Proteomics in Fish and Aquaculture Research

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Abstract The demand for animal protein for human consumption is currently on the rise fueled mainly by an exponential increase of the world population. The higher demand of fishery products and capture restrictions as a result of wild fish stock exploitation made aquaculture an extremely important source of protein (mainly fish, shellfish, and algae) available in human diet. Production statistics database from FAO states a value of about 97.2 million tonnes, of which around 70.0 million tonnes of the total food fish and 27.0 million tonnes of aquatic plants. The awareness that nowadays competitiveness is extremely dependent on scientific knowledge and new technologies made the number of manuscripts published in this area to rise almost exponentially. Aquaculture faces many challenges in order to continuously deliver a high-quality farmed fish through a sustainable production system. In order to achieve this goal, new management strategies need to be addressed, and state-of-the-art technologies like proteomics have been applied to study many factors like welfare, safety, nutrition, and diseases, which are directly responsible for the end-product quality.

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In this review we will address the latest proteomic studies published in each one of these influencing factors, giving a special importance to welfare since this is seen as a complex interaction of all the other factors. Also a brief review on the actual genomic resources is presented.

1 Proteomics and Fish Welfare

In fish with specific reference to aquaculture, the relationship between fish welfare, stress, and health is a complex interaction of many different variables making welfare in aquaculture a difficult subject to define. For all animals there are some fundamental definitions that should be considered when animal welfare is assessed. These include freedom from hunger, thirst, discomfort, pain, injury, disease, fear and distress, and ability to behave in a "normal way" and are discussed in detail by Ashley (2007). However several of these definitions are clearly difficult to transfer to fish (Berrill et al. 2012; Huntingford and Kadri 2014), but as a starting point, it does give clear lines that can be investigated. It can be hypothesized that when fish are in a good welfare state, they will perform well, have efficient conversion of food to growth, have a well-functioning immune system capable of dealing with immunological challenges, and in general result in a high-quality product. Compromised welfare not only reflects poorly on those who maintain the fish but is also of societal concern; hence there is a demand for high welfare status of farmed fish. Gauging the welfare status of fish is far from being easy, as we cannot easily perceive the emotional well-being of a large number of fish. The basic assumption for fish welfare is that the physiology and behavior do not significantly deviate from what is expected as normal (Prunet et al. 2012). The normal zone of tolerance for many physiological parameters needs to be assessed in relation to stress, nutrition, health, physiology, and behavior, with major changes potentially being indicators of compromised welfare. Developing markers, and how to interpret them, has been a goal in defining welfare in recent years mostly driven by the enormous growth in the aquaculture industry. So two aspects need to be considered: acute welfare issues (such as stress) and chronic welfare issues, which may be ongoing environmental changes such as water quality, environment, and health.

From a proteomic perspective, there are a number of core processes that can be examined and give indications of deviation from the expected normal, with the ambition of developing biomarkers for welfare assessment (Marco-Ramell et al. 2016). This term of "expected normal" requires a baseline to be established for the abundance and presence of proteins or how these proteins are posttranslationally modified. Such approaches have been carried out, and a recent example is reported in carp, where a multi-organ transcriptome and proteome have been assessed

(Kolder et al. 2016). Other papers have examined single tissues such as ovarian fluid (Johnson et al. 2014) and the brain (Gebriel et al. 2014). With the assumption that such analysis is performed on fish in a state of high welfare, the proteome and relationship of abundance of proteins can be useful in comparative investigations.

Acute stress in fish has been extensively studied, and there are clear markers including increased cortisol levels (Ellis et al. 2012), behavioral changes, food intake, and partitioning of energy requirements (Santos et al. 2010). From these observations, it is clear that multiple metabolic processes are changed, and many of these may be related to reduced food intake and not as a direct response to the stressor. Fish handling, netting, and reducing water volume are known to be major acute stressors of fish and are likely to induce perturbations. Repeated handling in Senegalese sole (*Solea senegalensis*) was examined for stress-induced responses in the liver (Cordeiro et al. 2012) where fish were repeatedly handled once a week for 4 weeks. Although the stress events were described as scarce, they could represent handling conditions in the commercial environment. Over 300 proteins were found to be consistently modulated in expression between handled and control fish relating to cellular response to redox stress, and a large number of heat shock proteins (HSPs) were found altered. These results were in line with earlier studies (Alves et al. 2010) where both repeated handling and crowding were used as stressor.

As fish are ectotherms, they have a temperature range where they have maximal performance and when confronted with annual changes in water temperature will acclimate accordingly (Johnston and Dunn 1987). However in culture conditions they cannot move to a more suitable temperature. Incorrect temperature induces stress by increasing oxygen demand, along with overall metabolic rate. Additionally, lower temperatures can also result in an unbalanced fish physiology. Fish behavior and its relation to temperature choice have been shown also to be linked with immune capacity as described for zebra fish (Boltaña et al. 2013). A number of studies have examined the proteome in relation to changing temperatures. Larval sea bream has been examined in relation to warming ocean temperatures (Madeira et al. 2016). Although focused on future climate change, the paper has relevance for aquaculture welfare. Whole animal proteomics showed that larval fish were unable to modify proteins relating to energy metabolism as would have been anticipated with warmer temperature, resulting in other physiological stresses. Although only 15 proteins were identified, some interesting conclusions were drawn. HSPs and protein degradation-related proteins were increased, suggesting dysregulation of protein folding. Other stress-related processes were changed including intracellular transport and porphyrin metabolism indicating reduced oxygen transport. Wild sturgeon larvae exposed to different temperatures (18 and 26 °C) in combination with selenium (Silvestre et al. 2010) were examined for proteomic changes induced by temperature, following 2-DE. Fifteen proteins were identified suggesting processes relating to protein folding, protein turnover (protein synthesis and protein degradation), ATP supply, and structural proteins changed in abundance in response to heat and/or selenium. These possible biomarkers could act as early indicators of dysfunction of larval development. These examples which are based on studies of whole larval fish do not allow for tissue-specific responses to be ascertained and may mask important changes in key tissues.

Natural changes in water temperature can help interpret when fish are stressed or in a state of compromised welfare. The murrel (*Channa striatus*) native to northeast India inhabits streams emerging from hot springs and can live at temperatures up to 38 °C. In this work, fish were acclimated to this temperature and compared with fish at a stable aquaculture temperature of 25 °C. The proteome analysis revealed a panel of HSPs at higher levels in the warmwater fish as well as a number of antioxidant proteins (Mahanty et al. 2016). In temperate latitudes, natural populations of grayling (*Thymallus thymallus*) that naturally inhabit warm or cooler water were examined for muscle proteomics (Mäkinen et al. 2015). Nearly all proteins identified were associated with Gene ontology related to muscle development and are interpreted "as driving the population closer to or to the thermal gene expression optimum." As these fish naturally tolerate and live in such environments, it may be debatable if these can be viewed as markers of welfare or a normal biological response to natural environmental fluctuations.

Although most worries are related to increasing water temperature for fish, as oxygen levels drop and metabolic stress is more likely to occur, warmer water species such as sea bream can have welfare issues at decreased lower winter temperatures. Winter disease occurs when water temperatures drop below about 12 °C, and a combination of organ malfunctions occurs including ionic regulation by gills, poor digestion, and compromised immune function (Castillo et al. 2009). To assess the key hepatic changes during a lowering of temperature in sea bream, fish acclimated to 20 °C were transferred to 8 °C for 10 days before a proteome comparative analysis of fish at the two temperatures was performed. There was a clear shift in the proteome with more proteins being reduced in abundance than increased (Ibarz et al. 2010b). The proteins identified that were changed in abundance suggested that protein and amino acid metabolism was being altered as seen by increased abundance of proteasome components and trypsinogen; secondly, changes in antioxidant activity were evidenced by increase in catalase and glutathione *S*-transferase. Taken together the authors concluded the cold shock resulted in hepatic oxidative damage and might potentially impact on winter disease in sea bream. Diets have been developed (winter feed, WF) to help mitigate these conditions, based on high marine protein and krill oil diets (Silva et al. 2014a) on which the fish grew and performed better. To define at a proteomic level the impacts of the WF and define potential protein markers for improved performance, plasma (Schrama et al. 2016) and liver (Richard et al. 2016) proteins related to protein metabolism, lipid metabolism, and immune function were identified. Authors suggest that fish fed the WF diet had improved oxidative stress capacity and increased amino acid metabolism.

Behavior and emotions are key aspects of behavior with such activities being controlled by brain function. However with the brain being such a complex tissue and often overlooked by aquaculture-related researchers, there is little known regarding the fish brain proteome. An interesting example is the zebra fish being used as a model for sleep disorders where these fish were maintained in continuous light/dark conditions (Purushothaman et al. 2015). These researchers were interested in circadian biology and endogenous daily rhythms controlled by the internal

clock with 78 proteins found altered as a result of changed photoperiod. Several proteins related to γ-aminobutyric acid (GABA)ergic receptors were modified as shown by 2-DE, and further circadian clock genes found modified by real-time PCR. These results could be expanded to the aquaculture environment where fish are often kept on artificial photoperiods for enhanced food intake or for controlling key life history events (Lorgen et al. 2015). Changes in brain proteome have also been examined in carp following anoxia, a species that can survive anoxic conditions, but little knowledge is known on how the brain deals with the lack of oxygen. Smith et al. (2009) found a decrease in abundance of proteins involved in the glycolysis pathway as well as proteins related to repression of neuronal apoptosis and decrease in neuronal degradation, demonstrating coping strategies for this fish species to environmental extremes it can face in natural environment.

Fish diets in aquaculture have changed significantly in recent years, with a move away from wild-sourced marine fish meal and fish oil to terrestrial plants and oils. Such diets can have impacts on fish welfare as they may contain anti-nutritional factors that interfere with digestion and intestinal function (Krogdahl et al. 2015; Król et al. 2016). To assess the impacts on the proteome of fish feeding on such diets, both the liver and intestine have been examined for potential metabolic changes that could indicate changed metabolism and welfare issues. Rainbow trout fed soybean meal rich diets had proteome alterations in the liver (Martin et al. 2003; Vilhelmsson et al. 2004) suggesting changes in lipid-binding proteins and primary energy metabolism. The intestine tissues themselves have received little in the way of proteome analysis; however Vasanth et al. (2015) found that microbial feed additives were able to reduce Atlantic salmon intestinal inflammation and showed five proteins that could be associated with poor intestinal morphology. Interestingly calreticulin, a multifunctional protein involved in extracellular matrix, was also altered in the skin of salmon that were being fed functional feeds associated with reduced sea lice burden (Micallef et al. 2017). Starvation is also directly relevant to welfare in fish; however as in many examples above, the biology of fish species is so plastic in that there is debate when starvation in salmonids becomes a welfare issue. Short-term food withdrawal (2 weeks) has been examined in rainbow trout (Martin et al. 2001) where several enzymes including cathepsin D suggested changes in protein turnover were occurring. More recently the impact of a 4-week food withdrawal was assessed for the intestinal tissue proteome of rainbow trout. In this study several immune-related function proteins and cellular stress showed significant changes (Baumgarner et al. 2013).

2 Proteomics in Fish Nutrition

Nutrition is a central topic in aquaculture research due to its essential role in fish metabolism, growth, health, and welfare. As such, it is not surprising that proteomic techniques have been extensively applied in this field in order to measure biological effects associated with particular dietary treatments or nutritional factors. Given the

wide range of feeding behaviors, digestive physiologies, and nutritional tolerances displayed by different species of fish, as well as the continuous introduction of new alternative ingredients in fish feed formulations, the use of such untargeted approaches can be seen as particularly beneficial by increasing the probability of detecting unforeseen nutritional effects.

Though most proteomic studies in fish nutrition focus on the liver as the target tissue, given its central role in regulating metabolism and adapting to nutritional changes, the muscle seems to be another common target, due to its importance as a peripheral energy-demanding tissue and its role in growth processes. Of particular relevance to nutritional studies is also the gut/intestine, due to its direct contact with bulk digesta and its particular susceptibility to the presence of anti-nutritional factors, as well as its essential role in the immune system and in modulating nutrient intake. Besides these, skin mucus and blood plasma are also seen as attractive targets due to the possibility of sampling them through nonlethal methods, being particularly suited to study the effects of dietary treatments on fish welfare and health. Finally, some studies simply perform protein extraction and analysis of the whole-body proteome, particularly when analyzing larvae or small fish, due to the difficulty in isolating specific tissues.

An important area of research concerns the general physiological effects of feeding (Mente et al. 2017), starvation, and refeeding (Baumgarner et al. 2013; Enyu and Shu-Chien 2011; Martin et al. 2001), as well as the impact that dietary energy intake levels can have on fish nutritional status (Jury 2005; Jury et al. 2008; Kolditz et al. 2008). For example, the works of Martin et al. (2001) and of Enyu and Shu-Chien (2011) show that starvation affects not only energy metabolism (glycolysis, gluconeogenesis, electron transfer chain) and oxidative stress response (peroxiredoxin, catalase, heat shock proteins), as one would expect, but also pathways such as methionine metabolism and lysosomal proteolysis (cathepsin D). Also, some of these works underline the dynamic nature of the hepatic proteome in particular and the need to consider the effect of, e.g., subjecting fish to fasting prior to sampling on proteomic observations. In general, this line of research is essential to assist in the correct interpretation of proteome alterations in fish nutrition studies.

The introduction of alternative ingredients in fish feed formulations (such as plant proteins, vegetable oils, and processed animal proteins) is seen as an important topic in aquaculture, and many proteomic studies focus on this issue, given the potential for unexpected deleterious effects (Ghisaura et al. 2014; Jessen et al. 2012; Kolditz et al. 2007; Kwasek 2012; Martin et al. 2003; Nuez-Ortín et al. 2016; Vilhelmsson et al. 2004; Wulff et al. 2012). Some of the proteins that consistently seem to be affected by the replacement of fish meal by vegetable ingredients include apolipoproteins, fatty acid-binding proteins, heat shock proteins, nitric oxide synthase, homogentisate 1,2-dioxygenase, and methionine/homocysteine metabolism proteins (adenosylhomocysteinase and betaine-homocysteine methyltransferase). Still within this context is supplementation of feeds with amino acids, particularly those displaying low abundance in vegetable ingredients. In this sense, the effect of diets containing variable levels of lysine on the muscle

and whole-body proteome of zebra fish has been characterized (de Vareilles et al. 2012; Gómez-Requeni et al. 2011), showing a high impact not only on structural proteins (actin, myosin, tropomyosin) but also proteins such as apolipoprotein A-I, Pdlim7, and proteins associated to energy metabolism. Another recent concern is the use of genetically modified organisms in fish feeds and its possible impact on fish health and nutritional safety. One study on the effect of genetically modified soy (compared to a near-isogenic non-GM soy) on Atlantic salmon displayed a minimal impact on its hepatic proteome, which suggests this particular strain of GM soy induces no obvious deleterious impact on fish nutrition and health (Sissener 2009; Sissener et al. 2010).

Understanding the effects of dietary micronutrient levels on fish metabolism and health is essential in the context of ever-changing feed formulations, where the possibility of micronutrient deficiencies is not negligible. In this sense, studies of the dietary effects of micronutrient supplementation through proteomic approaches have been undertaken, with works published both on phosphorus (Veiseth-Kent et al. 2013; Ye et al. 2016) and vitamin K (Richard et al. 2014) supplementation.

A particular issue with fish larvae is their high phospholipid requirements, which complicate the formulation of adequate replacements for live feed. Given this, some researchers studied the effect of different levels of soybean lecithin supplementation on the liver proteome of pike perch (Hamza et al. 2010). Results showed growth differences between dietary treatments, which were attributed to observed changes at the level of proteins related to oxidative stress (increased peroxiredoxin and reduced GRP75 and glutathione *S*-transferase with increasing lecithin levels), energy metabolism (changes in the levels of pyruvate carboxylase, phosphoglucomutase, fructose-biphosphate aldolase, and propionyl-CoA carboxylase), and choline metabolism (increased level of sarcosine dehydrogenase with increasing lecithin levels).

There are also studies on the impact of functional feeds, which are formulated or supplemented with particular additives with the purpose of boosting the metabolic and immune status of fish, to help them cope with particularly stressful situations (Richard et al. 2016; Schrama et al. 2016) or ward off infections (Jensen 2015; Jensen et al. 2015; Provan et al. 2013). A particularly strong trend in the field of functional feeds is the use of probiotics (nonpathogenic microorganisms) and bioactive substances derived from microorganisms (e.g., β-glucan), given their putative effects in terms of fish health and even growth performance (Ghaedi et al. 2016; Hosseini et al. 2016; Sveinsdóttir et al. 2009).

Finally, there are studies which focus on the effects of other dietary additives on fish proteomes: ranging from nucleotides (Keyvanshokooh and Tahmasebi-Kohyani 2012) and carbon sources, like α-ketoglutarate (Ibarz et al. 2010a) and glycerol (Silva et al. 2012), to secondary plant metabolites, like maslinic acid (Matos et al. 2013; Rufino-Palomares et al. 2011). These underline the versatility of proteomic approaches as general tools in fish nutrition studies to screen for potential effects at the level of cellular stress and metabolism.

An important detail in proteomic studies of fish nutrition is that the proteomes are intrinsically dynamic and context-dependent, which can make the interpretation

of the results highly challenging. In this sense, improving the design of experiments and data analysis approaches can bring real benefits to fish nutrition studies that leverage proteomic techniques. One of the ways of dealing with this complexity and context-dependence is to include more than one reference (control group), such as a negative control and a positive control. For example, if one is interested in knowing whether a particular feed additive induces nutritional stress, it might make sense to include a positive control diet (i.e., basal diet with an additive known to be stress-inducing) beside the negative control diet (i.e., basal diet). With such approach, we can convert ambiguous questions ("are the treatment samples similar to the negative control samples?") into more objective ones ("are the treatment samples more similar to negative control samples than to positive control samples?"). Following this concept that nutritional effects on proteomes should be interpreted in relative terms compared to reference group(s), rather than in absolute terms, one also should consider, particularly in long-term studies, the possibility of taking and analyzing samples from the start of the experiment and use them as a reference group. Another important detail that can contribute toward correct interpretation of proteomic observations is the co-measurement of complementary information, from easy-to-measure zootechnical parameters (such as fish body weight, body length, condition factor, hepatosomatic index, etc.) to other biological information obtained through the use of high-throughput profiling techniques (metabolomics, transcriptomics). This type of information can be used, on one hand, to isolate the treatment effect from other confounding effects (e.g., when comparing two groups of different mean weight, it is important to ensure that the treatment effects cannot simply be explained by body weight differences) and, on the other hand, to confirm the plausibility and consistency of the interpretation of the results (e.g., if a certain pathway is shown to be affected both at the proteomic and transcriptomic levels, one can be much more certain that the observation is not spurious). With these improvements, and others, related to the technical evolution of higher-throughput gel-free techniques, application of proteomics to the problematics of fish nutrition can provide an invaluable complement to other classical and omics approaches.

2.1 Safety of Aquaculture Products and Fish Allergens

In aquaculture industry, safety is of enormous importance to prevent health hazards, such as biological (bacteria, parasites, and viruses), chemical (heavy metals, dioxins, and aromatic hydrocarbons), and physical (bones, plastic, and glass) hazards (Teklemariam et al. 2015). To control this, the Food and Agriculture Organization (FAO) of the United Nations stabilized a code of practice for fish and fishery products (FAO 2012) where handling of fresh and frozen fish is described following the rules of hazard analysis and critical control points (HACCP). The European Union established Directive EC No 2073/2005 for regulation of microbial contamination (European 2005) and recently published EC No 1379/2013 for labeling and traceability characteristics to control fishery and

aquaculture products (European 2013). Authentication and labeling of fish species these days is very important as the human population is easily mislead by seafood identity substitution, as more than 20000 species of fish and seafood are known to be consumed (Rasmussen and Morrissey 2008).

More recently, proteomics has been emerging in the aquaculture field as a promising approach toward a high-quality end product (Mazzeo and Siciliano 2016). To achieve this goal, these advanced technologies have been used to improve the knowledge regarding potential biomarkers for environmental monitoring, risk assessment, including allergens' detection, traceability, and authenticity (Addis et al. 2010; Mazzeo and Siciliano 2016; Tedesco et al. 2014). Proteomics has been shown in numerous studies to deepen the genomic and transcriptomic approaches since it allows the study of the proteome, which reflects the physiological state of a fish at a given moment, in response to a stimulus. Although the lack of available information at the genome level registered for the majority of the aquaculture species is an enormous obstacle, a deeper proteome coverage of these species was achieved due to complementary studies comprising proteomics, genomics, and transcriptomics (Barbosa et al. 2012; Rodrigues et al. 2012). In case of traceability and authentication, several proteomic-related studies have been performed using fish species such as perch (Berrini et al. 2006), cod, mackerel (Martinez and Jakobsen Friis 2004; Martinez et al. 2007), hake (Pineiro et al. 2001; Carrera et al. 2006), sea bass, sea bream, and tilapia among others (Mazzeo et al. 2008). Muscle samples were used to identify specific proteins, such as parvalbumin, actin, tropomyosin, and myosin light chains. Recently, overexpression of the parvalbumin protein was detected in farmed gilthead sea bream against the wild species using shotgun proteomics (Piovesana et al. 2016). Using 2-DE and MALDI-TOF-MS, species of hake and grenadier were differentiated by the analysis of parvalbumin patterns in white muscle. This differentiation was confirmed using de novo sequencing of nucleoside diphosphate kinase B (Mazzeo and Siciliano 2016). Procedures like 2-DE, MALDI-TOF-MS, and PCR have been contributing in an extensive way for fish authentication (Siciliano et al. 2016; Carrera et al. 2013).

Depending on the research aim, the protein expression levels (comparative proteomics) and the posttranslational modifications (PTMs) can be assessed (Barbosa et al. 2012).

Food allergies are a worldwide issue and it is increasing fast. In 90% of the cases, an allergic reaction is caused due to a food protein of the Big 8, which includes milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish (Ahsan et al. 2016). The majority of food allergic reactions are mediated by immunoglobulin E (IgE). In case of fish allergy, it is estimated to affect up to 2% of adults and up to 7% of infants (Ballmer-Weber et al. 2015) and might cause symptoms like asthma, diarrhea, abdominal pain, or even anaphylaxis (Kuehn et al. 2014). As these symptoms might be severe, it is important to characterize, identify, and quantify all protein allergens (Di Girolamo et al. 2015). Allergens are the proteins used to mediate the allergenicity, and the major fish allergen has been identified as parvalbumin (Kuehn et al. 2014). Proteomics can be an important tool to characterize fish allergens. The major fish allergen can now be detected in less than 2 h using proteomic approaches using selected MS/MS ion monitoring (SMIM) in a

linear ion trap (LIT) mass spectrometer (Swoboda et al. 2002; Carrera et al. 2011, 2012). All these approaches result in a new "omics" era, namely, the allergenomics. After extraction of the proteins and separation by 1-DE or 2-DE, the visualization of fish protein allergens can be performed using immunoblotting with sera of allergic patients, and the N-terminal amino acids can be sequenced after the Edman degradation. The quantification of these allergens can be done by an ELISA using specific antibodies. Characterization and mapping of the IgE epitopes can be performed using liquid chromatography combined with a tandem mass spectrometer after 2-DE separation of the fish proteins (Fig. 1) (Di Girolamo et al. 2015). A different method for absolute allergen quantification has been developed by

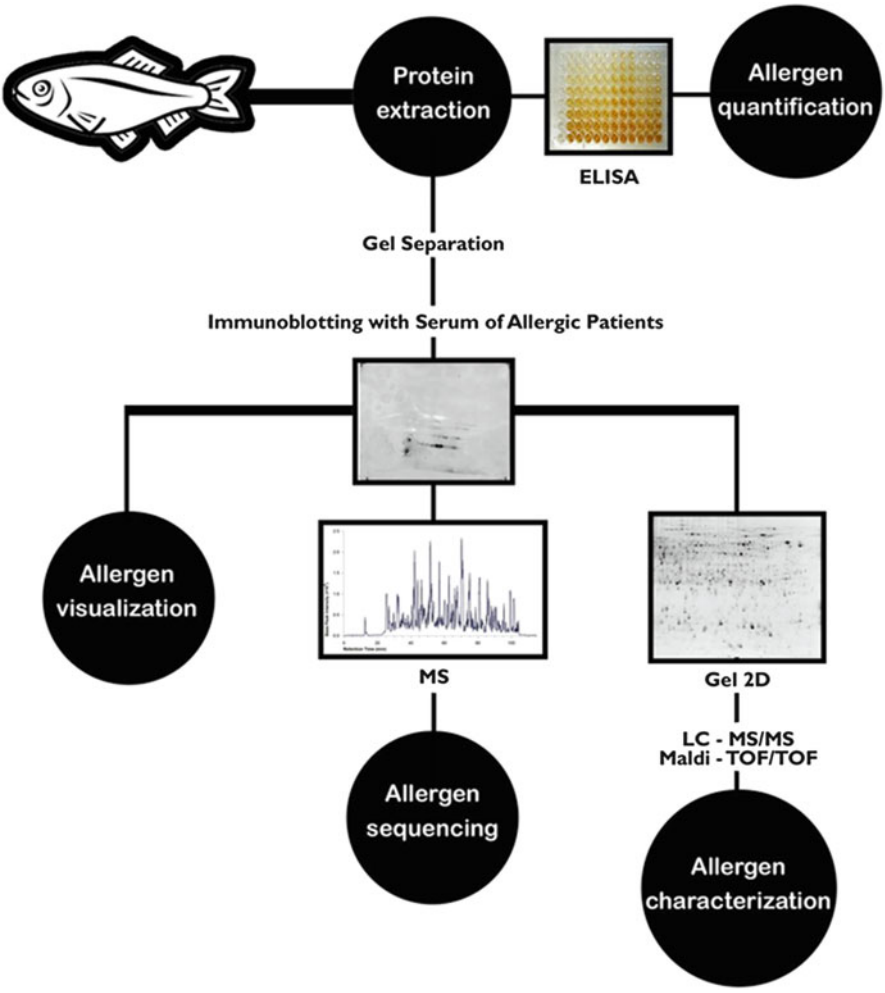

Fig. 1 Fish allergens identification using a proteomic approach

the way of triple quadrupole (QQQ) mass spectrometers using selected reaction monitoring (SRM) in plural multiple reaction monitoring (MRM) (Picotti et al. 2009), but this method is limited to known allergens (Ahsan et al. 2016). More recently Kobayashi and colleagues quantified 22 species of fish by their parvalbumin content using SDS-PAGE. They observed that parvalbumin is present in higher quantities in white muscle and that large-sized translocating species like tuna, swordfish, and salmon show lower quantities of this protein and lower reactivity of IgE from allergic patients (Kobayashi et al. 2016b). They showed in a different study that the amount of parvalbumin determines allergenicity and not the molecular differences of the allergen between species (Kobayashi et al. 2016a).

Different isoforms of parvalbumin have been identified in freshwater carp, and it has been shown that divergent developmental stages may express other isoforms (Brownridge et al. 2009). A commercial antibody against parvalbumin has been used to show its presence in various fish species and also demonstrates that heat treatment of the muscle alters the recognition of the antibody (Saptarshi et al. 2014). A few years earlier, it had been shown that in smoked fish species like salmon, mackerel, and haddock, a novel band of parvalbumin appeared at 30 kDa, and altered immunogenicity was shown on processed cod, salmon, trout, and pickled herring (Sletten et al. 2010). Recent proteomic-based studies identified enolase, tropomyosin, and creatine kinase as novel allergenic proteins, between others (Tomm et al. 2013), and characterized the allergenome of transgenic and non-transgenic fish, showing no difference in expression of parvalbumin and triose-phosphate isomerase, between others (Nakamura et al. 2009). The analysis of parvalbumin allergenicity in different fish species showed that the β-lineage is the most identified, and the International Union of Immunological Societies Allergen Nomenclature Subcommittee (www.allergen.org) contains 21 parvalbumins registered from 12 fish species (Kuehn et al. 2014).

3 Fish Diseases

Farmed fish are susceptible to a wide range of bacterial, viral, parasitic, and fungal infections, and losses through disease not only constitute a serious constraint to this industry, making a significant impact on the quality and volume of the fish produced in Europe and throughout the world (Hill 2005), but also have led people to question the safety of aquaculture (Adams and Thompson 2006).

Several pathogen detection methods (traditional, immunological, molecular) have been extensively used to improve fish health (Parrington and Coward 2002; Burge et al. 2016). And since scientific advances in aquatic health continue to close the gap with clinical and veterinary medicine, new techniques are becoming a reality that offers untold benefits to the aquaculture industry (Adams and Thompson 2006; Oskoueian et al. 2016). Proteomics, still mostly focused on gel-based techniques (Silva et al. 2014b), is one of those new tools and constitutes one of the best approaches for health management in aquaculture (Rodrigues et al. 2012, 2016; Silva et al. 2011) and to better understand fish diseases and epidemiology (Alves et al. 2010).

Fish diseases can be divided in two main areas: infectious fish disease and noninfectious fish diseases.

Infectious fish diseases are caused by pathogens such as virus, bacteria, fungi, and parasites and are the main source of economical loss in farm fish industry (Shinn et al. 2015).

Several proteomic studies related to infectious diseases have been described in the literature in areas like pathogenesis (Park et al. 2012), vaccine development (Lee 2001; Chen et al. 2004), disease diagnosis (Chen et al. 2004), disease resistance (Almeida et al. 2015), physiological response to pathogens (Rodrigues et al. 2012; Peng 2013; Addis et al. 2010), pathogen characterization (Dumpala et al. 2010; Buján et al. 2015; Fernández-Álvarez et al. 2016), immune proteins and immune system characterization and responses (Encinas et al. 2010; Coates and Decker 2016), disease biomarkers (Braceland et al. 2015), and organism response to disease treatment products (Varó et al. 2010).

In Table 1, a summary of some of the proteomic techniques applied in the study of infectious fish diseases is presented. Interestingly the number of proteomic studies in parasites is far lower than the number of studies in virus or bacteria. This is probably due to the availability of more DNA, RNA, and protein information from virus and bacteria in comparison with fish parasites in different databases (Burge et al. 2016).

Noninfectious fish diseases are mostly related to an external stimulus caused for instance by nutrition or the environment. These are normally associated with the production technology and can be the cause of several problems to aquaculture production as malformation, low growth rate, tumors, anorexia, poor quality of the product, or even high death rates (Forné et al. 2010).

The study of the influence of these external factors using proteomics is addressed in several papers such as the ones describing fish response to contaminants like PAH or PCBs (Galland et al. 2015), exposure to heavy metals or radioactive compounds (Hogstrand et al. 2002; Smith et al. 2015; Yadetie et al. 2016), exposure to toxins (Karim et al. 2011), response to stressors (Cordeiro et al. 2012), physical trauma (Wu et al. 2004) or fish development characterization used to reduce malformation incidence (Chicano-Gálvez et al. 2015), characterization of gas bubble disease caused by hyperoxygenation of the tanks (Salas-Leiton et al. 2009), and characterization of fish tumors (Stentiford et al. 2005; Lerebours et al. 2013).

As can be observed in Table 1, most proteomic studies in this field use top-down approaches (mainly 2-DE, followed by mass spectrometry). The major reason for this is related to the use of proteomics in aquaculture being still in its early days and progress in defining fish proteomes is expected to be slower than genome sequencing. Also, datasets from diseased fish and from fish pathogens need to be collected and available on a large scale before this technology can be fully used. In addition, although 2-D electrophoresis is the main technique used for detecting variation in the expression of proteins, this procedure is time-consuming and expensive, and reproducibility is a problem. Even in combination with mass spectrometry, only the more abundant proteins can be detected, thus indicating the need for new technologies (Zhou et al. 2012; Rodrigues et al. 2016).

Table 1 Summary of some of the proteomic techniques applied in the study of infectious fish diseases

Fish species	Aetiological agent	Disease	Tissue	Proteomic technique	Publication
Vírus					
Singapore grouper	Iridovírus	–	Iridovirus envelope proteins	1-DE-MALDI-TOF/TOF-MS/MS and LC-MALDI-TOF/TOF-MS/MS	Zhou et al. (2011)
Common carp	Spring viremia of carp virus	Spring viremia of carp	Epithelioma papulosum cyprini cells	2-DE MALDI-TOF/TOF	Liu et al. (2013)
Atlantic salmon	Salmonid alphavirus subtype 3	PD disease	Serum	2-D nanoflow UHPLC-ESI-MS/MS	Braceland et al. (2013)
Zebra fish	Rhabdovirus	Viral hemorrhagic septicemia	Whole body	2-D-DIGE MALDI-TOF/TOF	Encinas et al. (2010)
Zebra fish	Megalocytivirus	Infectious spleen and kidney necrosis virus	Whole body	2-DE MALDI-TOF/TOF	Xiong et al. (2011)
Bacteria					
Gilthead sea bream	*Moraxella* sp.	Bacteria	Kidney	2-D PAGE	(Addis et al. 2010)
Channel catfish	*Edwardsiella ictaluri*	Bacteria	Head kidney	2-D PMF MALDI-TOF-MS/MS	Booth and Bilodeau-Bourgeois (2009)
Turbot	*Edwardsiella tarda*	Bacteria	Bacterial strains	DIGE MALDI TOF/TOF	Buján et al. (2015)
Various species	*Flavobacterium columnare*	Columnaris disease	*F. columnare*	2-D LC ESI MS/MS and 2-DE MALDI TOF/TOF MS	Dumpala et al. (2010)
Sea bass	*Aeromonas salmonicida* subsp. *salmonicida*	Bacteria	Multiple organs	MALDI-TOF-MS	Fernández-Álvarez et al. (2016)
Various species	*Vibrio anguillarum*	Bacteria	*V. anguillarum* outer membrane proteins	2-DE LC-nano ESI-Q-TOF MS/MS	Kao et al. (2009)
Salmonids	*Yersinia ruckeri*	Bacteria	*Y. ruckeri*	Nano LC-ESI	Kumar et al. (2016)
Various species	*F. columnare*	Columnaris disease	*F. columnare* outer membrane proteins	SDS-PAGE RP-HPLC MS/MS	Liu et al. (2008)

(continued)

Table 1 (continued)

Fish species	Aetiological agent	Disease	Tissue	Proteomic technique	Publication
Various species	*Flavobacterium psychrophilum*	Bacteria	*F. psychrophilum*	2-DE LC-MS/MS	Ponnerassery et al. (2007)
Rainbow trout	*Aeromonas salmonicida*	Bacteria	Acute response system to vaccine	2-D-PAGE MALDI-TOF and ESI MS/MS	Russell et al. (2006)
Various species	*Edwardsiella tarda*	Hemorrhagic septicemia	Virulence determinants	2-DE ESI tandem MS	Srinivasa Rao et al. (2004)
Parasites					
Atlantic salmon	Sea lice, *Lepeophtheirus salmonis*	–	Epidermal mucus	LC-MS/MS	Provan et al. (2013)

4 Genomic Resources

Genomic resources provide the bioinformatic tools needed for proteomics. In general, the proteome is dynamic in different cells, organs, growth stages, and environmental conditions, and the differences in the proteome may be affected by a number of factors. For instance, differential splicing of RNA or alternative splicing generates multiple protein translated products produced from a single gene. There are posttranslational processes that result in the modification of protein products. Therefore, proteomic studies that complement genomic information can provide a useful tool to investigate the entire biological, physiological, and metabolic processes in an organism. Genomics is defined as the systematic study of genomes, which refers to the entire genetic material of an organism. A database of animal genome sizes, which have been estimated using haploid DNA contents (C-values, in picograms), has been constructed with genomes available for over 5600 animal species (http://www.genomesize.com/). Recent advances in DNA sequencing technologies and bioinformatics have brought revolutionary advances in genomics for several aquatic animals (Table 2). In addition, more genomic information for

Table 2 Genomic databases of aquatic animals

Species	Website
Zebra fish (*Danio rerio*)	http://zfin.org/cgi-bin/webdriver?MIval=aa-newmrkrselect.apg
Salmon (*Salmo salar*)	http://web.uvic.ca/grasp/ http://www.salmobase.org/
Fugu (*Takifugu rubripes*)	http://www.fugu-sg.org/index.html
Catfish (*Ictalurus* spp.)	http://catfishgenome.org/
Rainbow trout (*Oncorhynchus mykiss*)	https://www.genoscope.cns.fr/trout/
Oyster (*Crassostrea gigas*)	http://www.oysterdb.com/FrontHomeAction.do?method=home
Shrimp (*Litopenaeus vannamei*)	http://www.shrimp.ufscar.br/en/introduction/ http://shrimpgpat.sc.mahidol.ac.th/ShrimpGPATV2/
Marine genomic database	http://mgnew.clemson.edu/
Medaka (*Oryzias latipes*)	http://mepd.cos.uni-heidelberg.de/mepd/ http://utgenome.org/medaka/ http://asia.ensembl.org/Oryzias_latipes/Info/Index http://mbase.nig.ac.jp/mbase/medaka_top.html
Pufferfish (*Tetraodon nigroviridis*)	http://www.genoscope.cns.fr/externe/tetraodon/ https://www.genome.gov/11008305/
Stickleback (*Gasterosteus aculeatus*)	http://sticklebrowser.stanford.edu/cgi-bin/hgGateway?hgsid=21904
Tilapia (*Oreochromis niloticus*, *Astatotilapia burtoni*, *Metriaclima (Maylandia) zebra*, *Pundamila nyererei*, *and Neolamprologus brichardi*)	http://cichlid.umd.edu/CGCindex.html https://www.broadinstitute.org/tilapia/tilapia-genome-project

aquatic animals are expected to be accessible in the near future. The applications of genome technologies have implications for fisheries sciences and aquaculture such as the management of fish genetic resources, improvement of aquaculture productivity for food security, and environmental sustainability of the aquaculture industry (Wenne et al. 2007; Quinn et al. 2012). Genomic research areas include structural genomics, functional genomics, epigenomics, and metagenomics.

Structural genomics describes genome structure, organization, and evolution including genetic map construction, genome sequencing, and the determination of a protein and its three-dimensional structure. Recently, salmonid genomes provide the valuable sources of whole genome duplications, which have been an important landmark for vertebrate evolution (Berthelot et al. 2014; Lien et al. 2016). The National Center for Biotechnology Information (NCBI) genomic information organizes databases on whole genome sequences, maps, assemblies, and annotations of over 80 fishes (https://www.ncbi.nlm.nih.gov/genome/browse/). The genome sequences have been published for a number of aquatic animals (Spaink et al. 2014) (Table 2). In addition, Ensembl (http://asia.ensembl.org/index.html) has been available as a genome browser for supporting the comparative genomic information of vertebrates. With the extensively growing number of genomic databases, whole genome-based selection for aquaculture species is expected to be possible in the near future. The genetic information of the mitochondria of fish has also been extensively determined and used for taxonomy study. To date, a number of mitochondrial genomes of fish have been available, and the mitochondrial genomes or mitogenomes of fish have been provided in a database at http://mitofish.aori.u-tokyo.ac.jp/ (Satoh et al. 2016). Furthermore, DNA bar codes of fish are derived from the 5′ end of the cytochrome c oxidase subunit I gene of mitochondrial gene sequences (Kochzius et al. 2010); international participants have been called to submit the bar codes of all fishes worldwide at http://www.fishbol.org/.

Functional genomics describes gene expression, function, and interactions on a genome-wide scale. Functional genomics integrates bioinformation from large-scale and high-throughput analysis to explore dynamics of gene expression in a range of processes including transcription and translation under various experimental or environmental conditions. Functional genomics also investigates the complex relationship between genotype (both protein-coding genes and regulatory noncoding regions) and phenotype during various biological processes such as growth, development, metabolism, immunity, and reproduction (Rossi et al. 2007; Panhuis et al. 2011; Sun et al. 2013). The most common technologies for functional genomics in aquatic animals have been sequencing-based approaches such as expressed sequence tags (ESTs) and high-throughput sequencing of mRNA or RNA sequencing (RNA-Seq) and hybridization-based microarray analysis (Rossi et al. 2007; Panhuis et al. 2011; Liu et al. 2012; Qian et al. 2014; Salem et al. 2015). ESTs are generated from the 5′ or 3′ end of cDNA libraries. ESTs provide information of transcription-active regions or transcriptomics, which are a primary source for gene databases. The EST database has contributed important genomic bioinformation for the identification of gene expression. For instance, EST resources provide sequence databases for gene discovery, identification of single

nucleotide polymorphisms (SNPs) and microsatellites, microarray development, and genome annotation. To date, EST data in public databases have been available for various aquatic animals including at the NCBI (http://www.ncbi.nlm.nih.gov/dbEST/), the Unigene database (http://www.ncbi.nlm.nih.gov.unigene), the Gene Index database (http://compbio.dfci.harvard.edu/tgi/), the Sigenae EST Contig (http://publiccontigbrower.sigenae.org:2020/index.html), and the USDA National Animal Genome Project (http://www.genome.iastate.edu/bioinfo/). RNA sequencing (RNA-Seq) uses high-throughput sequencing techniques to provide transcriptomic information or the complete set of transcription in both quantitative and qualitative manners. RNA-Seq information have been published for various aquatic animals (Sun et al. 2013; Liu et al. 2013; Salem et al. 2015). Microarray has been a useful technique for analyzing gene expression profiles at a transcription level in an organism under various developmental stages, involving the immune system, disease resistance, and response to environmental conditions (Peatman et al. 2007; Drivenes et al. 2012; Matsumoto et al. 2014). Microarray analysis and construction should be compliant with the Minimum Information About a Microarray Experiments guidelines (MIAME guidelines) and meet the standards of the Microarrays Gene Expression Data (MGED) society. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) has been commonly used to evaluate the individual gene expression to confirm EST, RNA-Seq, and microarray analysis results. To date, functional genomics offers databases for the application of SNP analysis and quantitative trait loci (QTL) mapping which provide the valuable bioinformatics for powerful DNA markers.

Other genomic tools have been gaining attention recently in the aquatic sciences (Ardura et al. 2011; Williams et al. 2014; Moghadam et al. 2015). For example, the study of epigenetics focusing on heritable modification in gene expression does not involve changes to the DNA sequence. The epigenetic modifications affect gene expression due to several known mechanisms such as DNA methylation and histone modification (Chatterjee and Eccles 2015). Epigenomics refers to the whole bioinformation of epigenetics which offers an understanding of transcriptional regulation. In addition, metagenomics which has been referred to environmental genomics or ecogenomics provides the bioinformation on the genetic material of microbial ecology. Since there are a number of uncultivated microorganisms in nature, which cannot be determined by cultivation-based methods, PCR-directed sequencing (shotgun) offers a useful methodology to explore the entire microorganism community in nature (Xing et al. 2013).

5 Concluding Remarks

This chapter offers a brief overview of the potential of proteomics-based technologies in aquaculture management strategies describing its use in factors like welfare, nutrition, safety, or diseases, which pose some of the main constrains in this industry nowadays. Limitations to the use of this technology are mostly related

to the lack of gene annotation for most fish-farmed species. Here, we are sure to see a major change with the development of high-throughput sequencing facilities and sequencing cost reductions. It is also most likely that proteomic technologies will move away from 2-DE and rely more directly on gel-free approaches.

The need of integration with other OMICS technologies like genomics or metabolomics together with the more broad use of bottom-up proteomic techniques, the development of protein arrays, the increased capacity of centralized databases, networks, data repositories, and contingency plans, and, in particular, antibody microarrays might hold potential for a boost of application of proteomics in aquaculture.

Ethical issues also need to be considered as a possible hindrance. New practices such as genetic modification (transgenic and gene editing) will potentially lead to welfare issues, and the functional outputs of such changes will be increasingly assessed by proteomics.

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