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Principles and Methods of Counteracting Harmful Salmon–Arthropod Interactions in Salmon Farming: Addressing Possibilities, Limitations, and Future Options

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The arthropod salmon louse (*Lepeophtheirus salmonis*) is a major threat to Atlantic salmon aquaculture and wild salmonids. Essentially like in monoculture, very high concentrations of susceptible hosts may result in high reproduction and severe production of waves of pests. Pest management is crucial both for fish health and protection of wild fish populations from aquaculture influence. Various methods have been utilized to control salmon lice infestations, such as pesticide use, physical treatments, construction modifications, fallowing, breeding, vaccination, and biological control. Most of the methods are partially successful, but none completely fulfills the necessary pest control strategy. Like in agriculture, lice/pest management is an arms race, but the marine environment makes it even more difficult to precisely hit the target pest and avoid unintended negative effects on general wildlife. In this study, we provide an overview of the methods and principles of salmon lice management and address current possibilities and limitations. We also highlight the potential of emerging strategies and enabling technologies, like genome editing, RNA interference, and machine learning, in arthropod management in aquaculture.

Keywords: enabling technologies, genome editing, marine arthropod, salmon lice, delousing, medical treatments, non-medical treatments

INTRODUCTION

Human population is projected to increase to 11.2 billion by the end of the century, and the buying power is expected to continue to increase (UN Economic & Social Affairs, 2019). These increases will drive the need for human food, and scarcity is expected to be a great challenge for humans in the coming century (FAO, 2020a). The cultivable land needed for agriculture is decreasing and the future of food production is likely in the marine environment. At least one-third of agricultural output is currently lost due to damage caused by pests and diseases (Oerke et al., 2012). Arthropods, by far the largest invertebrate phylum that include approximately eighty percent of all animal species inhabiting the earth (Zhang, 2013; Ghafor, 2020), cause a main problem. Agricultural losses due to arthropods are enormous (Bradshaw et al., 2016), and major attention has been paid to the study of terrestrial arthropods. Comparatively, the marine arthropods and parasites have received less attention.

Over the last 70 years, global fish and seafood production has been a success story and the production has increased sevenfold (FAO, 2020b). The production value of the Atlantic salmon and other salmonids added up to 13.1 billion euros in 2018. Vaccination programs and best practice in cultivation have resulted in a drastic reduction in disease outbreaks as well as in medical treatments. The use of antibiotics in salmon farming in Norway alone has, for example, been reduced from approximately 2.13 μg/kg fish in 2006 to 0.14 μg/kg fish in 2019 (Directorate of Fisheries, 2020; Norwegian Institute of Public Health, 2020) mainly due to mass vaccination of juvenile salmonids. During these years, the use of antibiotics has also been drastically reduced in Scotland and Canada (Love et al., 2020). Pest control still represents, however, a major challenge and limits the growth potential of the salmon industry. As in terrestrial agriculture, the cost of arthropods to the salmon industry is very high. Salmon lice (*Lepeophtheirus salmonis*) are a major threat to both farmed and wild Atlantic salmon in the North Atlantic region (Costello, 2006; Torrissen et al., 2013), and *Caligus rogercresseyi* is considered a major threat to salmon in Chile (Gonzalez et al., 2000; González et al., 2015). *L. salmonis* is known to have two allopatric subspecies, *L. salmonis salmonis* from the Atlantic and *L. salmonis oncorhynchi* from the pacific, each having biological, morphological, and genetic differences (Skern-Mauritzen et al., 2014). The financial losses caused by lice infestation amount to about 9% of overall production revenue (Abolofia et al., 2017). The first-hand value of salmon in 2019 was approx. 6 billion euro in Norway (SSB, 2020), whereas in Scotland it was valued at approx. 1.2 billion euro (Munro, 2020). The expenses for combating salmon lice in the Norwegian salmon industry was estimated to be around 500 million euro (Iversen et al., 2019), 17 million euro in Canada, 304 million euro in Chile, and 78 million euro in Scotland in 2019 (Just Economics, 2021). Salmon lice limit the further growth of the salmon aquaculture industry.

In this study, we present a broad overview of current scientific advances as well as methods and principles employed to combat this significant marine parasite (**Figure 1**).

History

The Norwegian-Danish Bishop Erik L. Pontoppidan first described the salmon lice in a text, stating that the salmon had partly returned from the sea to freshwater to get rid of greenish vermin by rubbing and washing in the rapid stream of waterfalls (Pontoppidan, 1755; see Torrissen et al., 2013). Salmon louse was later classified by the Danish zoologist Henrik Nikolai Krøyer as *Lepeophtheirus salmonis* in 1837 (Krøyer, 1837; IMR, 2009). Severe infestation of sea lice on fish, causing fish deaths in Canada, was described in a 1940 report (White, 1940; see Torrissen et al., 2013). In the early 1970s, Harald Skjervold and Trygve Gjedrem developed modern principles for the breeding of the Atlantic salmon and pioneered an important industry in Norway (Syrstad, 2009). The first outbreak of sea lice in aquaculture facilities was reported in the 1960s (Misund, 2018). It is therefore worth noting that salmon lice were present in salmon populations as a natural parasite long before aquaculture. Adverse reactions of salmon lice to other salmonids and to wild salmon were recorded for the first time in 1992. The later industrialized farming of salmon increased the number of hosts, which in turn increased the number of lice and, subsequently, the infection rate of both farmed salmon and wild salmonids (Heuch and Mo, 2001). The number of salmonids in fish pens in Norway has risen from approximately 9.5 million in 1994 to 445 million in 2019, according to data from the Norwegian Directorate of Fisheries. Chile is the world's second largest producer of salmon after Norway, accounting for 30% of total farmed salmon production (FAO, 2019). Salmonid industry is also booming in the United Kingdom and Canada, and the number is rapidly increasing.

Impact of Salmon Lice

The salmon louse is a salmonid parasite specialized on host fish of the three genera *Salmo, Salvelinus,* and *Oncorhynchus* (Wootten et al., 1982). Salmon lice have a significant effect on salmonids during the marine part of their life cycle since they feed on fish mucus, blood, and epidermal tissues (Costello, 2006). The effects of these parasites on fish include physiological stress, growth reduction, immune system suppression, and osmoregulation imbalance (Johnson et al., 2004; Costello, 2006). Higher rates of infestation lead to skin lesions, secondary microbial and viral infections, and, ultimately, increased mortality in the absence of treatment (Grimnes and Jakobsen, 1996; Pike and Wadsworth, 1999). The infestation of salmon lice has a huge economic impact on the aquaculture industry and is projected to escalate further in the coming years (Liu and Bjelland, 2014). In Norway, salmon lice levels are regulated by law in order to protect wild salmon (traffic light system) (Fiskeridepartementet, 2015), and this increases the intensity of treatment and handling, which drives up costs and causes fish welfare issues. Increased cost of production due to salmon lice come from medical and non-medical treatments, cleaner fish, net cleaning, stress and increased mortality, reduced weight gain, fish handling costs, and higher ratios of feed consumption (Iversen et al., 2018, 2019). Salmon lice may also be reservoirs of fish pathogens (Gonçalves et al., 2020).

Control of Salmon Lice

Control of salmon lice includes non-medical approaches and medical delousing. Non-medical approaches are divided into preventive and physical delousing methods. Due to its consistency and efficacy, the most common delousing method is medical treatments (Aaen et al., 2015). Attempts to develop resistant fish and vaccines against salmon lice have also been reported (Kaur et al., 2015; Contreras et al., 2020; Swain et al., 2020). Regulatory authorities in salmon-producing nations have established mandatory and maximum thresholds on the number of mature or motile lice per farmed fish at production sites to limit the transmission of sea lice and sea-lice larvae from farming facilities to wild salmon smolts. There is a legal limit in Norway for the maximum mean number of lice per farmed salmon, as well as obligatory reporting of lice numbers to authorities and delousing if the limit is exceeded (Heuch et al., 2005). The regulatory requirement of lice abundance threshold in various locations is summarized in **Table 1**.

MEDICAL METHODS

Medical Treatment and Resistance

Medical treatment has been widely used to combat the problem of sea lice, as it is the most productive and predictable measure (Aaen et al., 2015). In 1974, Norway began treatment of sea lice with the use of organophosphate metrifonate, followed by Scotland in 1979, Chile in 1981, and Canada and Faroe Islands in the mid to late 1990s (Grave et al., 2004; Aaen et al., 2015). Since then, different forms of chemicals have been used as bath treatments, e.g., organophosphates, pyrethroids and hydrogen peroxide, and as feed additives, e.g., emamectin benzoate and benzoyl urea (**Table 2**) (Burridge et al., 2010; Aaen et al., 2015). The cost of medication is relatively high and was estimated to be in the range of 1–2 billion NOK (100–200 million euro) in 2014 (Iversen et al., 2018), excluding the costs of Chile, the United Kingdom, Canada, Ireland, Faroe Islands, and the United States.

The extensive use of chemical agents to combat sea lice has led to an inevitable drift toward drug-resistant parasites (Aaen et al., 2015). Successful treatment of the pest depends on the doses administered. For parasites like sea lice, the dosage is also determined by the host's ability to tolerate the toxicity of the agent. A smaller reduction in dosage may reduce the effect on parasites and generate resistance driven by natural selection in pests (Kunz and Kemp, 1994). Various genetic resistance mechanisms, such as point mutation in a target gene, upregulation of detoxification metabolism and efflux pumps in the intestines of parasites, changes in the thickness of the cuticle and other mechanisms to reduce chemical penetration, have been documented in arthropods (Brattsten et al., 1986; Aaen et al., 2015).

Resistance to a number of commonly used delousing chemicals has been registered, as well as ineffective treatment with emamectin benzoate and pyrethroids since 2008 (Aaen et al., 2015; Grøntvedt et al., 2016; Fjørtoft et al., 2020). Treatment failure and low treatment efficacy with azamethiphos, first noted in 2009 after re-introduction, is widespread along the coast (Kaur et al., 2015; Grøntvedt et al., 2016; Jensen et al., 2017). Losses of sensitivity to hydrogen peroxide is also reported (Helgesen et al., 2017). The number of prescriptions for medical treatment of sea lice is decreasing in recent years. Chemical agents are not prescribed when the efficacy of the treatment is low due to resistance. This could have contributed significantly to the decrease in prescription rates (Helgesen et al., 2017).

Chemical agents used against salmon lice might have negative effects on non-target species. Spillover from treatment around the fish farm could pose a significant risk to non-target organisms such as lobster (Olsvik et al., 2015), shrimp, and other crustaceans and bivalves. Local treatments in the marine environment have limitations due to, for example, changing volume of water, addition of solvent to large volumes, and water currents, making precision difficult. Negative effects on many non-target species studied have been observed at lower concentration levels of chemotherapeutic agents than those used for salmon lice treatment (Macken et al., 2015; Urbina et al.,

TABLE 1 | Lice abundance threshold in fish farms in various locations.

Country	Lice limit (average)	Number of fish	Frequency	Sources
Norway	0.2 adult female lice per fish sensitive period* In Nordland, Troms, and Finnmark: week 21–26, otherwise week 16–22	20 per cage	Weekly (4°C or above) Bi-weekly (below 4°C)	Ministry of Trade, Industry and Fisheries, 2013, 2017
	0.5 lice adult female lice per fish during rest of year	10 per cage		
Scotland	2 adult female lice per fish	10 per cage	Weekly	Luthman et al., 2019; Scottish Statutory Instruments, 2021
Canada	3 motile lice per fish at all times	10 per cage	Monthly	Luthman et al., 2019
Ireland	0.5 adult female lice during sensitive period, 2 adult female lice outside sensitive period	60 per site	14 inspections per year plus follow up if required	Jackson et al., 2013
Faroe Islands	1.5 adult female lice	10 per cage	Bi-weekly	Gislason, 2018; Luthman et al., 2019
Chile	1.5 adult female during winter, 3 motile lice per salmon at all times	10 per cage	Weekly	Luthman et al., 2019
ASC Salmon Standard	0.1 adult female lice during sensitive period for wild salmonids.	10 per cage, at least 50% cage over 2 weeks	Weekly or monthly, depending on wild stock populations in the proximity	Luthman et al., 2019

**Sensitive period: Wild salmonids migration.*

TABLE 2 | Chemicals, Vaccines, and Repellents used in salmon lice control, as well as the concerns associated with them.

Groups/compounds	Primary site of action/MOA	Resistance in salmon lice	Resistance mechanism	Sources
Ivermectin: Oral treatment				
Emamectin benzoate	Chloride channel (CC) activators	Prevalent, overexpression of metabolic enzymes, and downregulation of GABA-gated CC and neuronal acetylcholinesterase (AChE) receptors.	Reported in nematodes and arthropods. Target site insensitivity due to knockdown (KD) mutations. Metabolic resistance associated with cytochromes P450 (CYPs), carboxylesterases (CST) and glutathione-*S*-transferases (GST). Changes in glutamate- and histidine-gated ion channels.	Arena et al., 1995; Igboeli et al., 2012; Carmichael et al., 2013; Sutherland et al., 2015; Lam et al., 2020
Benzoyl ureas: Oral treatment				
Diflubenzuron (DF) Teflubenzuron (TF) Lufeneron (LF)	Chitin synthesis inhibitor (CSI)	Yes. Also, poor absorption of DF and TF from the digestive tract	Overexpression of CYPs. Mutation in the chitin synthase gene I (CHSI)	Pimprikar and Georghiou, 1979; Olsvik et al., 2015; Douris et al., 2016; Poley et al., 2018
Organophosphates: Bath treatment				
Azamethiphos Metriphonate Dichlorvos	Acetylcholinesterase (AChE) inhibitor	Mutation in AChE coding gene: Phe362Tyr mutation	In arthropods: AChE mutation, overexpression of metabolic enzymes Up-regulation of cuticle proteins, metalloproteinase, trypsin, ABC transporters and GST Greater protective effect of two mutated AChE alleles.	Denholm et al., 2002; Kaur et al., 2015, 2017; Valenzuela-Muñoz et al., 2015; Jensen et al., 2017; Helgesen et al., 2019
Pyrethroids: Bath treatment				
Deltamethrin Cypermethrin	Voltage-gated sodium channels (VGSC) modulator	Prevalent. Deltamethrin: Mutations in mtDNA. No association with previously identified mutations in VGSC	Arthropods: Target site insensitivity due to KD mutations, Metabolic resistance associated with CYPs, CSTs, and GSTs.	Martinez-Torres et al., 1998; Hemingway and Ranson, 2000; Santolamazza et al., 2008; Soderlund, 2012; Tschesche et al., 2021
Hydrogen peroxide: Bath treatment				
	Gas bubble formation in haemolymph, mechanical paralysis.	Yes Reported in Norway and Scotland	Reported in bacteria and fungi. Bacterioferritin comigratory protein is important in H_2O_2 resistance.	Aaen et al., 2015; Helgesen et al., 2015; Singh et al., 2017; Liu et al., 2019
Preventive medicine				
Vaccines: Oral or Injectable				
	Delivery method	Availability	Issues	
	Vaccination of fish, oral, injectables, and immersion	There is one commercially available injection anti-sea lice vaccine. (*C. rogercresseyi*: Providean Aquatec Sea Lice, Tecnovax)	Only injectable vaccines have satisfactory efficacy. Alternative delivery methods, effective adjuvants, and vaccine targets are required. Injection candidates have provided 31–56% reduction in adult females.	Latorre and Grosman, 2013; Leal et al., 2019; Contreras et al., 2020; Swain et al., 2020 (https://www.tecnovax.com.ar/productos/provideanaquatec-sea-lice/)

(Continued)

TABLE 2 | Continued

Repellents: host masking components				
Compound	**Origin**	**Species**	**Effect**	**Sources**
Garlic oil	Garlic	*Allium sativum*	Removed attraction to host-related cue (a-isophorone) at equal concentration	O'Shea et al., 2017
Diallyl sulfide, diallyl disulphide	Rosemary	*Salvia rosmarinus*		
Isothiocyanates	Plants	*Brassica genus*		
4-methylquinazoline 2-aminoacetophenone	Turbot	*Scophthalmus maximus*	Forty-three percent (43%) reduction in infection prevalence when a repellent is present	Hastie et al., 2013

2019). This may have an undesirable effect on the food web in coastal ecosystems of surrounding waters. Medical use has its limitations and alternative methods like vaccine development has gained scientific interest and financial support.

Vaccines

In the face of the current COVID-19 pandemic, research on vaccine development has received significant financial and political support. In the year 2020, a substantial number of studies using different approaches to vaccine development were tested by commercial and academic actors. Special attention has been paid to mRNA-based vaccines due to the high potency, rapid development, low-cost manufacturing, and high efficacy demonstrated in studies based on animal models (Sandbrink and Shattock, 2020). *In vitro*-synthesized mRNA-based vaccines combined with lipid nanoparticles have been the first to be approved against SARS-CoV-2 outbreak (Anderson et al., 2020; Mulligan et al., 2020). Although mRNA vaccines are not currently available in aquaculture, this brings hope for successful research and potential application in other areas where vaccines are needed, as well as vaccine research in general.

In aquaculture, the introduction of vaccines as a preventive method is a necessity for sustainable fish farming (Adams, 2019). From the experience of the viral and bacterial vaccines produced for salmon, we see how effective vaccines can be in aquaculture (Sommerset et al., 2005). However, cost-efficient vaccination against salmon lice remains an unsolved challenge. Vaccines against ectoparasites are still in their infancy, with a few successful commercial products providing reliable protection, such as against cattle tick (Willadsen et al., 1995). The complexity of interactions between vertebrate host and arthropod parasites is yet to be explored for potential vaccine targets (Raynard et al., 2002; Fuente et al., 2016). Translated research from advances in the tick vaccine have already provided promising results in peptide vaccines against salmon lice. Peptides from salmon lice were conjugated with T-cell epitopes (TCEs), that are universally immunogenic in mammalian systems (Panina-Bordignon et al., 1989; Leal et al., 2019). TCEs from tetanus toxin and measles virus are known to increase the immunogenicity in salmonid immune system (Leal et al., 2019; Contreras et al., 2020; Swain et al., 2020). Moreover, technologies, such as adjuvants and nanoparticles, in combination with conventional approaches for enhanced immunogenicity are additional perspectives for the future (Dadar et al., 2017; Angulo et al., 2020).

So far, there is only one commercial injectable vaccine available for sea lice, *C. rogercresseyi* namely Tecnovax's Providean Aquatec Sea Lice. The vaccine was reported to have efficacy of 61–86% reduction of the number of post-challenge parasitic stages of lice in immunized trout (Latorre and Grosman, 2013). Only injectable vaccines have provided positive results, but they are far from optimal. While protection is generally high, application is labor-intensive and stressful for the fish (Angulo et al., 2020). However, with the introduction of high-throughput injectable devices capable of injecting thousands of fishes under anesthesia every hour, application time has been greatly reduced. Furthermore, additional efforts in salmon lice vaccine research could also be directed toward alternative routes of administration. One of the preferred methods is oral administration, as it can be easily supplied as a component of the fish feed (Mutoloki et al., 2015), having the potential to be adopted by aquaculture industries. There is so far no oral vaccine available for salmon lice, but the challenge is addressed in the research project Mucoprotect (NFR, 2021). Oral vaccines, however, need to confer immunity at clinically relevant levels while being affordable for usage in the pre-smolt stage. Fish immunology is a rising field of bewildering complexity just on the verge of inception. It will require years of research to achieve cost-efficient and sustainable vaccination against salmon lice.

Repellents

Another class of compounds, repellents, which are a subclass of semiochemicals, act on parasite olfactory systems, interfering with the settlement on the host. These chemicals act as masking compounds for salmon-derived kairomones, a sensory cue for salmon lice. Some natural compounds derived from plants have been tested as novel feed-through repellents and shown positive results by masking host-related compounds in Y-tube behavioral bioassays (O'Shea et al., 2017). Interestingly, even compounds derived from other fish have been shown to act as repellents, significantly reducing the infection rate of *L. salmonis* (Hastie et al., 2013). Despite showing promising results in laboratory conditions, these repellants require further validation of their efficacy and cost-efficiency in open farms. It will likely be challenging to solve the problem of salmon lice infestation solely by introducing repellants due to the rapid dilution of chemical substances in open sea, but they may be employed in combination with other treatments.

NON-MEDICAL METHODS

There is a shift toward the use of non-medical solutions to control salmon lice infestation levels (Overton et al., 2019). This is, among others, as a result of the broad resistance developed against all available chemical agents (Aaen et al., 2015). Preventive measures such as cage depth manipulations, anti-lice functional feeds, lice skirts, and lice traps are part of salmon louse management plans. The use of direct physical and mechanical removal of lice and cleaner fish is growing. Furthermore, the relevance of environmental effects, such as temperature and local wind, and current trends in salmon louse management strategies with antagonistic selective effects that delay louse development should be considered when choosing different approaches (Jevne and Reitan, 2019; Coates et al., 2021). Current and novel innovations used to pursue non-medical alternatives are summarized in **Table 3**.

Preventive Methods

Cage Depth Manipulations

Salmon lice larvae have evolutionary preference for residing in the upper part of the water column, a strategy to increase the likelihood of finding potential hosts (Heuch et al., 1995). This phototropic behavior has been explored in countermeasures taken to prevent lice contact with fish. **Lice skirts,** where tarpaulin is wrapped 5–10 m around the upper part of salmon pens, may act as a shield to prevent infective stages of lice from entering the pens from outside the surface waters (Frank et al., 2014). The skirt may decrease the infestation levels, but it may also cause a serious decrease in oxygen levels available for fish inside the skirt (Stien et al., 2012).

Similarly, with **deep lighting and submerged feeding**, fish change their swimming behavior during the feeding process and are attracted to larger depths assumed to have lower lice larval concentrations. The lice population present at any given time on salmon was found to be lower with deep lighting alone than with submerged feeding alone (Frenzl et al., 2014). During the day, however, natural light may have an impact on the efficacy of deep lighting due to the preference of salmon for natural light and their migration to the upper part of the water column (Frenzl et al., 2014). Furthermore, submerged lights can have a negative influence because certain wavebands of light tend to attract lice and may therefore raise infection pressure (Alsvik, 2019; Bjørnstad and Solstad, 2019; Børset, 2019; Vatn, 2019; Andersen, 2020; Nordtug et al., 2021).

Snorkel cages create a barrier between salmon and parasites, where a net roof at a depth of 10–20 m in the salmon pen, with a snorkel at the center, keeps salmon in deep water. The purpose of the snorkel is to provide a protection zone with low lice larval concentrations that allows the fish to reach the surface to take air into their swim bladders while reducing contact with the infective stages of lice (Stien et al., 2016). In one commercial study, the use of snorkel-based technologies was reported to result in a substantial reduction of salmon lice (Geitung et al., 2019). Finally, when different strategies are integrated, they are more successful than if used independently (Jackson et al., 2018).

Anti-lice Functional Feeds

The stimulus substances in functional feeds are composed of pathogen-associated molecular patterns (PAMPs) that are recognized by the immune system as foreign using pattern-recognition receptors, initiating signaling that leads to immune response (Mogensen, 2009). Immunostimulants, which are feed additives that protect against salmon lice and secondary infections, have been developed and widely used in aquaculture. Available functional feeds in the market include exogenous nucleotides and yeast components that have given 11–41% reduction in *L. salmonis* infestation levels (Yossa and Dumas, 2016). In addition, feeds containing plant-based glucosinolates have been reported to reduce lice counts up to 25% in fish compared to control diets without glucosinolates (Holm et al., 2016; Skugor et al., 2016). These feed additives have to be applied for a prolonged period (3–10 weeks) and apparently do not provide long-term protection. Therefore, these methods should be regarded as a temporary supplement with the potential to be efficient, especially when combined with other methods.

Lice Traps

Salmon louse has several sensory systems that are involved in host location during the infective stages. These systems can be used as bait to attract lice in underwater traps (Nordtug et al., 2021). One such sensory system has to do with vision, which guides parasites to either a flickering light that resembles fish swimming through sunrays or a continuous light source. It has a longer distance range than mechanosensory and olfactory systems and is likely to be shared across lice species (Fields et al., 2018; Bjørnstad and Solstad, 2019). Furthermore, lice are capable of changing hosts during their adult life stage, thus making it possible to capture them in traps when changing hosts (Ritchie, 1997). These factors have contributed to the development of light-emitting traps (LET) with a light source and an air lift system to capture parasites (Pahl et al., 1999). LET represent an attempt to reduce sea lice infestation and risks of potential infection with smaller ecological impact and at a reduced cost when compared to the chemical treatments (Flamarique et al., 2009; Burridge et al., 2010). It has been shown that alternating light attracts adult salmon lice, whereas the larvae are attracted to continuous light (Flamarique et al., 2000). Thus, future prototypes of LET should have several light sources in order to efficiently capture lice at different life stages, and possibly be combined with salmon-related olfactory cues to enhance efficiency. Current LET based on the light-emitting diode have been tested under laboratory conditions and found to catch 70% of larvae and 8% of female adults, suggesting that females are probably also attracted to continuous light, although at a lower efficiency (Flamarique et al., 2009). Another prototype, by the Chilean company Indesol[1], is

[1] https://www.fishfarmingexpert.com/article/usinglights-to-lure-lice-to-their-deaths/

TABLE 3 | Overview of non-medical and biological control strategies for salmon lice management.

Non-medical methods	Description	Principle	Issues	Sources
Preventive methods				
Lice Skirt	Salmon lice position themselves at topwater columns: Barrier and avoiding contact, cage depth manipulations	Tarpaulin sheets mounted around the top of the salmon pen	Oxygen level drop in pen, slowed flow of water	Skirt (Stien et al., 2012; Frank et al., 2014) Snorkel (Stien et al., 2016; Wright et al., 2018; Geitung et al., 2019) Deep light (Hevrøy et al., 2003; Frenzl et al., 2014; Nordtug et al., 2021) Submerged cages (Glaropoulos et al., 2019; Oppedal et al., 2020)
Snorkels		Snorkel at the top of the net roof to keep salmon deeper in the water column.	Same as lice skirt but to a lesser extent. Feeding problems	
Deep lights/Submerged feeding		By placing lights or feeding systems deep within the pen	Natural light may have impact on efficacy in daytime. No proper control with submerged feeding alone could increase salmon lice pressure as they are attracted to lights	
Submerged cages		Submerged cage to avoid surface salmon lice	Negative buoyancy effect	
Anti-lice functional feed	Immune boost in fish and decrease in the ability of lice to attach to fish.	Use of glucosinolate in salmon, making heme unavailable for lice.	17–25% reduction in lice, more research required Short term protection	Burrells et al., 2001; Refstie et al., 2010; Covello et al., 2012; Holm et al., 2016; Skugor et al., 2016; Yossa and Dumas, 2016
Light traps	Salmon lice traps	Trap with light source (LED) and air lift system capturing parasites	Need for the attractants; prototypes need improvements and testing in the field.	(Flamarique et al., 2009; Nordtug et al., 2021) http://idsol.cl/, https://www.bluelice.no/english/
Physical delousing				
Thermal treatments (20–34°C)	Vulnerability of the lice to sudden changes in temperature	The fish are briefly passed through warm water, killing salmon lice.	Fish welfare	Elliot, 1981; Elliott and Elliott, 1995; Holan et al., 2017; Gismervik et al., 2019; Overton et al., 2019; Moltumyr et al., 2021
Freshwater treatment	Salmon louse freshwater sensitivity	The fish are briefly passed through fresh water, detaching the lice	Fish welfare, Freshwater resistance, Lice is initially affected, but recover Attached lice survive using ions from the host	Wright et al., 2016; Holan et al., 2017; Hjeltnes et al., 2019; Overton et al., 2019
Flushers/ Hydrolicer	Physical removal	Salmon lice are flushed out with jets of water while salmon move through a system in a boat or barge.	Fish welfare, Loss of scale, gill bleeding, and wounds	Nilsen et al., 2010; Gismervik et al., 2017; Hjeltnes et al., 2019; Overton et al., 2019; Walde et al., 2021
Laser treatment	Shooting with laser and killing	The system scans and shoots lice with a laser while laser beam is reflected from mirror-like fish skin.	Fish welfare, Insufficient laser pulse lethality rate.	Frenzl, 2017; Bui et al., 2020
Biological control				
Cleaner fish	Salmon louse predator	There are various types of fish that naturally feed on salmon lice	Cleaner fish welfare, ethical issues, sustainability costs	Bjordal, 1991; Skiftesvik et al., 2014; Imsland et al., 2015, 2018; Halvorsen et al., 2017; Powell et al., 2018; Overton et al., 2020
Biopesticides	Baculoviruses, fungi, parasites	Baculoviruses that are lethal to the hosts Almost all insect pests have at least one parasite that attacks them	No virus, fungi, parasite identified yet for salmon lice	Sparks et al., 2008; Sporleder and Lacey, 2013; Kamita et al., 2017; Williams et al., 2017

in the process of being patented. LET often require additional testing in the open sea, where they are exposed to sea currents which transport all stages of lice to downstream waters. The velocity of sea currents is typically higher than the swimming speed of lice, which may reduce the efficiency of LET. Lice traps have the potential to be an environmentally friendly form of lice management, but concrete research on their effectiveness and shortcomings in turbulent water and sea cages, and their effect on other phototactic organisms, is necessary.

Physical Methods

Thermal Treatments

Salmonids can tolerate a temperature of 20–34°C for a limited period of time (Elliot, 1981; Elliott and Elliott, 1995). In thermal treatments, the lice's susceptibility to abrupt increase in temperature is exploited for delousing. The salmon are crowded in grow-out cages and pumped into a thermal treatment system installed in a ship before being bathed in hot seawater for 30 s on board and allowed to return to sea cages (Noble et al., 2018). While thermal treatments are an effective approach for delousing, some reports have revealed that these treatments may cause tissue injury and severe welfare issues for the salmon (Gismervik et al., 2017, 2019). Other reports, however, conclude differently. Exposure of fish to a temperature of 34°C for 30 s in a recent study did not result in a significant increase in acute lesions apart from fin lesions (Moltumyr et al., 2021).

Flushers and Hydrolicer

Sea lice can be dislodged by water jets by passing salmon into a water jet system to flush out lice. Three companies currently use mechanical lice removal systems: Flatsetsund (FLS) Engineering AS, SkaMik AS, and the Hydrolicer®. The fish is injected into the flushing system for lice removal during treatment. FLS and SkaMik use similar systems, with the former using a flush/spray to remove lice and the latter including a brush system (Gismervik et al., 2017). Hydrolicer® pumps fish into a confined piping system and vacuums out lice using inverse water turbulence (Erikson et al., 2018; Overton et al., 2019). The flushers are attached to a boat or barge near the salmon pens. Fish are briefly pushed into the flusher where detached lice are removed, and the salmon thereafter are returned to the pen. Significant removal of mobile lice using these systems have been reported. There are no published studies on fish welfare and mortality, but losses of scale, gill bleeding, wounds and salmon mortality have been recorded (Gismervik et al., 2017; Holan et al., 2017; Hjeltnes et al., 2019; Westgård, 2020). A recent study has assessed the mortality of various delousing methods and concluded that thermal and mechanical delousing have the highest overall median mortality (Walde et al., 2021).

Freshwater Treatments

Salmon lice are more sensitive to freshwater (Wright et al., 2016) and this vulnerability is targeted in the delousing process of freshwater exposure. Freshwater treatment has historically been used to treat amoebic gill disease, but the use for salmon lice treatment is novel (Powell et al., 2015). Historically, it has been observed that wild salmon may migrate up the river to get rid of lice (Pontoppidan, 1755). A recent study of freshwater treatments in Central Norway showed a high reduction rate of salmon lice in all stages, as well as a very high reduction rate of *Caligus elongatus* (Gaasø, 2019). However, some reports have claimed that some attached lice can tolerate transfer into freshwater for 24 h. Transcriptome data shows upregulation of the proline synthesis pathway, which is used to offset cellular stress due to environmental effects (Liang et al., 2013; Borchel et al., 2021). Freshwater immobilizes the lice, but they might revive when they return to seawater (Andrews and Horsberg, 2020). To avoid the revival of lice in seawater, it may be necessary to filter the water before disposal. Adult stages of *L. salmonis* can live in low-salinity waters through a host–dependent interaction, where the lice absorb ions from the host to replace ions lost to the environment. This mechanism increases their tolerance to freshwater (Hahnenkamp and Fyhn, 1985; Johnson and Albright, 1991). The lice also detach as a result of the mechanical effects of crowding and handling before freshwater treatment, but most lice detach during the freshwater exposure (Gaasø, 2019). These detached lice are affected by freshwater exposure and die due to the changes in osmolarity compared to the few attached lice (Wright et al., 2016; Ljungfeldt et al., 2017). So far, freshwater treatment is considered one of the environmentally sustainable methods for delousing with less strain on fish welfare, but it is more time-consuming and expensive than thermal and mechanical methods. Some concerns have been expressed about the possibility that the lice may develop freshwater resistance.

Optical Delousing

Optical or laser delousing is achieved using a system composed of machine vision and targeted laser pulse removal. The laser pulses are directed to a single parasite detected by a submerged automated camera unit scanning the fish. The data generated by the computer vision is continuously transmitted to the database to further train the machine learning system. The laser pulses do not seem to damage the skin of salmon, and the system is able to recognize the fish's eyes and thereby prevent harm to them (Frenzl, 2017; Bui et al., 2020). Recent research suggests the lack of lethality of lasers rather than the lack of target detection requiring alternative delousing approaches (Bui et al., 2020). Optical delousing is a promising approach where physics meets informatics and pattern recognition in a multidisciplinary environment. New delousing methods currently under development are exploiting the possibilities of optical delousing. However, proper evaluation of the procedure and increasing the laser effectiveness are critical.

USE OF BIOLOGICAL CONTROLS

Cleaner Fish

Cleaner fish live in symbiosis with other fish species and feed on dead skin, ectoparasites and zooplanktons (Morado et al., 2019). Since the 1980s, cleaner fish have been used in preventative measures against lice (Bjordal, 1991; Torrissen et al., 2013). The use of cleaner fish as defense against salmon lice has increased steadily since 2008, with about 60 million cleaner fish

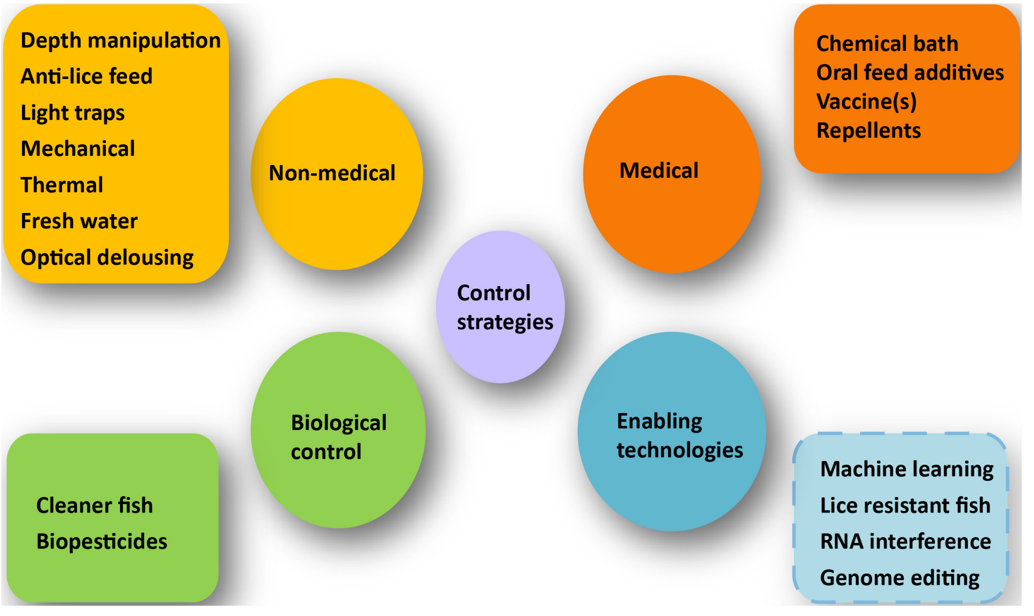

FIGURE 1 | Various control strategies for salmon lice management. The figure displays an overview of recent scientific advances, as well as methods and strategies for combating salmon lice, discussed in the text. The dotted blue box depicts the technologies that are still in the developing phase but might have a big influence on salmon lice management in the future.

used for the purpose in 2019 (Directorate of Fisheries, 2019). Biological control using cleaner fish has become a strong favorite among salmon producers, as new approaches that are less strenuous for salmon are deemed necessary (Barrett et al., 2020). Nowadays, cleaner fish, which include lumpfish (*Cyclopterus lumpus*), corkwing wrasse (*Symphodus melops*), ballan wrasse (*Labrus bergylta*), goldsinny wrasse (*Ctenolabrus rupestris*), and cuckoo wrasse (*Labrus mixtus*), are a prevalent alternative to current delousing control methods (Overton et al., 2020). This method is considered to be economical and less strenuous to salmon than physical and medical treatments, and the general public accepts the use of cleaner fish more readily than chemical treatments (Groner et al., 2013; Imsland et al., 2018; Powell et al., 2018; Overton et al., 2020).

Despite the wide acceptance and immense benefits, mixed results of the commercial success of the method have been reported. Easily accessible feed pellets, zooplankton abundance in the water, and prey located in biofouling may reduce the need for cleaner fish to feed on lice (Imsland et al., 2015). Concerns have also been raised about unsuitable environmental conditions that may reduce the efficacy and increase mortality among species of cleaner fish. Reports of diseases and high mortality of the cleaner fish deployed in salmon farms and ethical consideration of using vertebrates listed in animal welfare legislation are frequent (Nilsen and Colquhoun, 2014; Treasurer and Feledi, 2014). In addition, most wrasses are wild-caught, which can affect the abundance and population dynamics of the wild stocks negatively, and the sustainability of the use must be justified (Skiftesvik et al., 2014; Halvorsen et al., 2017). More focused, evidentiary use of cleaner fish could increase their effectiveness and help ease economic, environmental and ethical issues.

Biopesticides

Biopesticides are compounds used, instead of broad chemical pesticides, to manage agricultural pests through specific biological effects. They include biocontrol products like natural organisms or substances derived from natural products, such as genes or metabolites from animals, plants, bacteria, or certain minerals, that are used to manage pests (Sporleder and Lacey, 2013). Additionally, there are several reports of parasites that can manipulate and control arthropod behavior. The diversity of arthropod-manipulatory parasites varies from viruses to worms (Sporleder and Lacey, 2013). Viruses have been produced as biological insecticides for the control of pests in forests and agricultural crops. Baculoviruses are large, occlusive dsDNA viruses that infect arthropods (Anderson and May, 1980; Cory and Myers, 2003; Elderd et al., 2013). Many studies have shown substantial and important benefits for crop protection with both natural and genetically modified (GM) baculoviruses (Kamita et al., 2017). Further research on the use of salmon lice parasites, such as viruses or fungi, as a substitute for conventional chemical treatments opens the door to smart biological control of salmon lice in aquaculture.

ENABLING TECHNOLOGIES

The 20-first century is the era of biotechnology and information technology. Data availability and technological advancements have aided humanity in a variety of ways. We address some of the technologies that are or could be useful in counteracting salmon lice.

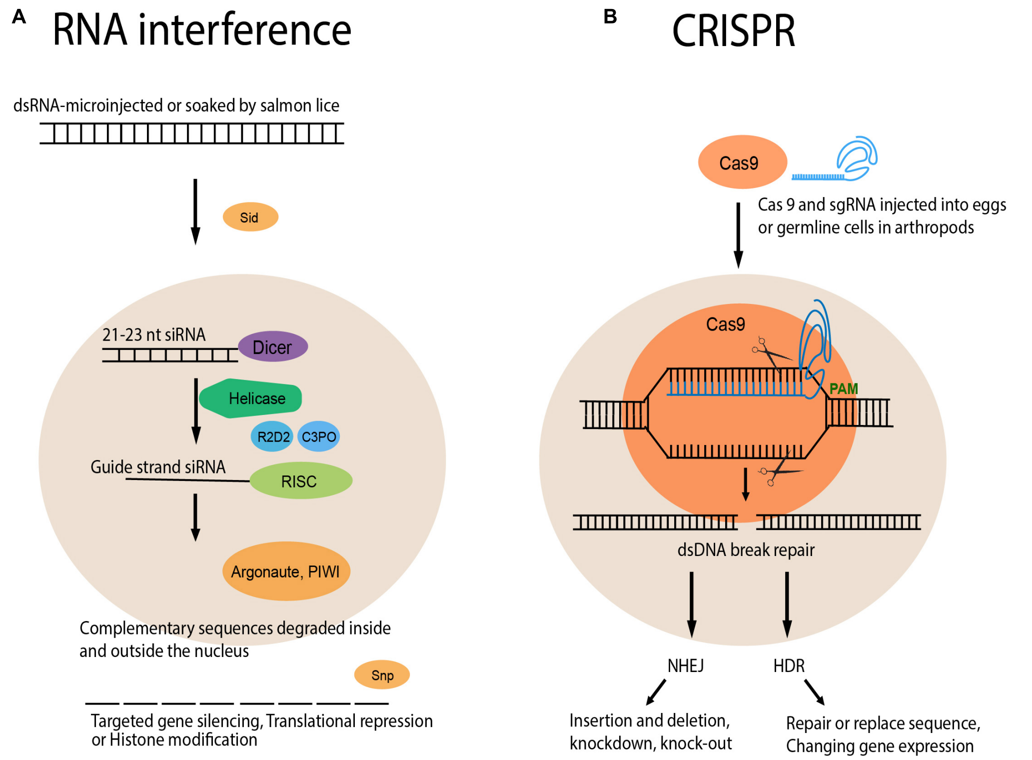

FIGURE 2 | Schematic representation of RNA interference and CRISPR/Cas9 technology. Two methods to target the activity of specific genes in the organism that are valuable for the functional study of genes and genetic elements. **(A)** RNA interference is a reverse genetics approach to study genes by knocking them down and then evaluating the effects. RNAi can be achieved in salmon lice by microinjecting dsRNA into pre-adult/adult lice or by immersing nauplii in dsRNA solution. dsRNA is incorporated in the cell with Sid, cleaved by Dicer into 21 nt small interfering RNA (siRNA), loaded into RNA-induced silencing complex (RISC) by R2D2 and C3PO. Argonaute and PIWI endonucleases degrade complementary RNA inside the nucleus, whereas Snp exonucleases degrades RNA outside. **(B)** CRISPR/Cas9 has the precision to target and knock out a single gene or genes in a gene family. Although the CRISPR/Cas9 is yet available for salmon lice, Cas9 and single guide RNA (sgRNA) can be injected into the eggs or germline cells similar to other arthropods. sgRNA forms a complex with Cas9 endonuclease, producing a dsDNA break. The dsDNA break is repaired by Non-homologous end joining (NHEJ) or homology directed repair (HDR). As a consequence, genes would be knocked out, knocked down, upregulated, or silenced. Adapted from Perkin et al. (2016).

Machine Learning

Machine learning (ML) uses computer algorithms that are improved automatically by experience, which can create models based on sampled data to make predictions or decisions without being explicitly programmed to do so. Computer vision represents an ML environment where it is impossible for traditional algorithms to execute specific tasks (Szeliski, 2011). For many years, computer vision has been used to identify and measure planktonic individuals (Kocak et al., 1999; Zheng et al., 2017; Luo et al., 2018; Li et al., 2020), making the operation more powerful than manual detection. The effects of the use of machine vision can be as strong as those of human experts.

Computer vision is utilized in pattern recognition and followed by laser shooting during optical delousing. It could also be developed to monitor the infestation levels of lice. In addition, studies of the behavior of planktonic lice, such as their responses to light stimulus, are carried out (Kvæstad et al., 2020). Besides, ML has been applied in the identification of diseased fish suffering from secondary infections based on mass spectrometry data (López-Cortés et al., 2017) and in a random forest-based approach for genome-wide SNP analysis (Jacobs et al., 2018). In future, ML has the potential to enable smart and autonomous control and monitoring of salmon lice infestations.

Monitoring of Salmon Lice

Computer vision may also be applied to monitor salmon lice infestations in salmon farms. This may imply the development of a fully automatic sea lice counter for continuous counting and sorting of sea lice on farmed salmon without the need for handling. The method provides a more comprehensive, impartial, and precise assessment of the lice situation in a fish cage. Since there is a limit on the maximum mean numbers of average female salmon lice per fish (Heuch et al., 2005), it is beneficial to have a system that provides real-time data for decision-making in intervention selection. Ecotone AS have developed a system called SpectraLice for this purpose, which can distinguish various stages of salmon lice using their proprietary hyperspectral imaging technology to detect light through the entire electromagnetic spectrum (Spectralice, 2021). Recently, the Norwegian Food Safety Authority (NFSA) approved the use of another louse counting technology, this time from Aquabyte, adopting their robust camera setup and patented optical architecture in 56 cages (Redaksjonen, 2021). NFSA have also given Stingray permission to use their image-based lice count system in 15 more cages (Drønen, 2021). One significant benefit of enabling technologies in lice monitoring is that they reduce costs in the long term and eliminate the need for fish handling and manual counting, which improves fish welfare.

Breeding and Use of Lice Resistant Fish

Selective breeding based on phenotypic values of a phenotype is typically used to generate genetic improvement of a quantitative trait in a population (Narain and Mishra, 1975). Using the same concept, salmon lice resistance can be improved by breeding new generations of farmed salmon using fish from families with low susceptibility to lice infestation. It has been verified that some select populations exhibit significantly reduced needs for chemical treatment to control lice outbreaks (Gharbi et al., 2015). QTL (quantitative trait locus) analysis for the evaluation of gene variation in the breeding candidate for genomic selection has been used to select lines that are resistant or have better tolerance to salmon lice (Aquagen, 2017). This method has been successfully used in the selection of salmon with higher degree of resistance against Infectious Pancreatic Necrosis (IPN), with fewer outbreaks of IPN in the short term (Houston et al., 2008; Moen et al., 2009). A crucial step to counteract the lice problem can be achieved through a breeding process, but it will likely take several generations of salmon to see the effect. A more direct approach will be to find the genetic differences between the Atlantic and Pacific salmon, since the latter is less attractive as hosts for sea lice, and use this genetic information in breeding or genetic modification of the Atlantic salmon (Moore, 2020; Robinson, 2021). This methodology is currently being developed as part of the CrispResist project sponsored by the Norwegian Seafood Research Fund (FHF).

RNA Interference

Technological advances in molecular biology approaches to salmon lice are an integral aspect of the study of gene function and identifying breeding targets. The key to salmon louse management could be found in the study of genes, and technical advancement in this area is warranted. RNA interference (RNAi) is a form of gene knockdown that targets mRNA (not necessarily only mRNA). For many years, RNAi technology has been applied in aquaculture research, contributing to our understanding of functional genomics and aquatic biology (Abo-Al-Ela, 2021). A schematic diagram is shown comparing RNAi to genome editing (**Figure 2**). The method of post-transcriptional silencing of genes using RNAi has been developed for salmon lice (Campbell et al., 2009; Eichner et al., 2014) and several important genes have been functionally characterized. RNAi has facilitated in the study of the molecular biology of the louse, such as the function of specific genes in developmental processes.

RNA interference screens have aided the study of host–parasite interactions, host recognition (Komisarczuk et al., 2017; Núñez-Acuña et al., 2019), and physiology at various life stages of lice (Sandlund et al., 2016, 2018; Komisarczuk et al., 2018, 2020; Braden et al., 2020; Guragain et al., 2020). RNAi has also facilitated in the functional studies of key genes involved in lice reproduction (Dalvin et al., 2009; Trößе et al., 2014; Eichner et al., 2015a; Khan et al., 2017; Borchel and Nilsen, 2018; Borchel et al., 2019; Heggland et al., 2019a,b). In addition, the method is used to identify the potential vaccine targets in *C. rogercresseyi* (Carpio et al., 2011; Maldonado-Aguayo and Gallardo-Escárate, 2014). The genes and pathways in salmon louse studied using RNAi are summarized in **Table 4**, which offers a broad range of information on gene function and various phenotypes resulting from gene knockdown.

Genome Editing

Genome editing, which includes precise manipulation of DNA sequences to alter the cell fate and organism traits, offers the potential to broaden our understanding of genetics and biology (Doudna, 2020). An attractive genome editing tool used in multiple organisms and cells, including arthropods, is CRISPR/Cas9 (Clustered, Regularly Interspersed, Short Palindromic Repeats/Cas9), which was discovered as a bacterial adaptive immune system (Ran et al., 2013). CRISPR/Cas9 genome editing can be utilized to target specific sequences in a genome and to destroy a specific gene activity or to modify the activity of the encoded protein (Anzalone et al., 2020). Furthermore, advancements in the Cas12 and Cas13 systems may open up new avenues for genome editing and RNA editing, respectively (Yan et al., 2019). Genome editing has resulted in a revolution in functional studies of genes by providing a tool for down to single nucleotide editing. This is done without leaving any foreign DNA in the edited organism/individual. Genome editing is already used to improve plant and animal traits and has a big potential both for targeted improvements and identification of traditional breeding targets. An international project that has as its goal to identify genetic salmon lice resistance markers in the Pacific salmon and use this information to modify the Atlantic salmon using the CRISPR/Cas9 technology has already been initiated. In contrast to salmon, where gene editing technology is well established, the technological development of CRISPR/Cas9 in salmon lice is more challenging because of problems associated with targeting of germline cells, the method of delivery, and the absence of a visible marker for mutant screening. When developed, genome editing methods for salmon lice will open a completely new toolbox and avenue for studies of salmon lice and likely offer great potential for the development of principles of salmon lice control. The genome sequence of salmon lice was reported in 2012 and provides a fundamental aid in identifying the targets[2].

FUTURE PERSPECTIVES

Over the last decades, numerous preventive methods and treatments have been developed, and scientific studies undertaken, to combat salmon lice. As we have outlined here, none of these methods have been highly successful in counteracting salmon lice infestations. Most preventive methods have shown some efficiency, and others have yet

[2]https://metazoa.ensembl.org/Lepeophtheirus_salmonis/Info/Index

TABLE 4 | An overview of RNAi studies and their outcomes in *Lepeophtheirus salmonis.*

Targets/Pathway	Genes	Developmental Stage	Phenotype	Sources
Tyrosine metabolism	*LsPAH;* phenylalanine hydroxylase	Nauplius I	Molting and swimming defect	Guragain et al., 2020
Myotropins	*LsMS;* myosuppressin	Adult	Muscle content reduction, defect on molting, spermatophore deposition and feeding	Komisarczuk et al., 2020
Chitin synthesis pathway	*LsGFAT;* glutamine: fructose-6-phosphate aminotransferase *LsUAP;* UDP-*N*-acetylglucosamine pyrophosphorylase *LsAGM; N*-acetylglucosamine phosphate mutase *LsCHS 1 and 2;* chitin synthase 1 and 2 *LsCDA 4557, 5169, and 5956;* putative chitin deacetylases	Nauplius I	*LsCHS1* – Swimming defects *LsCHS1* and *2* – Swimming defects *LsGFAT* – phenotypic irregularities *LsCDA5956* – Swimming defects	Braden et al., 2020
Key molecular contents in egg strings, Hemicentin family	*LsFCGS 1 – 6; female* cement gland secreted 1 – 6 *LsFCGMB1;* female cement gland membrane bound 1 *LsFCGPO 1 and 2;* female cement gland peroxidase 1 and 2	Preadult II female	Deformed egg strings preventing reproduction	Borchel et al., 2019
CD36-like protein (scavenger receptor class B (SCARB) family)	*LsHSCARB;* heme scavenger receptor class B	Adult female	Enlarged oocytes, shorter egg strings.	Heggland et al., 2019a
Ferritin	*LsFer1;* secretory ferritin heavy chain homolog *LsFer2;* secretory ferritin light chain homolog	Adult female	Impaired oocyte and egg string development, reduced egg hatching, no blood uptake.	Heggland et al., 2019b
Spermatophore generation Mucin-like spermatophore wall proteins	*LsMLSWP 1 and 2;* Mucin-like spermatophore wall protein 1 and 2	Adult male	Unorganized spermatophores, decreased reproduction	Borchel and Nilsen, 2018
TOR pathway	*LsTSC1/LsTSC2;* tuberous sclerosis tumor suppressor protein complex *LsTOR;* target of rapamycin *LsRheb;* Ras homolog enriched in brain *LsRaptor;* Regulatory-associated protein of TOR *LsRictor;* Rapamycin-insensitive companion of TOR	Adult female	*LsTOR, LsTSC1/LsTSC2* – reduced viable offspring *LsRheb* – hypotrophy, and necrosis in subepithelia, halted egg string production *LsRheb, LsRaptor*, *LsTSC1/LsTSC2, LsTOR* – abnormalities in the intestinal tissue	Sandlund et al., 2018
Lipophorin receptor	*LsLpR;* lipophorin receptor	Nauplius I, preadult II female, and adult female	Larvae – no phenotype Adult – female lice produced 72% less offsprings	Khan et al., 2018
Sodium–potassium pump	*LsNa$^+$K$^+$-ATPase;* sodium–potassium-ATPase	Nauplius I, preadult II female	Larvae – defect in muscle development Adult – impairment in feeding and reproduction	Komisarczuk et al., 2018
Fibronectin type II (FNII) domains expressed in tegumental type 1 glands	*LsFNII 1, 2, and 3;* fibronectin type II 1, 2, and 3	Preadult II female and adult male	No visible phenotype	Harasimczuk et al., 2018
Heme peroxidase	*LsHPX1;* heme peroxidase 1	Copepodid	Decreased swimming activity, abnormal leg development	Øvergård et al., 2017
Microsomal triglyceride transfer protein	*LsMTP;* microsomal triglyceride transfer protein	Preadult II female, young adult female	Offspring with reduced yolk content	Khan et al., 2017

(Continued)

TABLE 4 | Continued

Targets/Pathway	Genes	Developmental Stage	Phenotype	Sources
Ionotropic receptors	*LsalIR25a;* ionotropic receptor 25a *LsalIR8b;* ionotropic receptor 8b *LsalIR8a.1;* ionotropic receptor 8a.1	Nauplius I	Knockdown larvae settled on non-host fish that were rejected by wild-type lice Chemosensory system not fully activated	Komisarczuk et al., 2017; Núñez-Acuña et al., 2019
Ecdysone receptor	*LsEcR;* Ecdysone receptor	Copepodid Adult	Intestinal and muscle tissue abnormalities. Hypotrophy in neurological tissue, gonads. Combination with *LsRXR* knockdown resulted in complete molting arrest	Sandlund et al., 2016
Iron regulatory protein	*LsIRP1A;* iron regulatory protein 1A *LsIRP1B;* iron regulatory protein 1B	Adult	*LsIRP1B* – Shorter egg strings and fewer offspring *LsIRP1A* and *1B* – increased expression of Ferritin	Tröße et al., 2015
Chitinase	*LsChi2;* chitinase 2	Nauplius I	Abnormal and decreased swimming activity, shorter cephalothorax, lower infection rate	Eichner et al., 2015b
RXR type of nuclear receptor	*LsRXR;* retinoid X receptors	Adult female	Non-viable offspring	Eichner et al., 2015a
Secretory pathway	*LsKDELR;* KDEL receptor *LsCOPB2;* COPI subunitβ′	Preadult female	*LsCOPB2* – higher mortality and developmental defects *LsKDELR* and *LsCOPB2* – disturbed digestion and absence of egg strings	Tröße et al., 2014
Maternal yolk-associated protein	*LsYAP;* yolk-associated protein	Adult female	Lethality and deformity of offspring	Dalvin et al., 2009

to be tested commercially. We foresee that a key to future solutions could be unlocked through genetic studies of both sea lice and the Atlantic salmon, as well as of their physiological and ecological interactions. In addition, vaccine research, sophisticated engineering devices, and improvement in non-medical methods can provide us with the necessary tools to reduce the damage inflicted by salmon lice infestations. The ultimate biological goal in the quest to control salmon lice might be to breed super-resistant salmon, but there would likely still be a constant fight or arms race between lice and lice management strategies, comparable to the situation for terrestrial arthropods in agriculture. Cleaner fish provides good protection but have limitations of fish welfare and high cost. Another option might be to breed salmon that has been genetically modified to produce compounds that repel salmon lice without harming humans or fish. Natural enemies, such as biocontrol agents, could be another strategy for louse control that is less harmful to humans and the environment. The industry is using a wide range of counteracting measures to treat salmon lice in aquaculture. We have pointed to different strategies used, and the rapid development trend within the non-medical treatments.

We believe that a combination of multiple strategies is preferred to combat salmon lice until novel and better solutions become available in the future. The agriculture like approach, such as crop rotation or leaving fallow for greater protection, could be developed. Identifying key biological mechanisms in host–parasite interactions, metabolic profiling, and omics studies are critical. Methods such as RNAi and genome editing will play a central role in these types of investigations. The quest for better means of controlling salmon lice should not be stopped, and research activity should continue.

AUTHOR CONTRIBUTIONS

AMB and PG conceived and designed the study. PG, AMB and MT wrote the manuscript, with intellectual inputs from YO, PW, and ASB. All authors have reviewed and approved the manuscript.

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