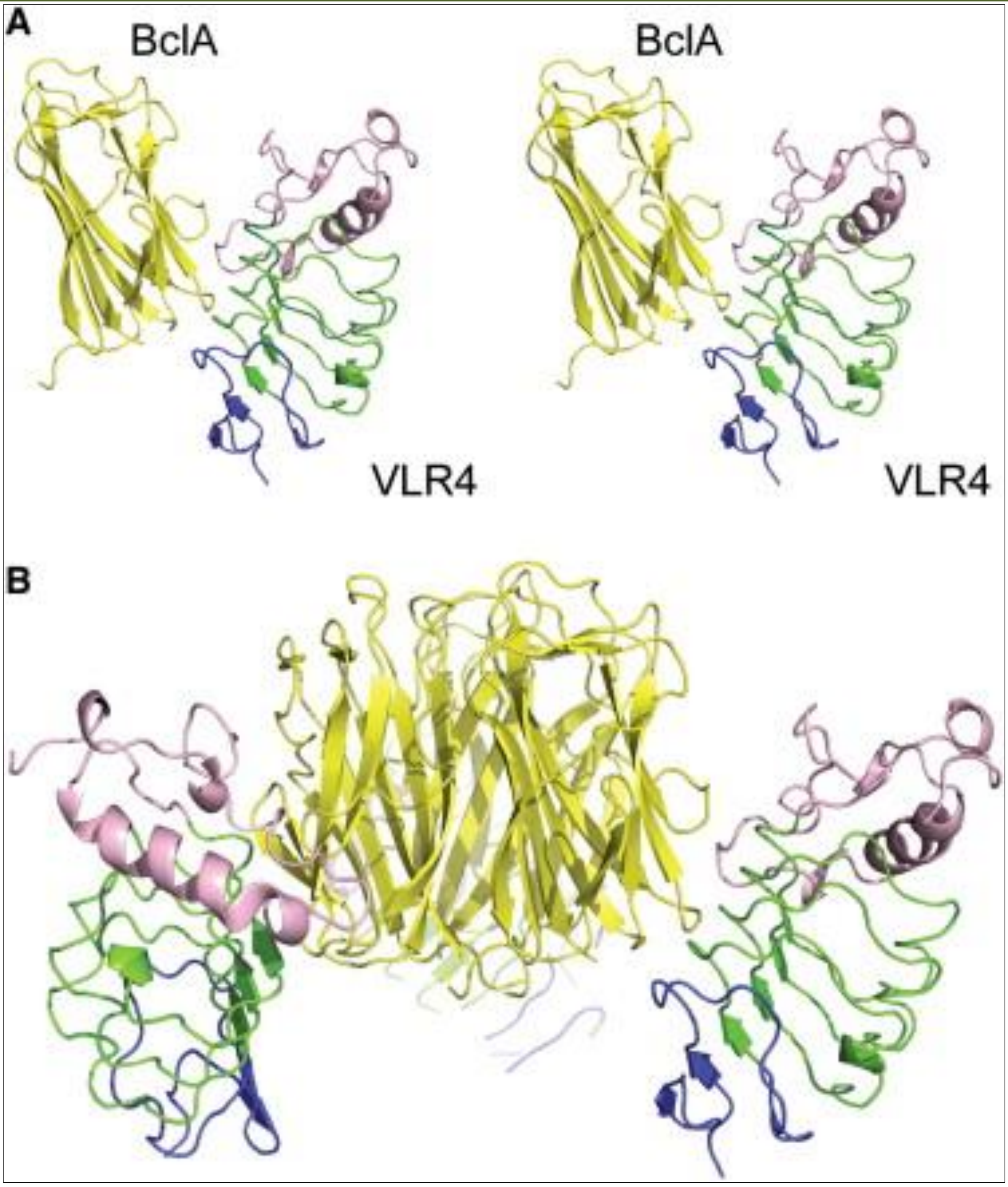

Figure 11: The VLR4-BclA Structure: VLR4 binds BclA using its concave surface (green) and LRRCT-loop (pink). The VLR4-binding site lies on the proximal end of BclA concerning the spore, near the termini. (A) Stereo view of VLR4 interacting with a BclA monomer. (B) Depiction of trimeric BclA decorated by VLR4
Source: https://doi.org/10.1016/j.str.2012.01.009

A study by the Feinstein Institute for Medical Research at Northwell Health and the Marine Biological Laboratory, USA, is critical. It could eventually hold promise in developing therapies to help repair the spinal cord in humans using the same or similar genes. Researchers have known for many years that the lamprey achieves spontaneous recovery from spinal cord injuries. Still, we do not know the molecular recipe that accompanies and supports this formidable ability (Ona Bloom of the Feinstein Institute) (Grillner, 2003; Green and Bronner, 2014; Cohut and Eric, 2019; Barany *et al.*, 2020; Aurangzeb, 2021; Li *et al.*, 2023).

For the study, the team followed the spinal cord recovery process in the lamprey. Samples of the brain and spinal cord were collected at various points in the process, from the first hours after the injury until three months, when they had recovered. They also discovered injury-induced changes in gene expression in the brain, which reinforces the idea that the brain changes greatly when there is a spinal cord injury (Ona Bloom of the Feinstein Institute) (Figure 12) (Kenski, 2000; Khidir, 2003; Li *et al.*, 2018; Aurangzeb, 2021; Du *et al.*, 2022; Maxson and Morgan, 2023).

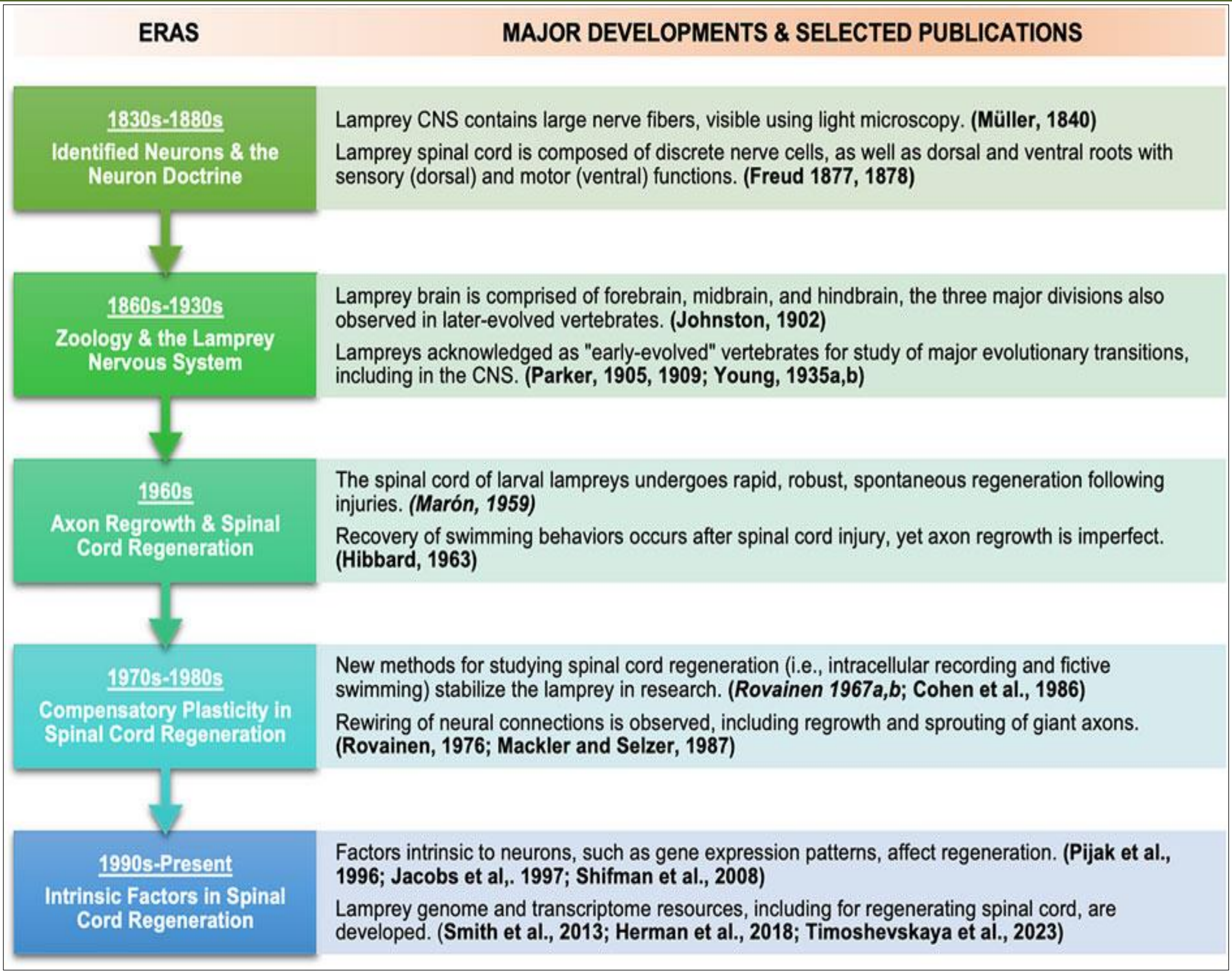

Figure 12: Timeline showing major eras and selected associated publications in lamprey neuroscience and regeneration research focused on spinal cord regeneration. Selected publications associated with each era are bolded. Since history does not lend itself to neat categorization, at some points major publications are listed and discussed in one time period but appeared in another (earlier) period, influencing later developments. Examples of such publications appear in italics

Source: https://doi: 10.3389/fcell.2023.1113961

3.2. Sticky Defense – The Mucus Can Heal Human Wounds - Clean Water – Production of Fabrics or Plastics

The lamprey defends itself by expelling the most viscous mucus in the animal kingdom. The lamprey is a snake-shaped fish that has almost 150 glands spread across its body. In stressful situations, such as when being chased by a predatory shark, these organs release two types of cells into the water, those that produce mucus and those that produce fiber. The mucus can heal human wounds and clean water, can heal human wounds and clean water (Figures 13-14) (Kenski, 2000; Parker, 2006; Nagawa *et al.*, 2007; Aurangzeb, 2021; Du *et al.*, 2022; Li *et al.*, 2023).

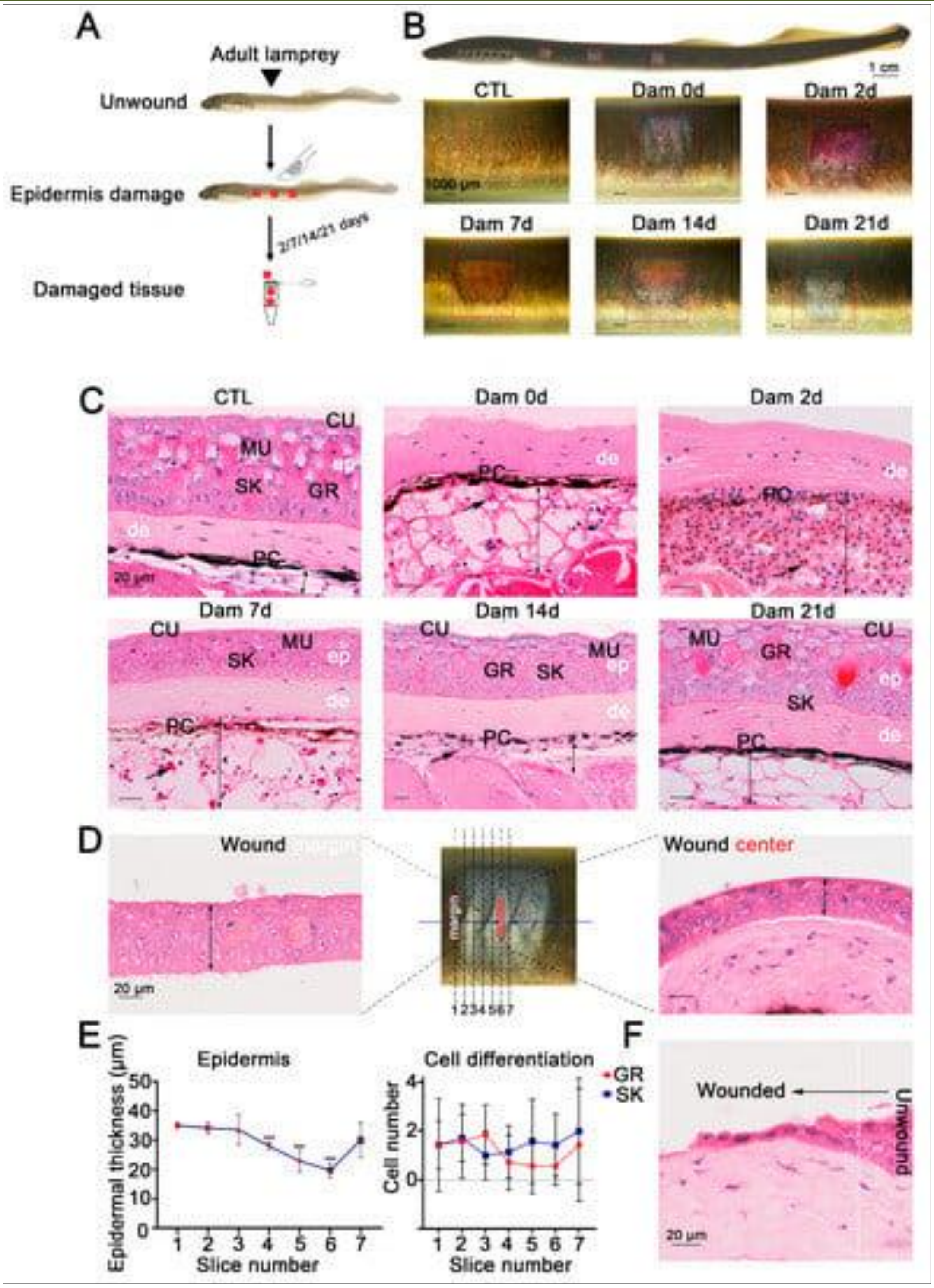

Figure 13: Wound healing process of the damaged lamprey *Lethenteron reissneri* (Dybowski, 1869)) epidermis. (A) Five-time points were selected to characterize the healing process of lamprey. (B) Representative images of the skin healing process of adult lamprey after epidermal damage; three wounds on each side are shown (red square). (C) Representative images of H&E-stained sections of the wound bed. Significant changes are visible in the subcutaneous fat layer, and massive red blood cell infiltration was detected (black arrow). Scale bars, 20 μm. (D) Serial sections were prepared from the wound edge to the center. (E) Statistical analysis of the numbers of granular cells and skein cells (left) and the epidermal thickness of sections 1 to 7. *** p < 0.001 versus slice 1. (F) Migration of epidermal basal cells to the wound bed. ep: epidermis; de: dermis; PC: pigment cell; MU: mucous cell; SK: skein cell; GR: granular cell; CU: cuticle

Source: https://doi.org/10.3390/ijms24043213

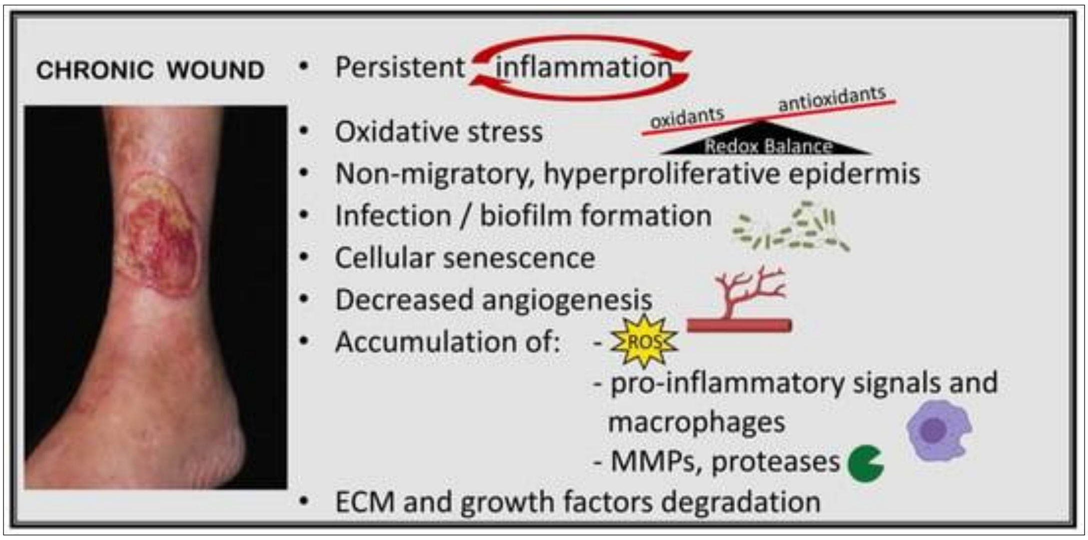

Figure 14: Pathologic abnormalities associated with delayed wound healing in chronic wounds. Persistent inflammation, as a hallmark of chronic wounds, is connected to the dysregulation of the immune response during wound healing by various factors and leads to excessive levels of pro-inflammatory signals, reactive oxygen species (ROS), changes in the proteolytic balance, and an increased amount of matrix metalloproteinases (MMPs) that eventually cause damage to the extracellular matrix (ECM) and impaired epithelialization and proliferation of keratinocytes. The molecular pathways and targets are summarized in. The image of the chronic wound is reproduced from

Source: Reprinted with permission from AAAS, 2014

In contact with water, mucus cells rupture. Mucin, the main protein in the slime, absorbs liquid and swells quickly, acquiring a gelatin-like consistency. Produces 20 liters in seconds. The other type of cell produces a long fiber 20 centimeters long, coiled like a ball. In the water, it unfolds. The gunk and fiber mix and get tangled. The result is a thick goo that envelops the lamprey and suffocates the shark's bite, allowing it to escape from it. When swallowed, the mucus induces the predator to vomit, and the game escapes unharmed (Figure 15) (Cohut and Eric, 2019; Aurangzeb, 2021; Du *et al.*, 2022).

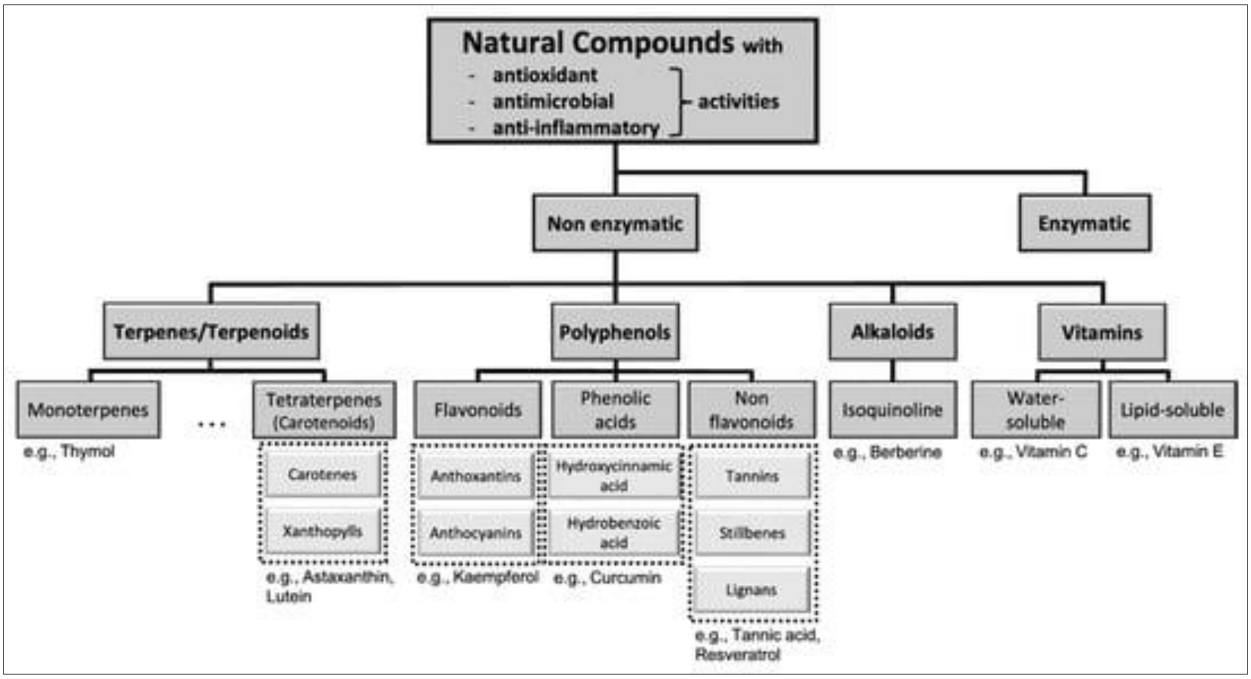

Figure 15: Overview of antioxidants and classification of non-enzymatic compounds based on their main groups: terpenoids, polyphenols, alkaloids, and vitamins. Selected compounds are given as examples

Source: https://doi.org/10.3390/ijms23094928

The lamprey, a fish that feeds on dead animals, can produce up to 20 liters of gunk in seconds if it defends itself. Their mucus combines protein with fiber to create the thickest, most viscous goo there is. This could result in the discovery of an incredibly strong biological polymer in the future, to be used in the production of fabrics or plastics (Figure 16) (Nieuwenhuys, 1998; Kenski, 2000; Pancer *et al.*, 2004; Parker, 2006; Nagawa *et al.*, 2007; Schilrreff and Alexiev, 2022).

Figure 16: Slime is everywhere. It shapes the consistency of bodily fluids, from the saliva in your mouth to the gunk that coats your organs. It protects you against pathogens, including coronavirus, while creating a home in your mouth for billions of friendly bacteria. Hagfish turn water into rapidly expanding goo, lampreys filter their food, and swifts build nests

Source: https://www.inverse.com/science/evolution-of-slime

3.3. Mucins and Human Health

When mucins (sludge) don't work properly, they can cause illness. People with a faulty CFTR gene develop cystic fibrosis, where their bodies cannot clear mucus from their lungs, making breathing difficult. Malfunctioning mucin regulation is also linked to cancer development (Pajic *et al*., 2022).

It protects you against pathogens, including coronavirus, while creating a home in your mouth for billions of friendly bacteria. Slime is made up of proteins called mucins, which are vessels for sugar molecules. These sugars are mainly responsible for making things slimy. Mucins generally take the form of long, rigid rods. These structures can adhere to other mucins and microbes, transforming the physical properties of the fluids surrounding them into a sticky, viscous substance (Omer Gokcumen and the conversation) (Figures 17-19) (Pajic *et al.*, 2022).

Figure 17: Slime slid into mainstream attention in 2017 when a truck on an Oregon highway overturned and 7,500 pounds (3,402 kilograms) of eel-like hagfish spilled out, slathering nearby vehicles with the slime they produced
Source: Photo/Oregon Police

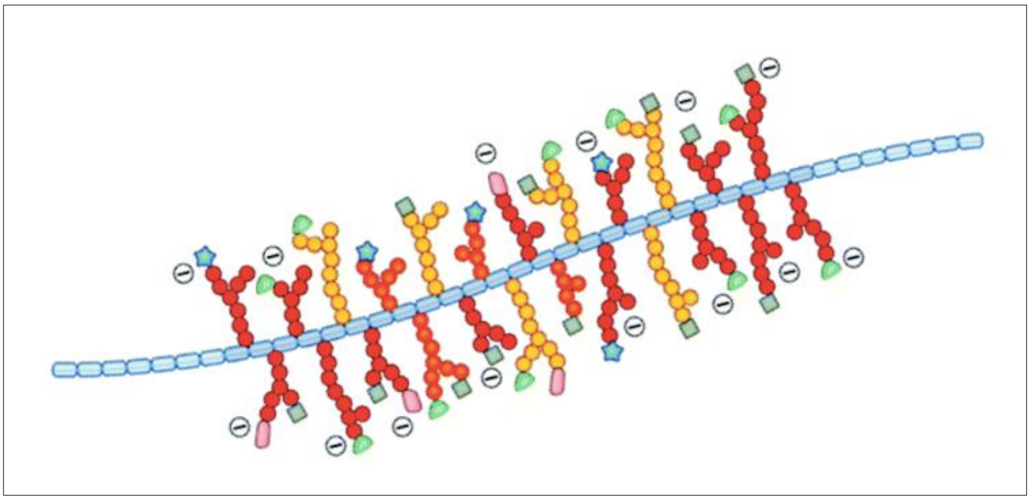

Figure 18: Mucins have a long protein backbone with sugars protruding along its length
Source: https://doi.org/10.1039/C8BM00471D

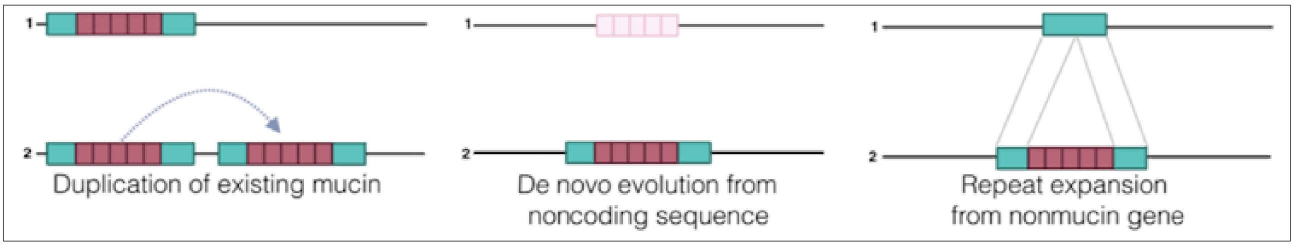

Figure 19: The researchers considered three possible ways mucins could have evolved: duplication of the entire gene, creating a new gene from scratch, or adding repetitive genetic sequences from existing proteins
Source: https://doi.10.1126/sciadv.abm87

Note: This article was originally published in The Conversation by Omer Gokcumen at the University at Buffalo.

4. CONCLUSION

Ecologists know that lampreys are responsible for maintaining the health of rivers. Doctors study them to understand their incredible ability to regenerate even after severe damage a healing factor that may offer a way to regenerate spinal injuries in humans.

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