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RESEARCH ARTICLE

The cellular basis of compensatory muscle growth in the teleost *Odontesthes bonariensis*

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ABSTRACT

This study evaluates white muscle growth and *in vivo* cell proliferation during a fasting and refeeding trial, using pejerrey (*Odontesthes bonariensis*) as animal model, in order to better understand the cellular basis governing catch-up growth. Experiments consisted of two groups of fish, a control group continuously fed *ad libitum*, and a group fasted for 2 weeks and then fed for another 2 weeks. We examined how the formation of new muscle fibers and their increase in size were related to muscle precursor cell (MPC) proliferation under both experimental conditions. During fasting, the number of 5-ethynyl-2′-deoxyuridine-positive (EdU^+) cells decreased along with myogenic regulatory factor (MRF) mRNA levels related to myoblast proliferation and differentiation, and the muscle stem cell marker *Pax7* mRNA level increased. Analysis of myomere cross-sectional area, distribution of muscle fiber sizes and number of fibers per myomere showed that muscle hypertrophy but not hyperplasia was inhibited during fasting. Both higher *igf2* mRNA level and the persistence of cell proliferation could be supporting new myofiber formation. In contrast, an exacerbated MPC proliferation occurred during catch-up growth, and this increase in cell number could be contributing to the growth of both pre-existing and newly formed small fibers. The findings that some MPCs proliferate during fasting and that muscle growth mechanisms, hyperplasia and hypertrophy are differentially regulated could help to explain why re-fed fish could grow at faster rates, and why they return to the lost growth trajectory.

KEY WORDS: Fasting, Compensatory growth, Cell proliferation, Muscle, Hyperplasia, Hypertrophy, Myogenesis, Pejerrey, Fish

INTRODUCTION

Each organism has a growth trajectory and a final body size determined mainly by genetic and epigenetic components (Nilsson, 2018; Sebens, 1987), with growth rates influenced by external factors (Alami-Durante et al., 2007; Johnston et al., 2011; Macqueen et al., 2008). One of the unsolved questions related to body growth rates is how organisms can grow at faster rates than controls after a period of delayed growth, and how deceleration occurs once the lost growth trajectory is attained. In fish, 'catch-up' growth (Boersma and Wit, 1997) that occurs after fasting has been related to an increase in food intake (hyperphagia) and efficiency in food utilization (Ali et al., 2003; Picha et al., 2014; Won and Borski, 2013). However, local regulation of cell proliferation and cell growth in this situation has been poorly described.

On average, if growth trajectories were compared between different taxa, endothermic mammals and birds would have higher maximum growth rates than similarly sized ectothermic fishes and reptiles (Werner and Griebeler 2014). In contrast, unlike mammals, the window of body growth covers nearly the entire life cycle in most teleost species and are considered to have indeterminate growth because body size never fixed (Froehlich et al., 2013; Mommsen, 2001; Sebens, 1987).

In almost all animal species studied, the fastest growing period is associated with an abrupt increase in muscle mass that corresponds to the period of fastest production of new muscle fibers (Alami-Durante et al., 1997; Koumans et al., 1993; Leitão et al., 2011; Veggetti et al., 1990), suggesting that growth rates are highly dependent on the rate of muscle hyperplasia (increase in myofiber number). Each new muscle fiber is primarily formed by the fusion of differentiated myoblasts or muscle progenitor/precursor cells (MPCs) that, once committed to terminal differentiation, became mitotically inactive. Further muscle fiber growth in length and diameter (hypertrophy) depends on protein synthesis and/or new absorbed differentiated MPCs (Johnston et al., 2011). Both muscle hyperplasia and hypertrophy depend on myoblast proliferation. Final body size attained by a species strongly correlates with maximum muscle fiber number, and clear evidence exists that both parameters are mainly genetically determined (Johnston et al., 2004; Rehfeldt et al., 2011). In teleost fish, post-larval muscle growth occurs by both hyperplasia and hypertrophy throughout most of the life cycle (Rowlerson et al., 1995; Rowlerson et al., 1997), whereas in mammals, the contribution of hyperplasia to muscle growth is restricted to prenatal or a quite small postnatal period and further muscle growth primarily depends on hypertrophy (Rehfeldt et al., 2011; Rowe and Goldspink, 1969). Very little is known about the mechanisms regulating the formation of myotubes in fast muscle (Johnston, 2006), and the regulation of muscle fiber number (Johnston et al., 2009).

In mammals, determination of the total number of fibers within a muscle is technically difficult, particularly in muscles of irregular shape, and because new fiber formation takes place during intrauterine growth (Brameld and Daniel, 2008). In intrauterine growth retardation (IUGR) syndrome, results are controversial because reports used a variety of methods for the estimation of hyperplasia process (Fahey et al., 2005; Greenwood et al., 1999; Nissen et al., 2003; Yates et al., 2014). In juvenile and adult fish, determination of the total number of fibers within a muscle is also technically difficult. Recent research to elucidate the role of hypertrophy and hyperplasia during muscle compensatory growth was achieved by transcriptomic analysis of muscle of adult fish during accelerated growth and hyperplastic growth zones of the

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List of symbols and abbreviations

EdU	5-ethynyl-2'-deoxyuridine
MPC	muscle progenitor/precursor cell
MRF	myogenic regulatory factor
Myog	myogenin
RT	room temperature

post-embryonic trout myotome, and suggests that accelerated muscle growth occurs by muscle hypertrophy (Rescan et al., 2017). However, the role of myoblast proliferation and the rate of myofiber generation in catch-up growth are still poorly described.

Increase in cell proliferation have been described in various mammal tissues after a short period of calorie restriction (Cerletti et al., 2012; Finkielstain et al., 2013), and deceleration of growth upon reaching final body size with age seems to be regulated not systemically but locally (Finkielstain et al., 2009, 2013; Roselló-Díez and Joyner, 2015), and it was associated with the downregulation of insulin-like growth factors and cell proliferation (Yakar et al., 2018). Paracrine/autocrine signals regulate cell proliferation and fiber growth in skeletal muscle. The insulin-like growth factors type 1 and 2 (Igf1 and Igf2) and myostatin are key regulators for the formation and maintenance of the skeletal muscle (Yakar et al., 2018). Igf2 is well established as a critical factor regulating cell proliferation, growth, differentiation and survival restricted to intrauterine growth or early postnatal development in humans and mouse (Nielsen, 1992). Igf2 concentration diminishes postnatally when growth-hormone-dependent Igf1 signaling dominates the signalling of these processes (Nielsen, 1992). In humans, a nonsense mutation in the *IGF2* gene, reported in a family of four members, was associated with prenatal and postnatal growth restriction (Begemann et al., 2015). Interestingly, unlike in mammals, *igf2* muscle expression does not cease in adult fish (Duan, 1998), suggesting that the expression of *igf-2* could be associated with indeterminate growth in teleosts, and possibly with muscle hyperplasia.

Pejerrey [*Odontesthes bonariensis* (Atheriniformes, Atherininopsidae)], a well-studied South American freshwater silverside, exhibits a broad window of growth and a relatively small size compared with other commercial fish, which show indeterminate body growth. Moreover, cross-sections of juvenile specimens are small enough to allow us to examine the whole musculature of juvenile fish under a microscope. In this context, the aim of the present work was to get inside the cellular basis of compensatory growth using *O. bonariensis* as teleost model, by analysing muscle cell proliferation using an EdU *in vivo* labeling assay, muscle hyperplasia and hypertrophy. We also studied the expression of muscular proliferation and differentiation molecular markers and paracrine/autocrine factors during both the non-growing phase and the phase of exacerbated growth.

MATERIALS AND METHODS

Fish husbandry, experimental design and sampling

Juvenile pejerrey [*Odontesthes bonariensis* (Valenciennes 1835)] were obtained by natural reproduction of brood stock of *O. bonariensis* belonging to the Laboratory of Aquaculture Biotechnology (LBA) at Centro Científico, Tecnológico y Educativo 'Acuario del río Paraná' (Rosario, Argentina) and kept at the facilities of the LBA for the trials. Juvenile pejerrey were maintained on a 14 h:10 h light:dark schedule at 21±1°C in a recirculating system containing 12×100 liter tanks with a mechanical and a biological filter. In all cases, the fishes were randomly divided into the experimental tanks, fed to satiation with a commercial diet (Shulet S.A., Argentina) and acclimatized for 2 weeks before the start of the trial. As a first step in studying compensatory growth in this fish species, a fasting and refeeding experiment was carried out in order to gain basic knowledge on its somatic growth response. Based on this result, a second fasting–refeeding experiment was designed to analyze *in vivo* MPC proliferation. In all cases, fish were anesthetized with Eugenol 10 mg l^{-1} or euthanized with Eugenol at 50 mg ml^{-1}. The first two experiments presented in this work were conducted assigning a group of fish per tank (three controls and three treated tanks). This approach was elected over the classical many fish in a single tank in order to minimize unpredictable effects of intra-tank interaction between individuals and growth, food ingestion and related variables under study in this work. Experiments consisted of two experimental groups: a control group, which was continuously fed *ad libitum*, and a treated group, which consisted of 2 weeks of fasting followed by 2 weeks of refeeding. In the first experiment (Fig. 1A), 120 fish (1.02±0.12 g body mass; 52.8±2.12 mm standard length) were distributed in six tanks (three control tanks and three treated tanks) and were allowed to acclimatize for 2 weeks to the new conditions. Body mass and standard length of six fish per tank were registered after acclimatization (time 0), fasting (2 weeks) and refeeding (4 weeks). At each time, three fish per tank were killed and muscle samples were taken for RNA extraction and histological analysis (see Histological and morphometric analysis, below). A second experiment was designed in order to quantify *in vivo* cell proliferation in white muscle (Fig. 2A). Fish (72 individuals) were distributed among 12 tanks. Fish in tanks 1, 2, 3, 7, 8 and 9 were continuously fed *ad libitum*, fish in tanks 4, 5 and 6 were starved for 2 weeks and fish in tanks 10, 11 and 12 were starved for 2 weeks followed by 2 weeks of refeeding. At days 9 and 23 after the start of the experiment, fish in tanks 1–6 and 7–12, respectively, received an intra-peritoneal injection of 10 mmol l^{-1} 5-ethynyl-2′-deoxyuridine (EdU) in PBS in order to track and label MPCs. The volume of the injection was adjusted so that each fish received a dose of 50 mmol EdU kg^{-1} body mass. Fish (four fish per tank) were euthanized after 2 weeks of treatment (tanks 1–6), and after the refeeding period (tanks 7–12). Then, a slice of 5 mm thickness was obtained from a distance of three-quarters of the total length from the head to the tail and frozen in isopentane that had been cooled (−160°C) in liquid nitrogen for 30 s. These samples were sectioned at 14 µm in thickness by cryostat and were stored at −80°C until histology and other analyses could be performed. To determine whether EdU^+ cells belong to muscle lineage, a third experiment was conducted. Thirty *O. bonariensis* juveniles of 4.06±1.14 g body mass and 8.05±0.93 cm total length were distributed in six tanks (five fish per tank). Fish from three of the tanks were subjected to fasting conditions for 10 days, while fish from the remaining three tanks were fed four times a day until satiety. On the tenth day of the experiment, the fish in each tank were euthanized. Following previously published methods (Froehlich et al., 2014), for the fish pool of each tank, cells were extracted from the white muscle and cultured *in vitro* in laminin-coated glass coverslips. The cells extracted from each tank were seeded in three culture coverslips to be counted and analyzed by immunofluorescence.

For all the experiments, the specific protocols were approved by the Animal Use Ethics Committee of Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Argentina (permit no. 361/2016).

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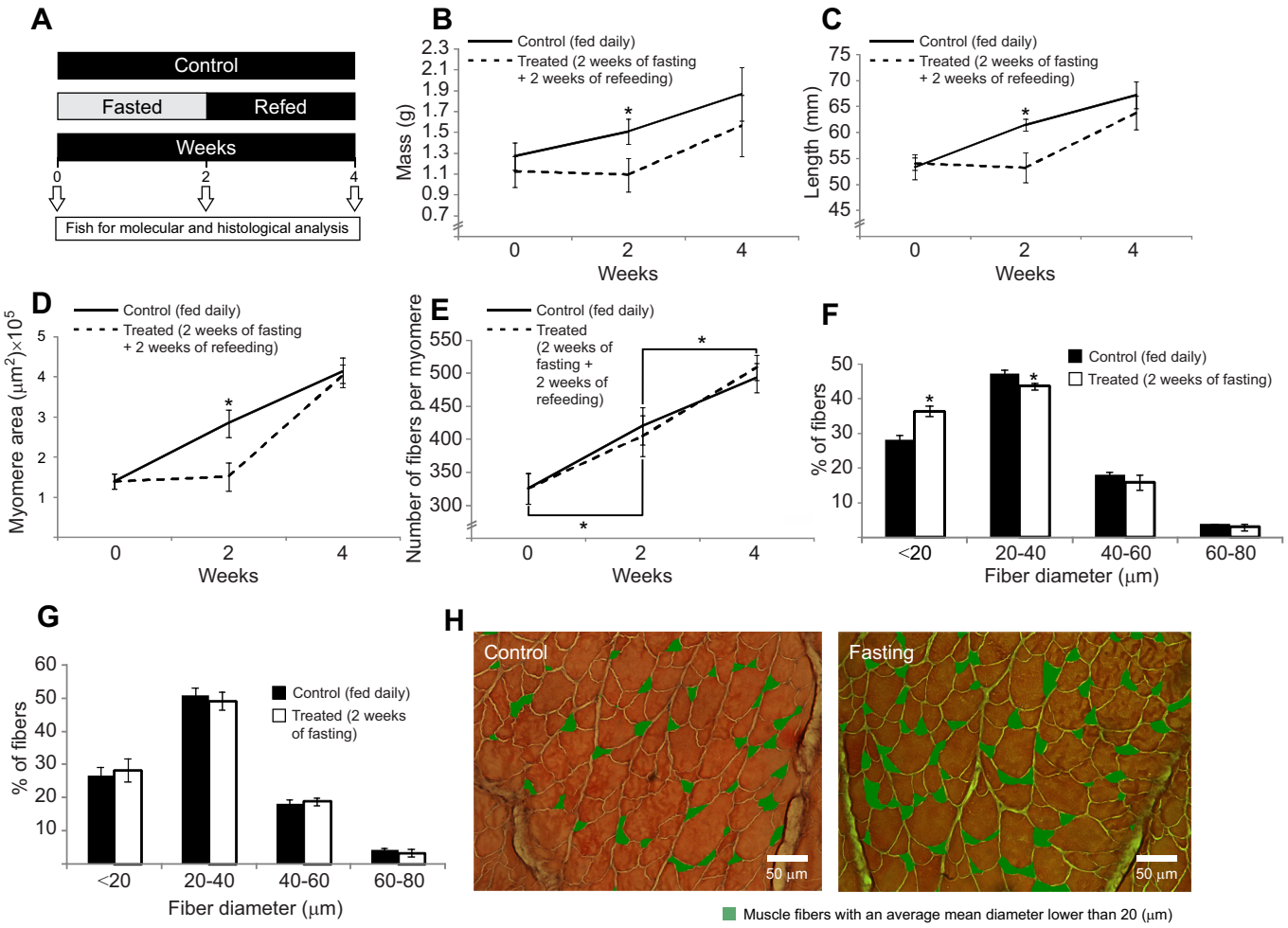

Fig. 1. Muscle hypertrophy and hyperplasia are differentially regulated during fasting and refeeding. (A) Schematic experimental protocol. Juvenile pejerrey individuals (53 mm mean body length) in the fast-growing phase were subjected to 2 weeks of fasting, and then to 2 weeks of re-feeding (fasted–refed group), or were subjected to daily feeding (control group). (B) Body mass and (C) length curves of pejerrey in fasted–refed and control groups. (D) Myomere area and (E) total number of fibers from a myomere were measure at 0, 2 and 4 weeks in fish from both groups. (F,G) The diameters of the myofibers were measured and the proportion of fibers of different diameters (<20, 20–40, 40–60 and 60–80 μm) per selected myomere were determined after 2 weeks (F) and 4 weeks (G) of treatment. (H) Representative image showing the small muscle fibers (<20 μm, in green) in a histological cross-section of fish at 2 weeks under control or fasting conditions. *Significant difference from controls (two-way nested ANOVA followed by Tukey test for B–E; one-way nested ANOVA for F and G; P<0.05). Data are presented as means±s.e.m. and compiled from the analysis of fish in three tanks per treatment, six fish per tank for mass and length measurements, and three fish per tank for histological analysis.

Immunohistochemistry

Muscle slices

Muscle slices were thawed for 15 min at room temperature (RT) and then incubated and fixed with 3.7% formaldehyde solution in PBS for 15 min at RT. To remove the excess of fixative, two washes of 30 s were performed with 100 µl of blocking solution (PBS 1X, pH 7.6, BSA 3%, BLOTO). All the washing steps mentioned in this section were carried out under the same conditions. Subsequently, the sample was incubated with 0.5% Triton X 100 solution in PBS pH 7.6 for 20 min for tissue permeabilization, and then three washes with BLOTO were performed. The sample was incubated with the built-in EdU development solution (Click-iT® EdU Imaging Kits, Thermo Fisher Scientific) for 30 min in the dark and then two washes were performed. Finally, the sample was incubated with anti-laminin antibody (Sigma L-9393) in a 1/40 dilution in BLOTO overnight at 4°C. The next day, three washes were performed and then the sample was incubated with anti-mouse IgG antibody conjugated to the Cy3 fluorophore (NB 120-6939, Jackson ImmunoResearch, West Grove, PA, USA) in BLOTO diluted 1/200 and a Hoechst 1x solution (Click-iT® EdU Imaging Kits, Thermo Fisher Scientific) for 1 h at room temperature. After the incubation, two washes were performed with 0.05% Tween 20-PBS, and finally the preparations were mounted with a cover-slip using DABCO assembly solution (Sigma Aldrich). The slices were stored at −20°C overnight and the next day were observed with a fluorescence microscope (Nikon Eclipse 800). To evaluate cell proliferation, all of the EdU^+ cells present on the half epaxial cross-sections of each fish were counted.

Isolated cells

A fraction of isolated cells from white muscle from control and fasted fish were incubated on laminin-coated glass coverslips (200,000 cells per cm^2) for 40 min and then washed twice with culture medium to remove any loosely attached or unattached cells. The coverslips were washed twice in 3% BSA in PBS (3% BSA solution) and the cells were fixed with 4% paraformaldehyde in PBS for 15 min at RT and washed twice for 5 min each with 3% BSA solution. Then, cells were permeabilized with 0.5% Triton X-100 in

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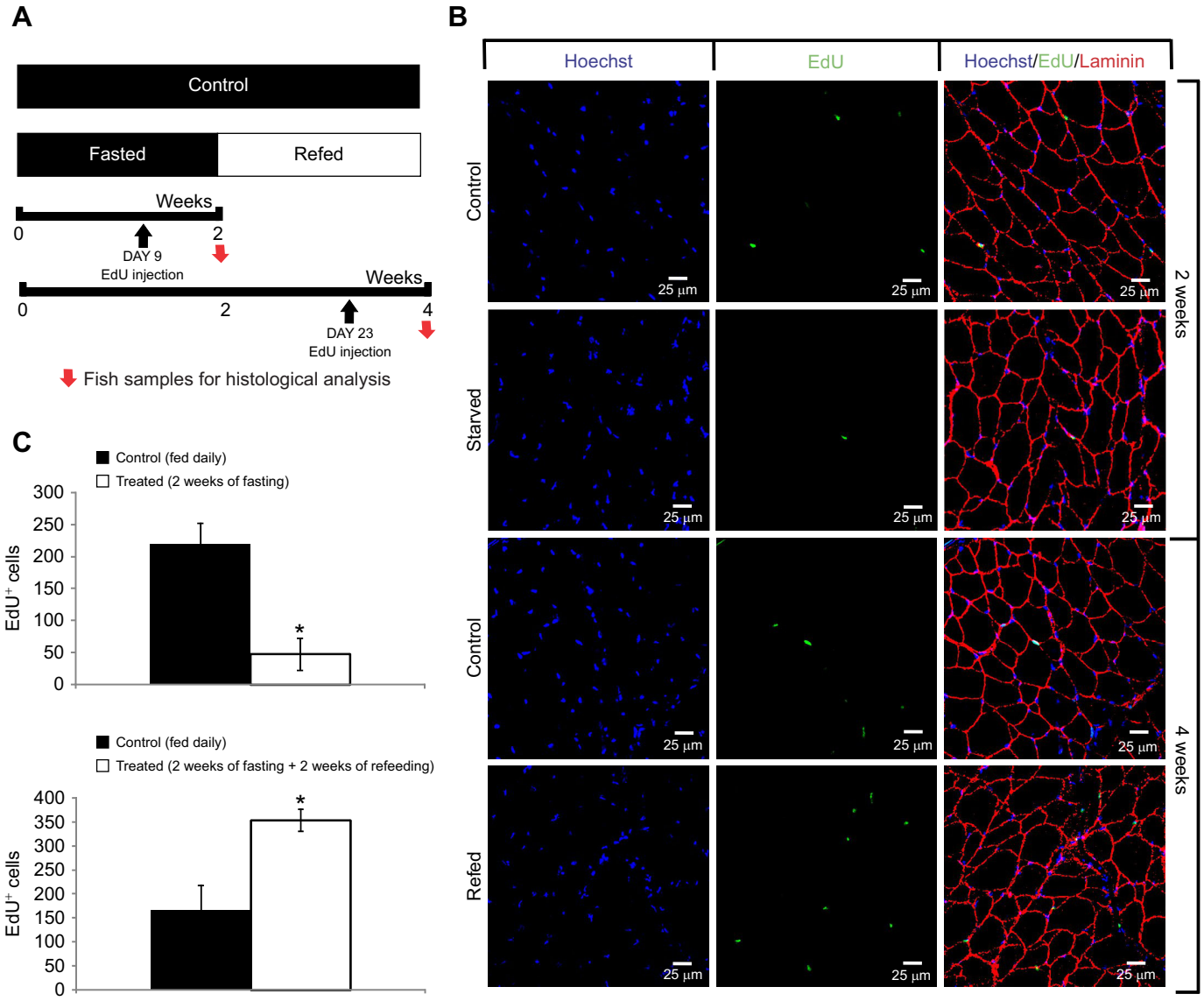

Fig. 2. Cell proliferation decreases during fasting and is enhanced during refeeding. (A) Schematic experimental protocol. Fish received an intra peritoneal injection of 5-ethynyl-2′-deoxyuridine (EdU) during fasting and refeeding periods. The same treatment was applied at fishes from control group. (B) Representative images of muscle pejerrey cryo-sections labelled with Hoechst (blue), anti-laminin (red) and EdU (green) after 2 weeks of treatment in control and starved groups, and after 4 weeks of treatment in controls and refed group. (C) Total proliferative EdU$^+$ cells on half epaxial muscle of pejerrey cryo-section of starved and refed fishes and the control groups. *Significant difference from control (one-way nested ANOVA, P<0.05). Values are expressed as means±s.e.m., three tanks per treatment, four fish per tank.

PBS for 20 min, and washed twice for 5 min each with 3% BSA solution. For the development of EdU, each coverslip was incubated in the dark for 30 min with the Click-iT® reaction cocktail (Click-iT® EdU Imaging Kit) at RT followed by two washes with BSA solution. Then, immunofluorescence was performed with Anti-Myod antibody (NBP1-54153, Jackson ImmunoResearch, West Grove, PA, USA) to detect Myod. Coverslips were blocked for 1 h on BSA solution and then incubated in Anti-Myod antibody 1/100 in 1% BSA in PBS ON at 4°C, followed by two washes with 3% BSA solution and 1 h incubation with secondary anti-rabbit IgG antibody Cy3 1/1000 in 1% BSA and Hoechst 33342. Coverslips were washed twice in 3% BSA solution and mounted using an anti-quencher solution. Using fluorescence microscopy, the EdU$^+$/Myod$^+$/Hoechst$^+$ cells were counted from three representative areas of each coverslip (more than 100 nuclei in each area) and these values were relativized to the total number of counted nuclei (Hoechst$^+$) in the three areas. Finally, the results obtained from the three pools of each condition were averaged to obtain the percentage of cells with different markers on each one.

The cells that did not adhere to the glass coverslips and another fraction of the total isolated cells from control and fasted fish were fixed with 4% (m/v) paraformaldehyde for 15 min and rinsed with PBS. Then, EdU$^+$ cells were revealed as mentioned earlier and the total nuclei were marked with Hoechst 33342. The concentration of EdU$^+$ cells in the suspensions was determined with a hemocytometer using a fluorescence microscope (Nikon Eclipse 800) and the percentage of EdU$^+$ cells adhered to laminin was calculated based on these values.

Digitization of images

The images were digitized using the program EZC1 3.9 Free Viewer (http://nikon-ez-c1-freeviewer.software.informer.com/3.9/).

Then, using each obtained image, the complete cross-section was reconstructed using the Image Composite Analyzer image overlay program (https://www.microsoft.com/en-us/research/product/computational-photography-applications/image-composite-editor/). Once digitized, the diagrams of the fibers and the calculations of their distribution, size and quantity were made using Image Pro Plus Analysis (http://www.mediacy.com/imageproplus).

Histological and morphometric analysis

Morphometric analysis was performed on digital muscle cross-sections, stained with Hematoxylin and Eosin, and photographed using an Andor Clara digital camera coupled to a Nikon Eclipse 800 fluorescent microscope. Analysis of the muscle myomere area, fiber diameter, number of fibers per myomere was carried out in a specific myomere. Each white fiber of the myomere was manually diagrammed on the scanned image (Fig. S1). All of the values of fiber number and area mentioned in the present work were obtained from the analysis of the fibers of the same type of myomere for all fish analysed (Fig. S1). The selected myomere was previously analysed on three different juveniles and did not show significant differences in the distribution of mean diameters of fibers of different size ranges compared with the diameter distribution of the total fibers in the half cross-section. Because the fiber cross-sections are not perfect circles, the mean diameter of each one is automatically calculated by the Image Pro Plus software as the average of the diameters measured at 2 deg intervals passing through the center of the object.

pax7, *myod*, *myf5*, *myog*, *igf1* and *igf2* mRNA expression

Gene expression on muscle was analyzed by RT-qPCR. The specific qPCR primers for ef1a and igf1 have been previously validated (Botta et al., 2016; Sciara et al., 2011). Primers for igf2, pax7, myod, myf5 and myog were designed using primer3web version 4.1.0 (https://primer3.ut.ee) based on sequences obtained from the *O. bonariensis* (pejerrey) genome (NCBI Genome txid219752). Amplified PCR sequences of igf2, pax7, myod, myf5 and myog were sent to the Macrogen sequencing service (https://dna.macrogen.com/#) to confirm their identity. Muscle tissue (50 mg) was immediately homogenized in 500 µl of TRIzol REAGENT (Invitrogen) for total RNA extraction following the manufacturer's instructions. RNA quantification and purity were determined using NanoDrop 2000 UV-Vis spectrophotometer (Thermo Fisher Scientific). To eliminate possible genomic DNA contamination, all samples were treated with DNase I (Promega, Madison, WI, USA) starting with 2 µg of total RNA according to the manufacturer's instructions. Then, first-strand cDNA synthesis was performed with M-MLV enzyme (Promega) for 50 min at 37°C followed by 10 min at 70°C using Oligo dT as the primer in a 10 µl final volume. RT-qPCR reactions were conducted on a Step One Plus PCR System (Thermo Fisher Scientific) in a 10 µl final volume with 5 µl of 5X PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific), 1 µl of forward/reverse primer mix (500 nmol l^{-1}; Table S1), 2 µl of cDNA template and 2 µl of water. Samples were run in duplicate and no-template controls were performed in every run for each set of primers. Primer efficiencies were calculated on every run for each tissue using LinRegPCR software (Ruijter et al., 2009). Quantification of cDNA was carried out by calculating the initial fluorescence (N0) per sample, which is representative of the initial amount of cDNA (Ruijter et al., 2009) and obtaining EGOI=N0GOI/N0RG, where EGOI is the expression of a gene of interest (GOI) normalized against a reference gene (RG), N0GOI is the initial fluorescence of a GOI and N0RG is the initial fluorescence of RG.

Statistical analysis

Results are presented as means±s.e.m. By means of nested ANOVA, it was confirmed that in the observed effect it is not dependent on the tank but on the treatment. One-way nested ANOVAs were run whenever two means were to be compared. All assumptions were tested for each test and if not met, an $\ln(x)$ transformation was carried out. For mass, length, fiber number and diameter, and myomere area, data were analyzed applying two-way nested ANOVAs and subsequent Tukey multiple comparisons in the case of significant differences. Compliance with the assumptions was verified through waste analysis (normality and equality of variances). In all cases, significance was considered at $P<0.05$.

RESULTS

Effects of fasting and re-feeding on growth performance, and the number and size of skeletal muscle fibers in juvenile pejerrey

To delay growth trajectory, juvenile pejerrey individuals (53 mm mean body length) in the fast-growing phase were subjected to 2 weeks of fasting, and then to 2 weeks of re-feeding (treated group) to test for compensatory growth, or were subjected to a daily feeding protocol (control group) (Fig. 1A). Fish (three tanks per treatment, six fish per tank) were weighed and measured for standard length at 0, 2 and 4 weeks. The masses and lengths of treated fish were constant after 2 weeks of fasting, but differed ($P<0.05$) from those of the controls (Fig. 1B,C). After 2 weeks of refeeding, no significant differences were found in the body size (mass and length) between groups (Fig. 1B,C), showing that fasted *O. bonariensis* undergo complete compensatory growth. The mean area of fasted fish myomere was significantly lower than that corresponding to control fish ($P<0.05$; Fig. 1D) and did not differ from the mean area of the myomere at the beginning of the experiment ($P>0.05$). After the compensatory growth period, no significant differences between myomeres areas in each group were found (Fig. 1D).

Histological analysis of white muscle fiber cross-sections showed that the mean number of fibers increased significantly between weeks 0–2 and 2–4 ($P<0.05$) for both groups, control and fasted–refed (Fig. 1E). The mean number of fibers did not differ significantly between treatments ($P>0.05$; Fig. 1E). Instead, the proportion of small fibers (mean diameter <20 µm) was significantly higher in the fasted group than in controls ($P<0.001$; Fig. 1F,H). In addition, the mean±s.e.m. diameter of small fibers (<20 µm) was smaller in the fasted group than in the controls (14.25 ±1.16 µm versus 17.07±1.08 µm, $P<0.05$). The data show that new muscle fibers were generated during 2 weeks of fasting, but they did not grow. No significant association between mass and number of white fibers ($r^2=0.4062$, $P=0.21$), nor between standard length and number of white fibers ($r^2=0.5043$, $P=0.11$), were observed in fasted fish after 2 weeks. In contrast, the association was significant between body mass and cross-sectional area of the myomere ($r^2=0.7657$, $P=0.006$), body mass and standard length ($r^2=0.9632$, $P=0.0000$) and between fish standard length and myomere cross-sectional area ($r^2=0.8966$, $P=0.0002$). Neither the number nor the distribution of myofiber sizes differed between groups after the re-feeding period (Fig. 1G). The percentage increase in mean myomere area and the number of myofibers was 165.8% and 25.7%, respectively, in refed fish, suggesting that hypertrophy is the process that mainly contributes to muscle compensatory growth.

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Table 1. Percentage of laminin-attached mononucleated cells isolated from white muscle and analyzed for EdU and Myod

Isolated cell markers	Control fish Mean±s.d. (%)	Fasted fish Mean±s.d. (%)
Myod$^-$/EdU$^+$	0±0	0±0
Myod$^-$/EdU$^-$	7.1±1.75	9.96±4.21
Myod$^+$/EdU$^-$	81.45±4.28	85.96±6.47
Myod$^+$/EdU$^+$	11.45±1.98	4.08±2.03*

*Significant difference from control (one-way ANOVA, P<0.05). n=3.

Effects of fasting and re-feeding on muscle cell proliferation in juvenile pejerrey

Considering that hypertrophy but not hyperplasia was inhibited in juvenile pejerrey during fasting under the experimental conditions, and that the formation of new myotubes requires cell proliferation, we tested whether cell proliferation in white muscle took place during the non-growing period. In order to assess the occurrence of cell proliferation, an assay for *in vivo* labeling of replicating DNA with EdU was standardized for juvenile pejerrey (Fig. S2). Then, an experimental fasting–refeeding approach (2 weeks fasting+2 weeks refeeding) was conducted in which EdU was injected into juvenile pejerrey 9 days after the beginning of the fasting period, and 9 days after the beginning of the re-feeding period in another two control and treated groups (Fig. 2A). EdU$^+$ cells were measured in a half cross-section of each fish after the completion of both periods. Cell proliferation still took place in muscle during the fasting period, but we observed fewer proliferating EdU$^+$ cells in fasted fish (43±31 EdU$^+$ nuclei) compared with controls (220±34 EdU$^+$ nuclei) (P<0.05; Fig. 2B,C). At the end of the re-feeding period, a significant increase in EdU$^+$ nuclei (354±21 EdU$^+$ nuclei) was observed in fasted–refed fish compared with the control group (164 ±52 EdU$^+$ nuclei) (P<0.05; Fig. 2B,C). In order to assess the identity of EdU$^+$ cells, mononucleated cells were isolated from white skeletal muscle of fasted and control fish. The number of EdU$^+$ cells from the total suspension and attached to laminin-coated coverslips were estimated. The percentage of isolated EdU$^+$ cells that adhered to laminin was 97.5% and 98.1% from control and fasted fish, respectively, without significant differences. For both treatments, the EdU$^+$ cells that bind to laminin also resulted in Myod$^+$ cells (Fig. S3, Table 1). The percentage of EdU$^-$/Myod$^-$ or Myod$^+$/EdU$^-$ cells did not show a significant difference between control and fasted fish. However, consistent with previous observations in muscle histochemistry, the percentage of EdU$^+$ cells obtained from control fish was significantly higher (11.45 ±1.98%) compared with the fasted group (4.08±2.03%) (P<0.05; Table 1).

Effects of fasting and re-feeding on gene expression patterns in muscle

The genes involved in muscle cell determination (*myod*, *myf5*) and differentiation (*myog*) showed significantly lower expression levels (P<0.05) during the fasting phase compared with control fed fish (Fig. 3). In contrast, the expression of *pax7*, a quiescent stem cell marker, was significantly higher (P<0.05) after 2 weeks of fasting, and no differences between groups were observed after the re-

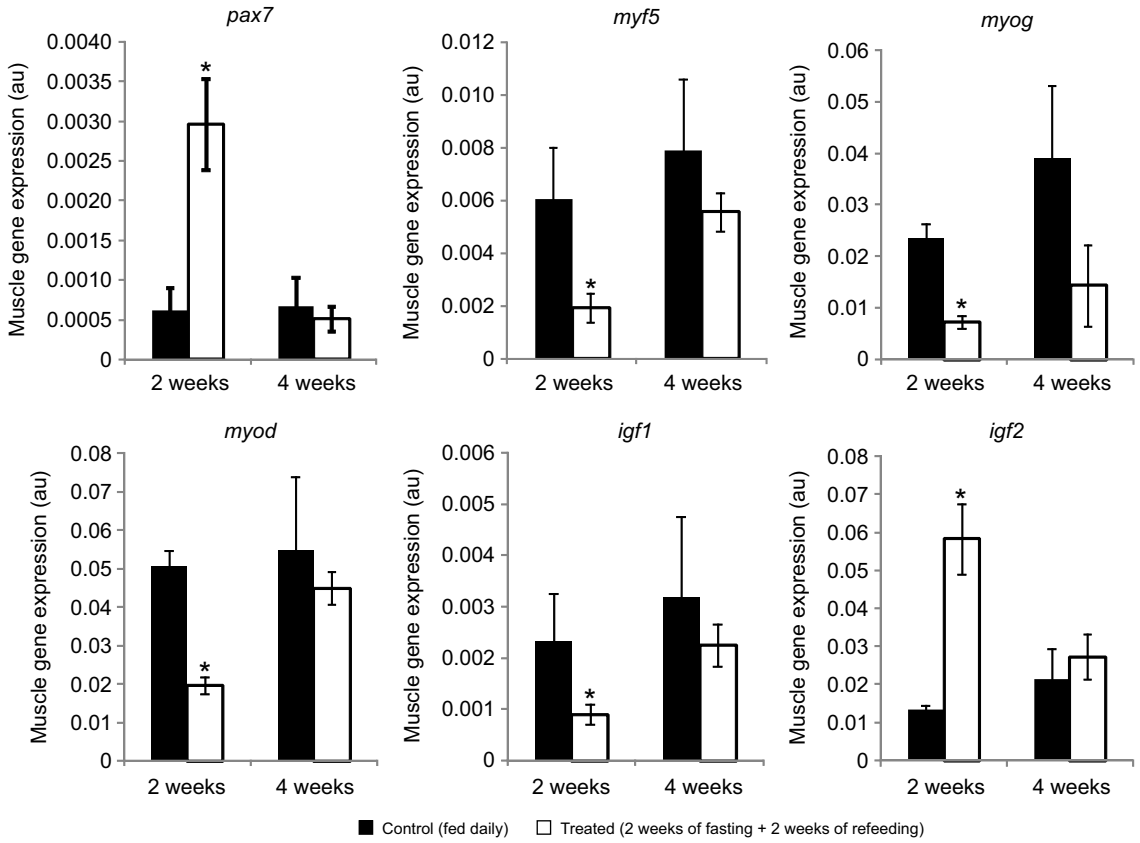

Fig. 3. Genes involved in muscle growth are differentially regulated during fasting and refeeding. Relative muscle mRNA expression (arbitrary units) of transcription factors pax7, myf5, myog, myod and growth factors igf1 and igf2 after fasting and refeeding. Standard deviation is depicted with positive and negative error bars. All qPCR graphs show gene expression normalized to ef1a. *Significant difference from control (one-way ANOVA, P<0.05), n=9 (three tanks per treatment, three fish per tank).

feeding period (Fig. 3). The analysis of growth factor transcript levels in white muscle samples showed that *igf1* and *igf2* expression are differentially regulated in muscle during fasting. After the fasted period, the level of *igf2* mRNA was higher, and *igf1* mRNA levels were significantly lower than in control fish ($P<0.05$; Fig. 3). No significant differences were found in the mRNA levels of the growth factors analysed after 2 weeks of re-feeding (Fig. 3).

DISCUSSION

One of the unsolved questions around body growth rates is related to how organisms can grow at faster rates than controls after a period of delayed growth. In fish, compensatory growth that occurs after fasting has been related to an increase in food intake (hyperphagia) and efficiency of food utilization (Ali et al., 2003; Picha et al., 2014; Won and Borski, 2013). However, the cellular bases of compensatory growth are poorly understood. Recent transcriptomic analysis of the genes that compose the compensatory muscle growth signature of adult rainbow trout and the genes that were upregulated in hyperplastic growth zones of the post-embryonic myotome suggests that accelerated muscle growth is mediated by myofiber hypertrophy (Rescan et al., 2017). The present work provides strong evidence that fiber hypertrophy is the main process of muscle compensatory growth, and adds a new perspective to explain catch-up growth. Our findings on full compensatory muscle growth after 2 weeks of fasting followed by 2 weeks of refeeding in juvenile pejerrey lead to the following conclusions: (1) muscle hypertrophy but not hyperplasia is mainly regulated by nutritional status, (2) a population of MPCs continues proliferating during fasting, and could be related to the new myofibers generated during the non-growing phase, (3) hypertrophy of muscle fibers, including the small muscle fibers formed during fasting, is the main mechanism that contributes to catch-up growth, and (4) the enhancement of MPC proliferation after food restriction could be a key cellular contributor of nuclei to the compensatory skeletal muscle hypertrophy.

Muscle hyperplasia and hypertrophy are differentially regulated

The pattern of myomeres observed in a whole-body cross-section at a given position on the anterior–posterior axis is highly conserved between individuals of a given teleost species. In juvenile pejerrey, there was a strong correlation between the cross-sectional area of a myomere, determined by the sum of the whole myofiber areas within it, and the mass and length of each fish. Determining the total number of myofibers from a cross-sectional area of a defined myomere is a powerful method to measure the occurrence of hyperplasia. Under the experimental conditions of the present study, the number of muscle fibers per myomere increased at similar rates (~40 myofibers per week) both in control and fasting–refeeding groups, showing that neither fasting nor refeeding induced changes in hyperplasia rate, while hypertrophy was highly dependent on food availability during the hyperplastic growth phase. The distribution of muscle fiber diameters in the myomere cross-section after 2 weeks of fasting suggests that not only hyperplasia but also atrophy could contribute to the increase in the proportion of small muscle fibers in fasted fish, as total myomere cross-sectional area did not change from 0 to 2 weeks of fasting, although new fibers were formed during this period. Previous data on the effect of starvation on muscle fiber size and number in juvenile fish are scarce (Beardall and Johnston, 1983; Johansson and Kiessling, 1991). Correlations between cross-sectional area of white muscle fibers and carcass mass have been previously observed in rainbow trout (Johansson and Kiessling, 1991; Weatherley et al., 1988). However, the studies on the effect of calorie restriction or starvation on hyperplasia are more elusive. In mammals, determination of the total number of fibers within a muscle is technically difficult, particularly in muscles of irregular shape, and because new fiber formation takes place during intrauterine growth (Brameld and Daniel, 2008). Calorie restriction during gestation seems to influence total fiber number only during primary myofiber formation in the embryo, but not during the production of secondary fibers during the foetal period (Kalbe et al., 2017; Wilson et al., 1988), whereas postnatal undernutrition exclusively affects fiber hypertrophy by means of reduced nuclear and protein accumulation (Rehfeldt et al., 1999). In fish, growth retardation during fasting conditions in post larval stages has been mainly associated with muscle atrophy and hypertrophy inhibition (Beardall and Johnston, 1983; Nebo et al., 2013). Only during larval stages do both muscle hyperplasia and hypertrophy seem to be conditioned by diet quality and temperature in fish (Campos et al., 2013; Canada et al., 2018; Johnston et al., 1999; Ontell et al., 1988; Ostaszewska et al., 2008). Interestingly, Rescan et al. (2015), using juveniles from a transgenic line carrying GFP cDNA driven by the myogenin promoter, showed that the distribution of *GFP*-expressing small muscle myofibers in the muscle of fasted trout was similar to that observed in the muscle of well-fed trout, and suggest that myogenin-positive muscle fibers are still produced in atrophied muscle from fasted trout. Our work provides strong evidence that the formation of new fast-twitch muscle fibers during the fast-growing phase is not influenced by temporal food deprivation during post-larval growth in teleost.

Our data also suggest that complete compensatory muscle growth strongly depends on accelerated hypertrophy of the pre-existing and newly formed myofibers during the fasting period. In this way, small fibers will grow more rapidly than larger ones (Weatherley et al., 1988). The fact that nutrient assimilative capacity by fibers is a function of their surface area and is influenced by the critical diameter of the myofibers supports this observation (Johnston et al., 2011). In addition, the percentage of small fibers is an indicator of the body growth potential (Canada et al., 2018; Valente et al., 1999). This is in accordance with previous data that showed that the stage of greatest growth coincides with that of the highest rate of hyperplasia (Veggetti et al., 1990). Our data allow us to hypothesize that skeletal muscle can grow faster and completely compensate growth only if growth delay occurs in a period in which new fibers are being generated. This could partly explain why catch-up growth is observed only during early phases of animal growth, when hyperplasia is still taking place (Finkielstain et al., 2013). Moreover, the fact that the new myofiber generation rate did not change between fasted–refed and control fish could partly explain why fasted–refed fish return to the control growth trajectory after the catch-up growth period.

Muscle progenitor cell proliferation during catabolic and anabolic stages

Muscle growth involves several processes: formation of new fibers, fusion of additional myoblasts to existing fibers and increase in cell volume per nucleus. The first two depend on previous myoblast proliferation. In this work, nutritional status affected muscle progenitor cell proliferation in juvenile pejerrey; while myoblast proliferation was reduced in fasted fish, it was clearly exacerbated during the refeeding period, showing that systemic metabolic state modulates MPC proliferation. Interestingly, a myoblast proliferation deficit was observed in the sheep IUGR model (Soto et al., 2017). In rainbow trout, *Oncorhynchus mykiss*, primary myogenic cell lines

isolated from fed animals were found to differ extensively in terms of proliferation rate to those isolated from fasted animals (Fauconneau and Paboeuf, 2000), suggesting that nutritional status influences the metabolic state of fish MPCs. Nowadays, a significant amount of evidence from mammalian model organisms demonstrates the molecular link between calorie intake and the physiology and function of muscle stem cells (Fulco et al., 2008; Purohit and Dhawan, 2019). In this work, muscle hyperplasia but not hypertrophy took place during fasting, and a smaller population of MPCs continued proliferating. This suggests that in teleost white muscle, a subpopulation of MPCs could be associated with new fiber formation and could have differential susceptibility to calorie restriction or different metabolic requirements. Interestingly, evidence that myogenic cells with distinct metabolic requirements could exist in adults and embryos was recently found in the mouse (Pala et al., 2018). Because both hypertrophy and hyperplasia persist during post-larval growth in fish, a major uncertainty is whether fetal-like myoblasts besides the satellite-like cells coexist in different niches in the teleost muscle architecture. Transcriptomic, metabolic state and niche characterization of muscle cell populations isolated from both fasted and refed fish will be the next step in order to clarify the existence of more than one muscle stem cell type/status and to develop molecular markers for further analyses. Previous analyses of larval zebrafish muscle repair (Knappe et al., 2015; Pipalia et al., 2016) revealed two Pax7-expressing myoblast subpopulations that accumulate, differentiate and fuse distinctly during regeneration (Pipalia et al., 2016). Moreover, the transcriptomic analysis and *in vitro* cell behavior of MPCs extracted from hyperplastic muscle of juvenile trout were better able to form myofibers than myogenic cells extracted from non-hyperplasic muscle (Jagot et al., 2018). Whether such myoblast diversity underlies fiber formation during development in vertebrates is still unknown (Roy et al., 2017).

MPC proliferation was exacerbated under our experimental conditions in refed pejerrey, and these nuclei probably contribute to the accelerated muscle hypertrophy that takes place during compensatory growth. The contribution of new nuclei to fiber hypertrophy was proposed for muscle growth during early stages of muscle differentiation and during early postnatal development in mice and rats, but seems to be absent in muscle hypertrophy at postnatal stages (Schiaffino et al., 2013). However, a similar proliferation effect was observed in the muscle of young and old mice after a short-term calorie restriction period (Cerletti et al., 2012). *In vivo* direct stimulation of myogenic cell proliferation by food intake has been previously described for a notothenioid fish (Brodeur et al., 2003).

Effect of nutritional status on myogenic regulatory factors and insulin-like growth factor expression in relation to muscle cell proliferation, differentiation and myofiber growth

The effect of a fasting and refeeding schedule in muscle gene expression profiles has been previously characterized in fish species of different taxonomic orders, such as Perciformes (Lavajoo et al., 2020; Nebo et al., 2013), Salmoniformes (Jagot et al., 2018; Rescan et al., 2007, 2017; Valente et al., 2012), Characiformes (De Paula et al., 2017; He et al., 2015) and Cypriniformes (Yang et al., 2019). Decreases and increases in muscle mass are clearly associated with protein degradation (for energy purposes) and protein synthesis (mainly myosin-related proteins), respectively (De Paula et al., 2017; He et al., 2015). Muscle hypertrophy occurs when the overall rates of protein synthesis exceed the rate of protein degradation (Schiaffino et al., 2013). In contrast, fasting induces breakdown of muscle mass and involves different proteolytic processes such as the autophagy–lysosome and the ubiquitin–proteasome systems (Bonaldo and Sandri, 2013; Schiaffino et al., 2013). Although transcriptomic analysis of white muscle from pejerrey during fasting and re-feeding will be a next experimental step in order to understand the metabolic pathways and biological processes influenced by external factors, the maintenance of the myomere area while new fibers are generated suggests the occurrence of proteolysis and a decrease in the size of pre-existing fibers, as could be observed in the lower percentage of fibers with a mean diameter between 20 and 40 µm in fasted fish. The production of nascent myofibers in the muscle of fasted pejerrey suggests that amino acids released from protein breakdown during muscle atrophy are in part reused for building new muscle fibers from activated myogenic cells, as proposed previously in trout (Rescan et al., 2015).

Based on gene expression profiles, some authors suggest that in compensatory growth, refeeding stimulates proliferation of fish myogenic cells (Lavajoo et al., 2020) and muscle fiber hypertrophy (Rescan et al., 2017). In this work, both the expression of genes and cell proliferation associated with muscle growth were studied during pejerrey compensatory growth.

The specification, determination and differentiation of the cells that will give rise to differentiated myoblasts or myocytes involve different cell populations and the expression of different genes (Comai and Tajbakhsh, 2014; Dumont et al., 2015). The transcription factors responsible for the specification of mesodermal cells into the muscle lineage (myogenic regulatory factors, MRF) are conserved in teleosts and mammals (García de la serrana et al., 2014; Hinits and Hughes, 2007; Rescan, 2001; Rossi and Messina, 2014). In mammals, Pax7 is the main marker of muscle stem cells during postnatal growth and has an anti-apoptotic effect (Buckingham and Relaix, 2015). During muscle growth or regeneration, proliferating myoblasts co-express Pax7 and Myod, the latter being the main marker of active myoblasts, along with Myf5 (Comai and Tajbakhsh, 2014). The myoblasts that enter the differentiation process express a series of transcription factors that determine the identity and function of differentiated cells, myogenin (Myog) and Myf6/MRF-4 being the most characterized in fish (Froehlich et al., 2013; Gabillard et al., 2010; Rescan et al., 2015) and mammals (Sabourin and Rudnicki, 2000). Studies conducted in *in vitro* primary cultures of myoblasts obtained from teleost fish showed that *pax7* is expressed in newly activated stem cells but not during late stages of differentiation (Froehlich et al., 2013; García de la serrana et al., 2014; Seiliez et al., 2015).

In this work, exacerbated MPC proliferation, accelerated myofiber hypertrophy and whole-body growth were correlated with the recovery of the expression levels of MRF genes (*myod*, *myf5*, *myog*) and of *igf1* downregulated during fasting when proliferation (and expected differentiation) of MPCs is also downregulated. In the gilthead sea bream (*Sparus aurata*), 30 days of fasting resulted in muscle fiber atrophy, a reduction in *myod2*, *myf5* and *igf1* expression, a lower number of Myod-positive cells, and decreased PCNA protein expression, whereas myogenin expression was not significantly affected (García de la serrana et al., 2014). The downregulation of myog transcript levels was observed in juvenile trout after 2 weeks of fasting, although *myog* expression levels did not differ between controls and starved fish after 4 weeks (Montserrat et al., 2007a). In Atlantic salmon (*Salmo salar*), the expression of *myog* and *stac3* has been correlated with the differentiation of myogenic cells in primary cultures, and the expression of both genes has been shown to be regulated by the availability of amino acids (Valente et al., 2012).

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In mammals, Pax7 is a satellite cell marker whose expression is restricted to quiescent cells and proliferating myoblast in postnatal growth and regeneration, and downregulated during terminal differentiation (Seale et al., 2000). In humans, homozygous individuals with a loss-of-function *Pax7* variant showed exhaustion of the satellite cell pool and, consequently, decreased muscle growth and regeneration capacity (Feichtinger et al., 2019). However, the role and regulation of Pax7 in teleosts is still poorly understood (Froehlich et al., 2013). Significant expansion of the $Pax7^{+}$ MPC population was observed during embryonic myogenesis in the dermomyotome of mutant fish that lack the muscle regulatory factor Myod (Hinits et al., 2011; Roy et al., 2017). Interestingly, *pax7* expression has also been associated with a quiescent MPC state in *S. salar*, as depriving isolated muscle progenitor cells of amino acids and serum led to a rapid increase in *pax7* and a decrease in *myod1* and *pcna* expression, indicating a transition to a quiescent state (Bower and Johnston, 2010). In rainbow trout, *pax7* along with MRF genes seem to be overexpressed in muscle hyperplastic zones of the late embryo myotome compared with adult fast muscle samples (Rescan et al., 2013). In this work, higher *pax7* mRNA levels in fasted fish could be associated with an increase in the number of quiescent MPCs or higher expression levels related to partial inhibition of cell proliferation associated with the delay in the growth process.

Levels of circulating and locally produced Igf1 have been extensively correlated with specific growth rate in numerous teleost species and are nutritionally regulated (Beckman, 2011; Gabillard et al., 2006; Pérez-Sánchez et al., 2018; Picha et al., 2006, 2014; Sciara et al., 2011). Although Igf1 and Igf2 had been both implicated in muscle cell proliferation and differentiation (Montserrat et al., 2007b), in the present study, opposite trends were observed between muscle mRNA of igf1 and igf2 after fasting and refeeding compared with controls. Strikingly, the mRNA level of igf2 significantly increased, and mRNA of igf1 significantly decreased after fasting. Igf genes appear to be differentially regulated indifferent teleost species (Jiménez-Amilburu et al., 2012; Lavajoo et al., 2020; Valente et al., 2012). The transition to a re-feeding schedule after 22 days of fasting involves upregulation of muscle Igf1 and downregulation of ifg2 transcript levels also in Atlantic salmon (Bower et al., 2008), and no effect of the fasting and refeeding treatment was observed on the expression of igf2 in muscle of rainbow trout (Gabillard et al., 2006; Montserrat et al., 2007a). In addition, Igf2 action seems to be mainly regulated at the muscular tissue level during growth depression (Pérez-Sánchez et al., 2018). Interestingly, fast-growing families of channel catfish express hepatic and muscle *igf2* at higher levels than slow-growing families (Peterson et al., 2004), suggesting same kind of relationship between genetically determined Ifg2 levels, hyperplasia rate and growth rates.

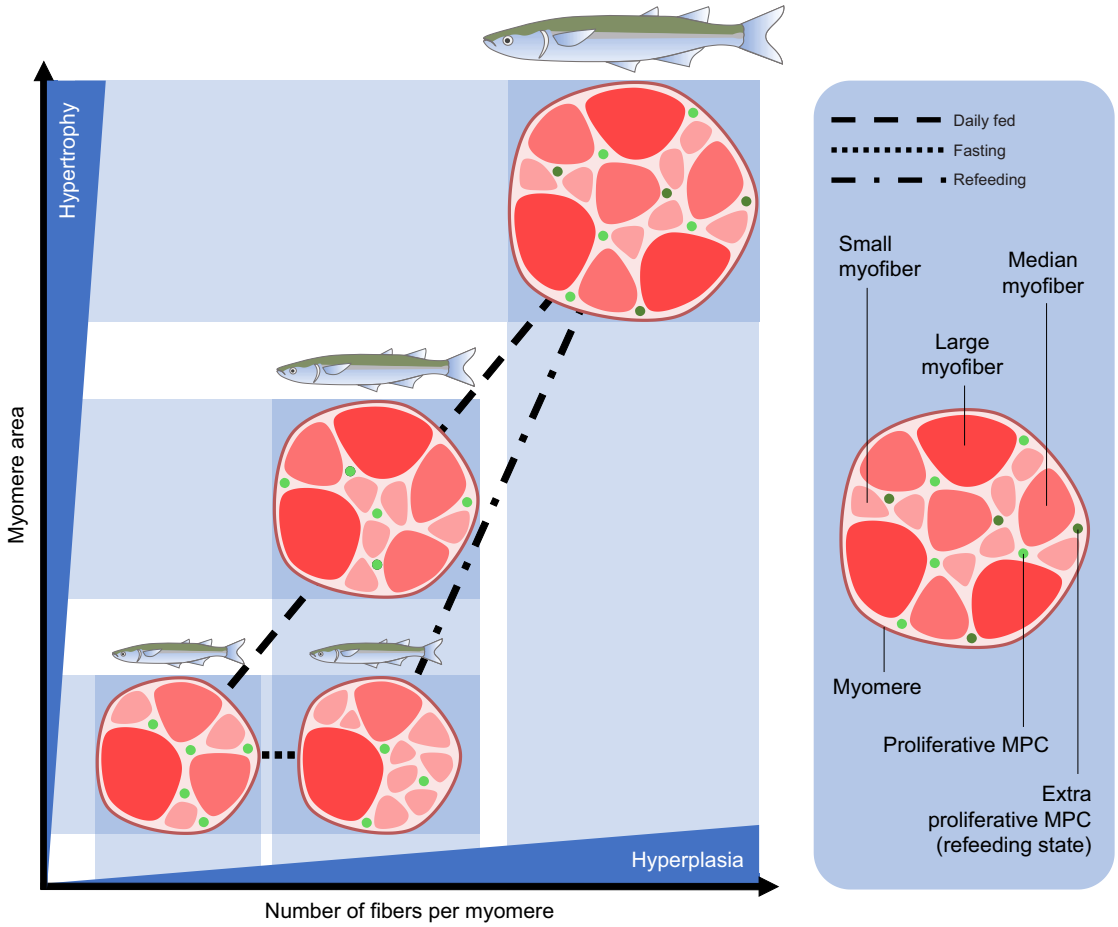

Fig. 4. Model depicting the cellular bases of compensatory growth in fish. This model assumes that muscle hypertrophy but not hyperplasia is mainly regulated by nutritional status. A population of muscle progenitor cells proliferate and contribute to new fiber formation during mosaic hyperplasia even under adverse nutritional conditions. Once adverse conditions cease, catch up growth is mainly the result of compensatory hypertrophy of the small muscle fibers formed during fasting, and is partly based on enhancement of MPC proliferation that contributes to fiber hypertrophy growth.

In summary, a model depicting the cellular bases of compensatory growth in pejerrey is proposed (Fig. 4) in which catch-up growth is a consequence of increased MPC proliferation that contributes new nuclei for the growth of pre-existing muscle fibers, some of which were formed, but did not grow, during the starvation period. Moreover, the combined observations of MPC proliferation, new fiber formation and the *ifg2* overexpression during fasting provide us with invaluable information to untie the catch-up growth Gordian knot in the future.

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Competing interests
The authors declare no competing or financial interests.

Author contributions
Conceptualization: I.S., S.E.A.; Methodology: I.S., M.F., D.A.F.; Software: D.A.F.; Validation: S.E.A.; Formal analysis: I.S., M.F., D.A.F., A.A.S., S.E.A.; Investigation: I.S., M.F.; Data curation: I.S.; Writing - original draft: I.S., D.A.F., S.E.A.; Writing - review & editing: M.F., D.A.F., A.A.S., S.E.A.; Visualization: I.S.; Supervision: S.E.A.; Project administration: S.E.A.; Funding acquisition: I.S., M.F., S.E.A.

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