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The Transcriptional Response of Skin to Fluorescent Light Exposure in Viviparous (*Xiphophorus*) and Oviparous (*Danio, Oryzias*) Fishes

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Abstract

Differences in light sources are common in animal facilities and potentially can impact experimental results. Here, the potential impact of lighting differences on skin transcriptomes has been tested in three aquatic animal models commonly utilized in biomedical research, (*Xiphophorus maculatus* (platyfish), *Oryzias latipes* (medaka) and *Danio rerio* (zebrafish). Analysis of replicate comparative RNA-Seq data showed the transcriptional response to commonly utilized 4,100 K or “cool white” fluorescent light (FL) is much greater in platyfish and medaka than in zebrafish. FL induces genes associated with inflammatory and immune responses in both medaka and zebrafish; however, the platyfish exhibit suppression of genes involved with immune/inflammation, as well as genes associated with cell cycle progression. Furthermore, comparative analyses of gene expression data from platyfish UVB exposures, with medaka and zebrafish after exposure to 4,100 K FL, show comparable effects on the same stress pathways. We suggest the response to light is conserved, but that long-term adaptation to species specific environmental niches has resulted in a shifting of the wavelengths required to incite similar “genetic” responses in skin. We forward the hypothesis that the “genetic perception” of light may have evolved differently than ocular perception and suggest that light type (i.e., wavelengths emitted) is an important parameter to consider in experimental design.

Keywords

Gene expression; RNA-Seq; bioinformatics; fluorescent light; biomedical models; stress; genetic response

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INTRODUCTION

Specific guidelines exist for fish care regarding temperature, noise levels, feeding schedules, food composition, water quality, and light cycle; however, little information exists regarding the required lighting conditions in regard to intensity or emitted wavelengths (Goodwin et al., 2016; Lawrence and Mason, 2012; Matthews et al., 2002; Sanders, 2012; Varga, 2016). The light sources utilized, the wavelengths emitted by each, and the potential effects of different light sources on gene expression seem not to have been studied. Intensity and wavelength differences between commonly utilized fluorescent bulbs vary greatly, and this parameter of animal care has not been examined to assess what effect, if any, the emission spectra may have on the genetic state of the animal despite the potential impact on research results. Fluorescent lights (FL) came into common use in the last ~60 years as a primary light source for homes, businesses, laboratories and animal facilities due to low cost of operation and long bulb life; however, specific wavelength spectral requirements have not been a major concern. Each FL source produces a different spectral output and none emits a spectrum resembling that of sunlight (Figure 1). FL spectra contain sharp peaks and valleys rather than a broad relatively equal distribution of visible wavelengths. It has become clear that light source and duration may have serious effects on vertebrate animals, and in humans may be linked to depression, obesity, sleep cycle alterations and illness (Badia et al., 1991; Borisuit et al., 2014; Lewy et al., 1980; Münch et al., 2006; Scheer et al., 1999; Veitch and McColl, 2001). In biomedical applications, specific light wavebands are being examined to improve clinical efficacy and reduce inflammation, and treat a growing list of human health issues (de Morais et al., 2010; Münch et al., 2006). For example, light emitting diodes (LEDs) of 400–550 nm are used to treat jaundice in infants (Agati et al., 1993; Vreman et al., 1998). Other examples include phototherapy between 300–325 nm used for psoriasis, phototherapy of 415 and 660 nm for treatment of acne vulgaris, and light of ~650 nm is used to treat inflammation (Papageorgiou et al., 2000; Parrish and Jaenicke, 1981; Qadri et al., 2007; Van Weelden et al., 1988). Because many of the studies consist of survey data, are based on external observations, or assess modulation of only a few known circadian oscillators, the effects of light exposure on gene expression begs further investigation, and in particular for animals utilized to model human disease.

Fish are widely used as biomedical models and use light for timing breeding cycles, incite feeding, as cues for migration, etc. (Degani, 1989; Jonsson, 1991). *Xiphophorus* fish species and interspecies hybrids represent a long standing melanoma cancer model (Meierjohann and Schartl, 2006; Nairn et al., 1996; Walter and Kazianis, 2001). Our recent studies indicate that varying light types, and specifically 50 nm light wavebands, can substantially impact the transcriptional profiles of *Xiphophorus* skin in unanticipated and source dependent ways. However, once a specific light induced transcriptional response has been discerned, the induced effect by that light source becomes predictable (Chang et al., 2015; Walter et al., 2015). For example, Chang et al. (2015) determined that specific transcriptional expression changes may be induced by light exposure within 50 nm intervals between 300–600 nm. Surprisingly, two of these exhibited considerably more effect on gene expression patterns (350–400 nm and 500–550 nm) than the other wavelength ranges tested. Exposure at 500–550 nm appears to induce cellular stress as a major response. Exposure to either 300–350 or

500–550 nm wavebands led to modulation of circadian gene activity and altered the activity of p53 gene targets, but via different mechanisms (*atm* at 350–400 and *atr* at 500–550 nm). Further, the effects of exposure to each 50 nm waveband is unique in modulating distinct genes in a manner expected to incite differential functions within key cellular pathways. For example, exposure of *Xiphophorus* males with two 50 nm wavebands only 100 nm apart results in transcriptional suppression, or activation, of genes involved in necrosis (i.e., suppression at 350–400 nm, activation at 450–500 nm), and apoptosis (i.e., suppression at 450–500 nm and activation at 550–600 nm). The ability to use waveband intervals to oppositely regulate transcriptional activity of genetic pathways is a novel observation and may lead to many practical applications. Of course, no commonly used FL source emits exclusively 50 nm wavebands, but these sources do emit a much less complex spectrum than sunlight, and often exhibit FL source specific peaks that correspond to one or more very narrow wavebands (Figure 1). Given these observations, we sought to compare the global transcriptional response in the skin of three commonly utilized biomedical fish models (*Xiphophorus maculatus* (platyfish), *Oryzias latipes* (medaka) and *Danio rerio* (zebrafish)) after exposure to 4,100 K “cool white” FL. Zebrafish have been used as neurological disease models (Burgess and Granato, 2007; Galvin, 2006; Montoya et al., 2006; Newman et al., 2007), hematological disease models (Shafizadeh et al., 2002; Taylor and Zon, 2011), tumor models (Liu and Leach, 2011; Avery-Kiejda, 2011; Santoriello et al., 2010), and many organ disease models including heart, muscle, kidney and eye (Bassett and Currie, 2003; Bibliowicz et al., 2011; Diep et al., 2011; Gieger et al., 2011; Kawahara et al., 2011; Knöll et al., 2007; Milan et al., 2009; Moosajee et al., 2008; Morris, 2011; Norton et al., 2011; O’Toole et al., 2010; Rihel et al., 2010; Sun et al., 2004; Swanhart et al., 2011). In addition, zebrafish have been used to investigate circadian regulation (Moore and Whitmore, 2014; Noche et al., 2011; Vatine et al., 2011) and light entrainable circadian control of internal organs (Whitmore et al., 1998). Likewise, medaka is also a popular human disease model especially throughout Europe and Asia. Medaka has been widely used to look at human disease states including heart disease (Murata et al., 2009; Shimada et al., 2009), Parkinson’s disease (Matsui et al., 2012, 2009) and cancer (Hasegawa et al., 2009; Schartl et al., 2012) to name a few. Knowing the response of *Xiphophorus* to a wide array of light sources, we sought to investigate these other two widely used human disease aquatic models.

RNA-Seq analyses employed to compare changes in gene expression after light exposure showed platyfish and medaka modulate about three times more skin genes than zebrafish. Further, the viviparous platyfish oppositely regulated both cellular proliferation and immune response compared to the oviparous medaka and zebrafish. Both oviparous fishes appeared to induce pathways leading to an immune and inflammatory response, but only zebrafish skin showed up-modulation in genes involved in the classical complement pathway for immune induction.

METHODS

Fishes Utilized and FL Exposure

Three mature adult male fish were used for FL exposure (40 min, 35 kJ/m^2) for each fish species (*Xiphophorus maculatus* Jp 163 A (platyfish), *Danio rerio* (zebrafish), *Oryzias*

latipes (medaka), Figure 2). Platyfish and medaka were both supplied by the *Xiphophorus* Genetic Stock Center at Texas State University and the zebrafish were from the Howard Hughes Medical Institute in Seattle, WA. All experimental and bioinformatics protocols were carried out as previously described (Walter et al., 2014, 2015; Yang et al., 2014). Three weeks prior to exposure, all animals were housed in a single aquarium per species in a common location under 10,000 K FL. The location where fish used in this study were maintained receives 99.5 kJ/m^2 of 10,000 K FL light over the diurnal cycle. The 35 kJ/m^2 of FL exposure is equivalent to 295 minutes of FL exposure in our standard animal housing conditions. Prior to light exposure, fish were placed individually into 100 mL of filtered home aquaria water and kept in the dark for 14 hr. FL exposure occurred in UV-transparent cuvettes (9 cm × 7.5 cm × 1.5 cm) in 90 mL of water. The exposure cuvettes were suspended 10 cm between two banks of two (total of 4 lights) unfiltered 4,100 K fluorescent lights (Philips F 20T12/CW 20 watts, Alto) mounted horizontally on each side of a wooden exposure chamber. Unexposed control fish (3 for each species) were dissected immediately after the 14 hr dark period. After FL exposure or sham treatment (no lights on), all fish were returned to the dark in 100 mL filtered aquaria water for 6 hrs to allow time for transcriptional remodeling (Gonzalez et al., 2017 this edition) and then euthanized and dissected for RNA isolation. All tissues (brain, liver, testes, heart, gill, fin, eyes, muscle and skin) were dissected into 300 μL RNA*later* (Life Technologies, Grand Island, NY, USA) and stored in the −80 °C freezer except for skin samples which were immediately placed in 300 μL TRI Reagent (Sigma Inc., St Louis, MO, USA) and flash frozen in an ethanol dry ice bath for immediate RNA isolation.

RNA Isolation and Sequencing

Total RNA was isolated from skin using a TRI Reagent (Sigma Inc., St Louis, MO, USA) chloroform extraction followed by the Qiagen RNeasy mini RNA kit (Qiagen, Valencia, CA, USA) isolation protocol. Skin was homogenized in 600 μL TRI Reagent using a handheld tissue disruptor followed by addition of 120 μL of chloroform. Samples were vigorously shaken and then phases partitioned by centrifugation (12,000 × *g* for 15 min at 4 °C). After extraction, the RNA was precipitated with 500 μL 70% EtOH and further purified using a Qiagen RNeasy mini RNA kit following the manufacturer's protocol. Residual DNA was eliminated with an on-column DNase treatment at 25 °C for 15 min. RNA quality was assessed with an Agilent 2100 bioanalyzer (Agilent Technologies, Santa Clara, CA), and quantified with a Qubit 2.0 fluorometer (Life Technologies, Grand Island, NY, USA). All samples sent for sequencing had RIN scores ≥ 8.0.

Differentially Expressed Gene (DEG) Analysis

RNA sequencing was performed on libraries constructed using the Illumina TrueSeq library preparation system that employs a polyA selection. RNA libraries were sequenced as 100 bp paired-end fragments using an Illumina Hi-Seq 2000 system (Illumina, Inc., San Diego, CA, USA). 70–80 million raw reads were generated for each fish skin RNA sample. All raw reads were subsequently truncated by similarity to library adaptor sequences using a custom Perl script and short reads were filtered based on quality scores by using a custom filtration algorithm that removed low-scoring sections of each read and preserved the longest remaining fragment (Table 1) (Garcia et al., 2012). Filtered reads were mapped using

GSNAP (Wu and Nacu, 2010) to either the *X. maculatus* (Ensembl v71), *Oryzias latipes* (Ensembl v79) or the *Danio rerio* (Ensembl v79) reference transcriptome. The percentage of reads mapped and nucleotide coverage were identified by SAMtools flagstat and depth, respectively (Li et al., 2009). Gene expression was assessed by eXpress (Roberts and Pachter, 2013), and differentially modulated genes were determined using the R-Bioconductor (www.bioconductor.org) package for pairwise comparison done with the exactTest in edgeR (Robinson et al., 2010) with a $\log_2$(fold change) ≥ |2.0| (p-adj < 0.05), (Table 2). Biological variance following gene expression analysis was calculated and plotted (Figure S1).

Genes identified as being differentially modulated in response to FL (excluding any sham effected genes) were further analyzed for species specificity. Venny 2.1 (Oliveros, 2007) was used to compare differentially expressed genes from each species to the other two and Ingenuity Pathway Analysis (IPA, Qiagen, Redwood City, CA) was used for functional specificity analysis. IPA-based gene expression analysis yielded gene clusters, genetic pathways, functional classes, and potential up-stream regulators to aid in mechanistic interpretation. Herein, the term “pathways” is short for canonical pathways assigned by IPA based on the light exposure input DEG data. In IPA, known pathways are drawn as pictures with input DEGs overlaid onto them that are identified by symbols and colors indicating known functions and direction of modulation. A z-score algorithm is used to determine if a pathway is up or down regulated based on the genes that fall into that particular pathway. IPA assignment of DEGs into “functions” or “functional classes” relates the input DEGs to known disease states and biological functions as published in the scientific literature. Functional classes are visualizations of the biological trends in the light effected DEG dataset and may be used to predict the effect of gene expression changes of the entire dataset on biological processes and known cellular functions. Function assignment uses an algorithm to assess the dataset as a whole and predict what is collectively occurring on a larger downstream scale.

Validation of RNA-Seq

NanoString (NanoString Technologies, Inc., Seattle, WA) with a custom panel for each species was used as an independent technology to confirm the DEGs identified using RNA-Seq. Aliquots of the RNA (500 ng) used for RNA-Seq were also used for the NanoString nCounter assay. Hybridization protocols were strictly followed according to manufacturer’s instructions (Geiss et al., 2008). Samples were hybridized overnight at 65 °C with custom probes and transferred to the NanoString Prep Station. The NanoString cartridge containing the hybridized samples was immediately evaluated with the NanoString nCounter based on unique color-coded signals. Probe counts were quantified through direct counting with the nCounter Digital Analyzer. Data analysis was performed by lane normalization using a set of standard NanoString probes followed by sample normalization using a set of 10 housekeeping genes. Fold changes were calculated on normalized counts and plotted using Microsoft Excel.

RESULTS/DISCUSSION

Comparison of DEG Numbers

Skin from three species; platyfish, medaka and zebrafish were compared following exposure to 35 kJ/m^2 4,100 K fluorescent light (FL). The number of genes differentially modulated as determined by EdgeR ($\log_2$(FC) > |2.0|, p-adj < 0.05) in skin was considerably greater in medaka (2277) than in the other two species (1757 and 613 in platyfish and zebrafish, respectively; Table 2 column 2). To compare the differentially modulated genes between each species, all fish Ensembl IDs were converted to HUGO IDs (Table 2 column 5). The dynamic range of modulation for differentially expressed genes (DEGs) in skin did not differ significantly among the three species (Figure 3, A); however, each fish species expressed a unique set of DEGs (Figure 3, B). Only 25% DEGs are shared between any two species and overall only 58 DEGs were shared among all three species. To confirm the DEGs in each species, NanoString's nCounter analysis was used. In total, 96% of the 74 differentially modulated transcripts tested were confirmed in both magnitude and direction (R^2 = 0.83, Figure 4).

Species Specific Analyses of DEGs

After 4,100 K FL exposure, platyfish skin DEGs analyzed by IPA showed modulation of 35 canonical pathways (Table S1). The most significant pathway change noted in skin after FL exposure, reflected by high z-score, was suppression of the insulin-like growth factor (IGF)-I signaling pathway. This change is consistent with a suppression of cell growth and proliferation (Figure 5) (Denduluri et al., 2015; Kennedy et al., 1997; LeRoith and Roberts Jr, 2003). Comparison of results from the different species indicates that cell growth and proliferation is the most enriched molecular and cellular function following 4,100 K FL exposure in platyfish skin, comprising 707 (40%) of the 1,757 modulated genes analyzed by IPA.

O. latipes skin showed 13 canonical pathways (11 up and 2 down) effected by 4,100 K FL exposure despite modulating ~25% more genes than platyfish. The most significant of the 13 pathways modulated involves the acute phase signaling pathway (**Error! Reference source not found.**). The remaining canonical pathways (Table S2) are associated with the acute phase signaling pathway and involve induction of an inflammatory response. For example, as shown in Figure 6, IL-6 signaling serves as a regulator of the acute phase signaling pathway (Gabay and Kushner, 1999; Heinrich et al., 1998), the ILK signaling pathway shares TNF-α induction into the JNK pathway (Bode et al., 1999; Brown et al., 1995; Wegenka et al., 1993), PPARA signaling is involved with acute phase signaling through the TNF-α regulator and has been associated with suppression of adipose differentiation and fatty acid oxidation (Varga et al., 2011). In addition, the antioxidant action of the vitamin C pathway is also involved with TNF-α regulation of gene expression in concert with NFκβ and JAK/STAT (Carcamo et al., 2002; Wilson, 2009). Overall, the most significant upstream regulator in medaka is TNF-α (5.8 fold, z-score 5.9) which controls 19 key regulators and 944 DEGs modulated in medaka skin after 4,100 K FL exposure. Given the high numbers of gene targets affected by TNF-α after FL exposure, it is reasonable to predict this highly

expressed regulator is largely responsible for inciting the FL inflammation response observed in medaka skin (Bradley, 2008).

Upon FL exposure, *Danio rerio* skin showed modulation of 22 canonical pathways (13 up and 9 down; Table S3). The zebrafish response to FL in skin, like medaka, is dominated by modulation of a robust set of inflammation associated genes piloted through the oncostatin M regulator and induced transcription of the oncostatin M signaling pathway (Figure 7) (Wallace et al., 1999; West et al., 2017). Systemic inflammation occurs following up-modulation of IL-6 after oncostatin signaling (Kordula et al., 1998). This pathway produces many of the precursors required for acute phase signaling, as well as necessary components for cell proliferation and cytokine signaling (Dey et al., 2013). Also, like medaka, the top regulator in zebrafish skin is TNF-α, controlling 30% (180 genes) of the zebrafish skin FL modulated DEGs.

Comparative Functional Analyses of DEGs

Upon FL exposure, all three fish models significantly modulated transcription of genes involved with cell cycle progression, cell death and/or cell proliferation in skin. However, analysis of potential upstream regulators based on the direction of transcriptionally modulated gene targets in skin of the oviparous species, medaka and zebrafish, indicate the cell functions affected are likely due to induction of the HDAC transcriptional regulator with concurrent induction of the telomerase signaling pathway (Figure 8, B and C). In contrast, platyfish exhibit suppression of cellular proliferation that is predicted to occur via suppression of HDAC with concurrent suppression of the telomerase signaling pathway (Figure 8, A) (Kyo and Inoue, 2002; Reichert et al., 2012). Thus, although approximately 25% of the FL modulated DEGs are shared between at least two of the three species; the direction of modulation and the genes not shared among modulated sets suggests the oviparous and viviparous species modulate expected functional differences in the same pathway.

Another example of species-specific differences in gene expression behavior after FL exposure was observed in the PPARα/RXRα signaling pathway. Platyfish significantly down-modulated the PPARα/RXRα pathway in skin upon exposure to FL; however, both medaka and zebrafish exhibited significant up-modulation of the PPARα/RXRα pathway following FL exposure (Figure 9). The PPARα/RXRα pathway is one part of a genetic cascade involved in an inflammation response incited by the FL exposure (Dubrac and Schmuth, 2011; Núñez et al., 2010; Zandbergen and Plutzky, 2007).

While skin from the viviparous platyfish males behaved differently compared with skin from the oviparous species (suppressing cell proliferation and the inflammation response), there were also noted differences when comparing medaka and zebrafish. Zebrafish induce genes involved in an immune response through both the classical and alternate complement system signaling pathways, while medaka only appears to utilize the alternate signaling pathway of the complement system (Figure 10). In addition, after 4,100 K FL exposure, the HDAC transcription regulator family appears to be inducing cell death (i.e., necrosis and apoptosis pathways) (Vashisht Gopal et al., 2006; Zhang and Zhong, 2014) only in the zebrafish. In contrast, medaka appears to utilize the HDAC regulator family to increase cellular

proliferation, without induction of necrotic genes or regulators. These subtle differences in the skin of medaka and zebrafish highlight species-specific gene regulation differences that occur in response to light exposure between the oviparous species tested.

Differences in Wavelengths May Explain Response Differences

Collectively, these effects suggest that differences between oviparous and viviparous fishes, and species-specific differences between medaka and zebrafish, in response to the same stimulus (35 kJ/m^2 of 4,100 K FL) likely are the result of adaptive evolution to optimize survival in the environmental niches specific to each species. We have reported that platyfish skin shows very different transcriptional responses after exposure of the intact animal to 50 nm wavebands between 300–600 nm. Chang et al. (2015) observed that the 500–550 nm waveband incited the largest number of DEGs and this waveband region induced cellular stress pathway genes as the most significant response (Chang et al., 2015). In addition, we have reported previously that exposure to UVB light (311 nm) incites, as the major response in platyfish males, the classical compliment pathway and many other genes associated with an inflammatory response (e.g., serpins) (Yang et al., 2014). This was not understood at the time since the expectation was a more robust DNA damage response after 311 nm UVB (ultraviolet B light) exposure. In the results presented here, we note that viviparous platyfish incited a robust inflammatory response to UVB exposure but the 4,100 K FL did not produce such a transcriptional effect in platyfish.

We have reanalyzed the data from the platyfish UVB exposures and compared this to the data presented herein for oviparous species exposed to 4,100 K FL (Table 3). The similarity in transcriptional responses, UVB for platyfish and FL for zebrafish, implies the genetics involved in light response are conserved between the three species, but the waveband intervals needed (311 nm for platyfish and ~550 nm for medaka and zebrafish) to incite a similar genetic response may be species specific, and due to long term evolutionary adaptation to very different specific environmental niches. For example, platyfish are found from the Rio Jamapa in Mexico to Belize and prefer ditches and shallow creeks with muddy bottoms and dense vegetation (Kallman, 1975). Medaka and zebrafish can be collected in a variety of environments from freshwater ponds to marshes and paddy fields; each of these niches has a different degree of turbidity, vegetation and salinity that effect light penetration (Hatooka et al., 2013; McClure et al., 2006). Thus, the “genetic perception” of light may have evolved under different constraints and in different directions than those involved with ocular perception, and suggest light type (i.e., wavebands emitted) and intensities may be an important parameter to consider in both animal housing and in biomedical experimental design.

In addition, previous studies (Boswell et al., 2015); 2017 this edition) have indicated that male and female *Xiphophorus* have unique genetic responses to light stimuli (UVB and FL). To expand on this idea, female medaka and zebrafish need to be exposed to FL to see if they have a unique genetic response or rather the response by female *Xiphophorus* is genetically perceived as a different waveband compared to sex matched oviparous species. It is currently also unknown how juveniles of any species tested are genetically effected by specific light sources and whether or not the effects of juveniles can be changed by altering the light

source after the animals reach sexual maturity. In order to assess and ultimately determine the best lighting conditions for housing, husbandry and experimental reproducibility each of these parameters (sex, species variations and age) will need to be tested under commonly used FL as well as specific wavebands.

CONCLUSIONS

In the interest of increasing reproducibility of experiments in different laboratories using different lighting conditions for their animals, we have addressed here the question of potential differences in transcriptional response to different light sources in three aquatic vertebrate species. These three species (platyfish, medaka and zebrafish) were exposed to 4,100 K “cool white” fluorescent light (FL) and the light induced modulation of their genetic profiles assessed in skin by employing RNA-Seq analyses. Notable differences were observed between each of the three-species tested. While considerable gene overlap was observed between platyfish and medaka in skin, it is clear from pathway and functional analysis that the viviparous platyfish responded in a unique manner compared to the two oviparous aquatic models in response to FL exposure.

Comparative analyses of data from platyfish UVB exposures, and for oviparous species exposed to 4,100 K FL, suggests the three fish species tested show similarity in response when the platyfish genetic response to UVB exposure is compared to the medaka and zebrafish response to “cool white” FL. We suggest the response to light is conserved, but that long-term adaptation to the environmental niche of each fish has resulted in a shifting of the wavebands needed to incite a similar “genetic” stress response in skin. We forward the hypothesis that the “genetic perception” of light may have evolved differently than ocular perception and suggest that light type (i.e., wavebands emitted) and intensities may be an important parameter to consider in animal housing and experimental design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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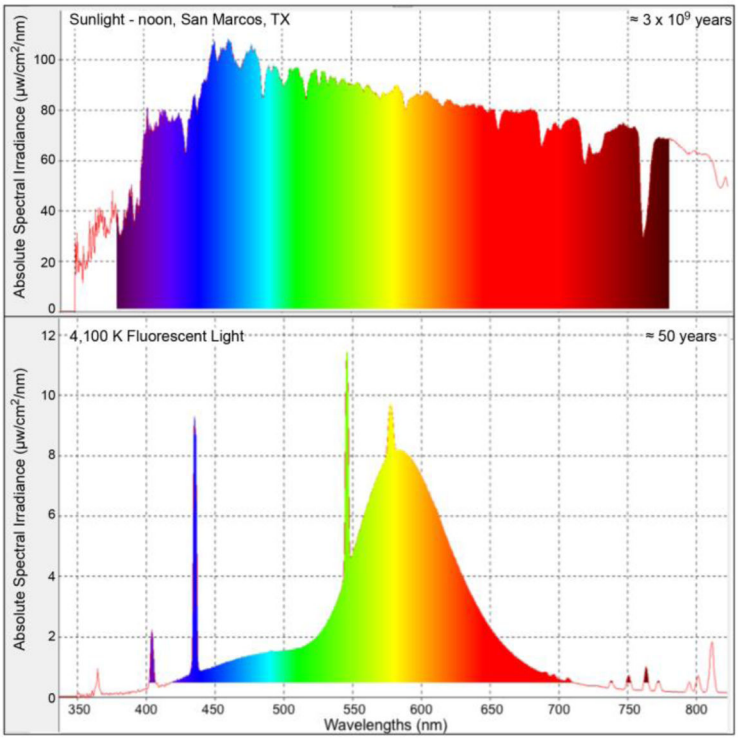

Figure 1.

Comparison of solar spectrum with that of 4,100 K FL light utilized in the reported experiments.

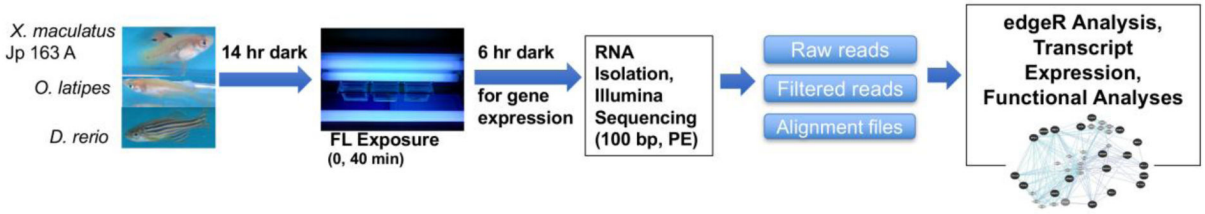

Figure 2.

Experimental Overview. Three species were individually tested in triplicate following exposure to 35 kJ/m^2 FL. RNA was isolated and sent for Illumina sequencing. Functional analysis was performed on processed reads to determine pathways and up- stream regulators effected by FL.

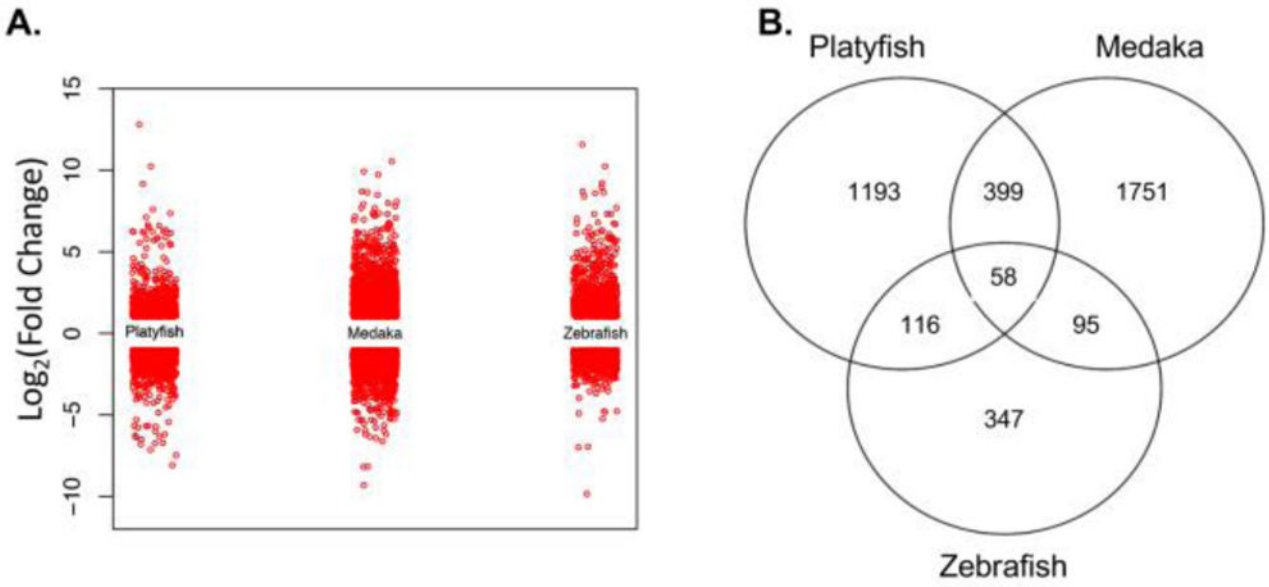

Figure 3.

Dynamic range (Panel A) of gene expression in platyfish (left), medaka (center) and zebrafish (right). Each red circle indicates a significantly modulated transcript ($log_2(\pm 1)$, fdr<0.05). Venn Diagrams (Panel B) indicating gene overlap between platyfish, medaka and zebrafish in skin following exposure to FL.

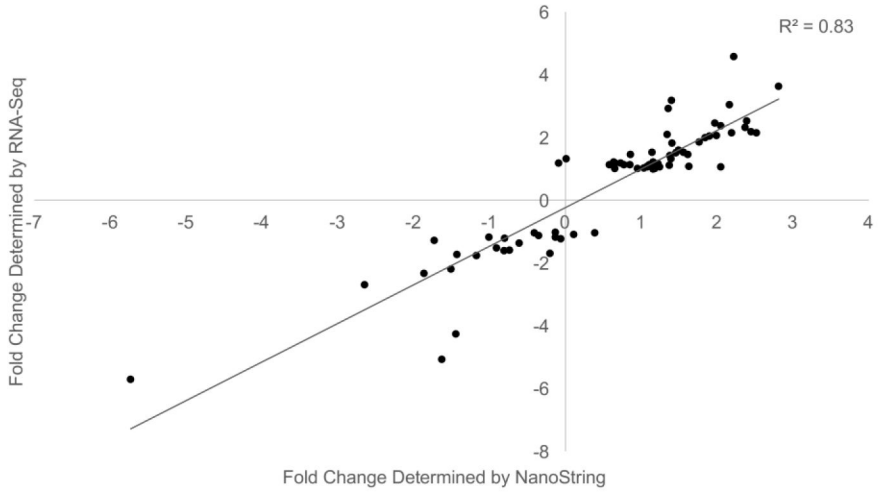

Figure 4.

NanoString nCounter analysis (x-axis) was used to confirm the RNA-Seq data (y-axis) for 71 out of 74 transcripts tested in both magnitude and direction ($R^2 = 0.83$) following FL exposure.

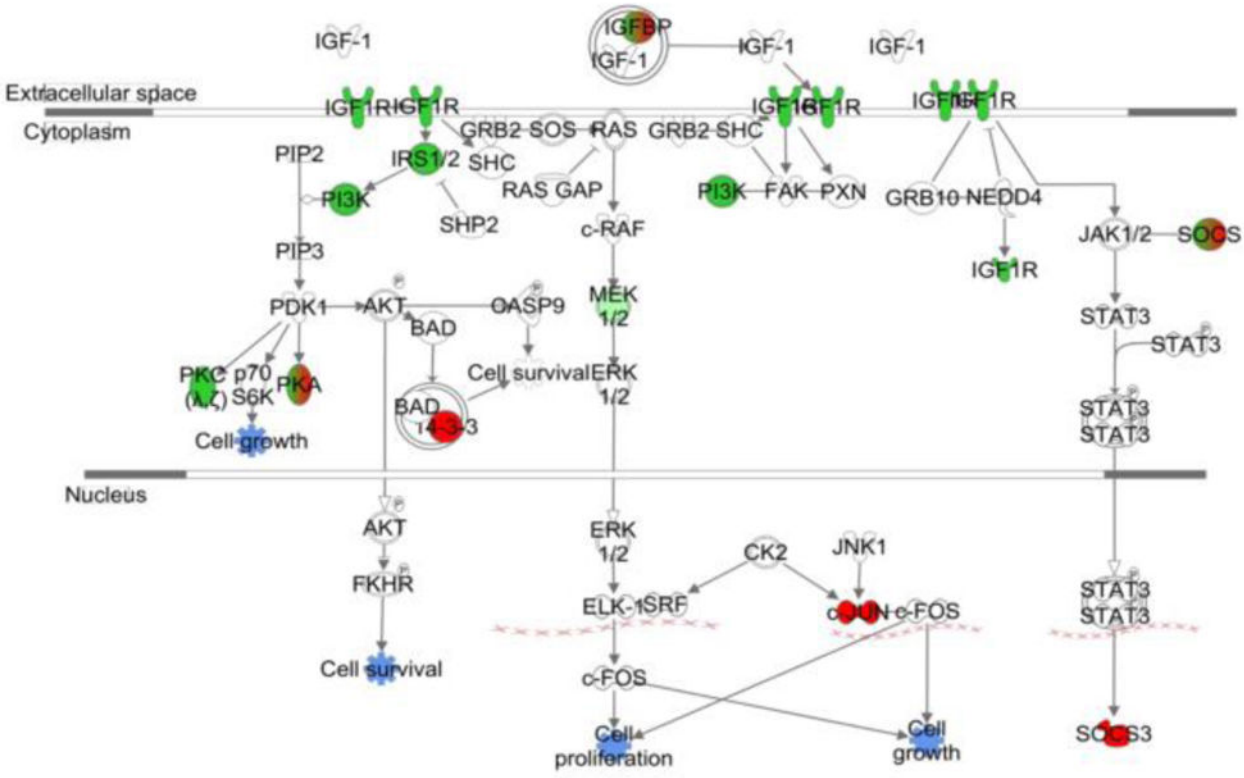

Figure 5.

Platyfish significantly down modulate the IGF signaling pathway leading to a suppression of cell proliferation, cell growth and cell survival in skin following FL exposure. Molecules shaded in green represent down modulated transcripts and molecules shaded in red represent up-modulated transcripts (Fold Change see Table S4). Functions shaded in blue are predicted to be suppressed and in orange are induced (IPA z-score -4.1).

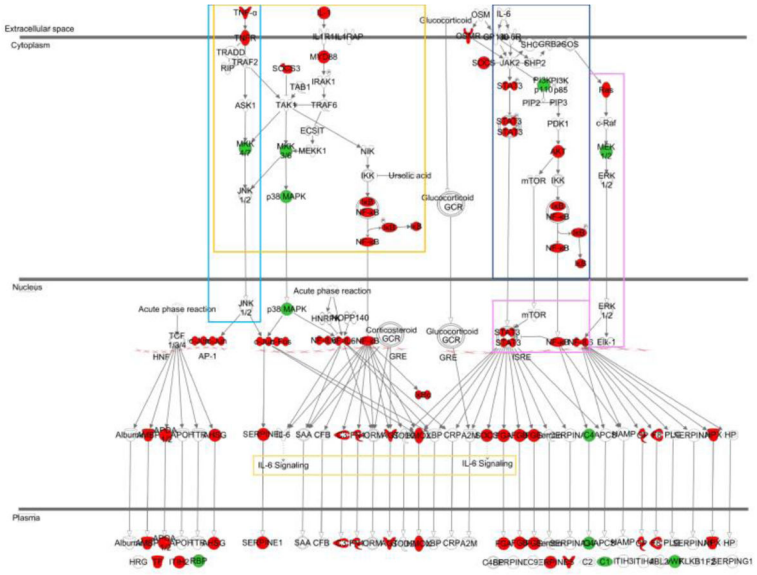

Figure 6.

The most significantly modulated pathway in medaka skin was the acute phase signaling pathway (IPA z-score 3.2) leading to an increase in the inflammation response; other pathways that play a role in the inflammation response such as IL-6 (boxed in yellow), ILK signaling (light blue), PPAR signaling (pink) and the Vitamin C pathway (dark blue) are also found within the acute phase signaling pathway. Genes up-modulated are represented in red; down modulated are in green (Fold Change see Table S5).

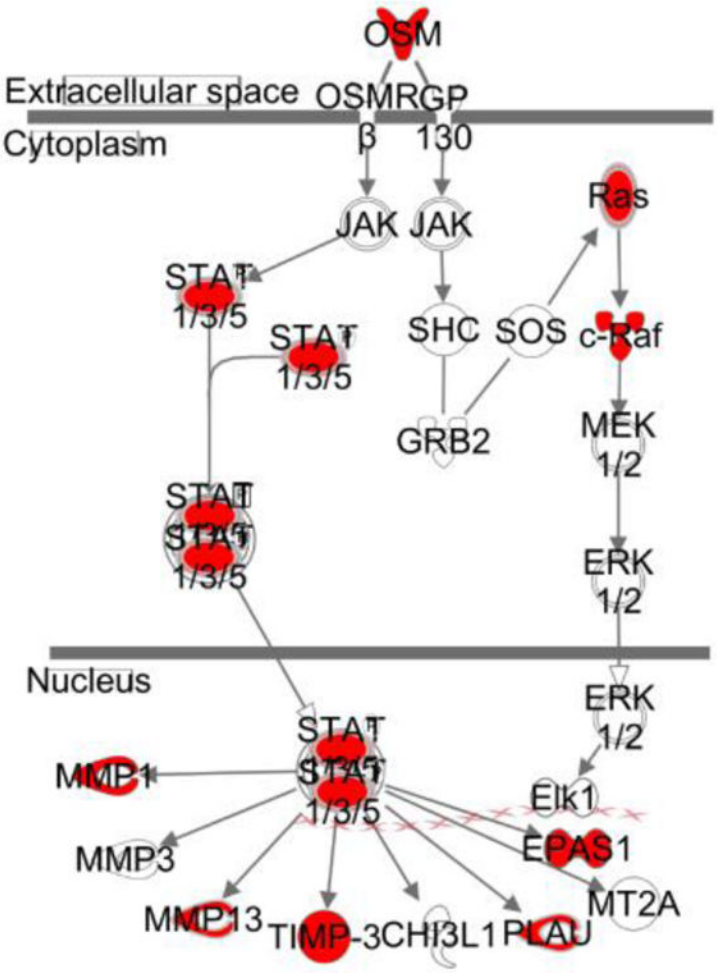

Figure 7.

In zebrafish following FL exposure, the most significantly modulated pathway in skin is the oncostatin M pathway. Molecules shaded in green represent down modulated transcripts and molecules shaded in red represent up-modulated transcripts (Fold Change see Table S6, IPA z-score 3.1).

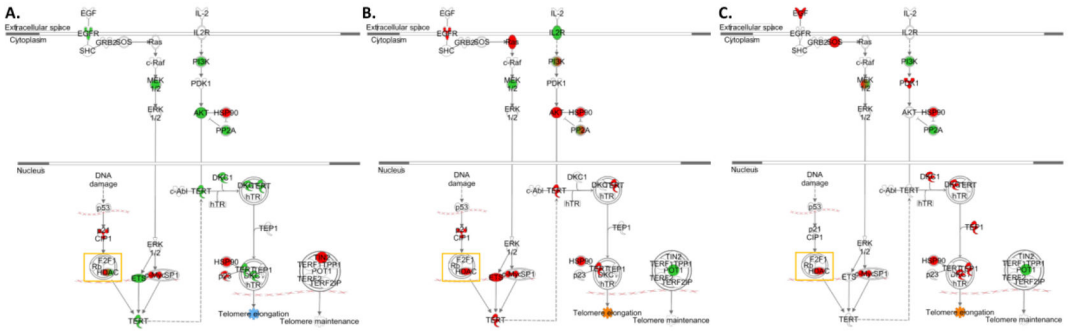

Figure 8.

The telomerase signaling pathway is oppositely modulated in platyfish (A) compared to medaka (B) and zebrafish (C) following FL exposure. The opposite modulation of the HDAC regulator (boxed in yellow) is predicted to be responsible for the opposite modulation of the telomerase signaling pathway. In each plot, molecules shaded in green represent down modulated transcripts and molecules shaded in red represent up-modulated transcripts (Fold Change see Table S7). Functions shaded in blue are predicted to be suppressed and in orange are induced (IPA z-score -2.0 platyfish, 2.1 medaka and 2.3 zebrafish).

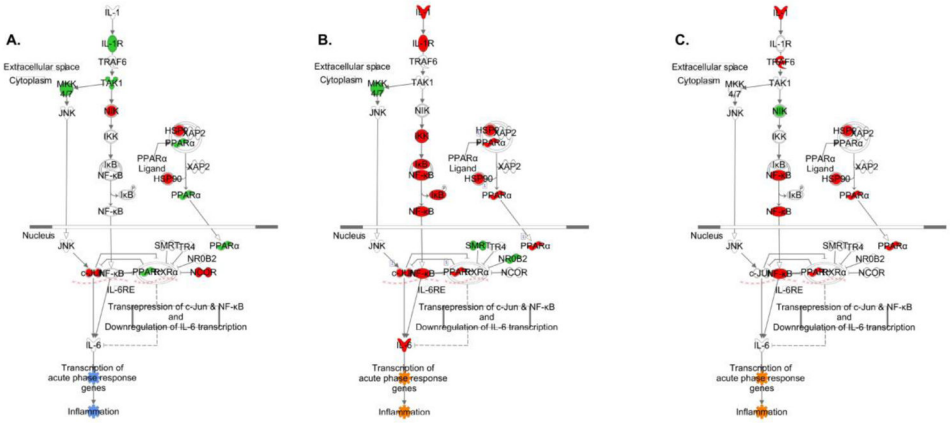

Figure 9.

Platyfish skin (A) significantly down modulates the PPARα/RXRα signaling pathway in response to FL; however, both medaka (B) and zebrafish (C) significantly up-modulate the PPARα/RXRα pathway in skin following FL exposure. In each plot, molecules shaded in green represent down modulated transcripts and molecules shaded in red represent up-modulated transcripts (Fold Change see Table S8). Functions shaded in blue are predicted to be suppressed and in orange are induced (IPA z-score -2.8 platyfish, 2.3 medaka and 2.3 zebrafish).

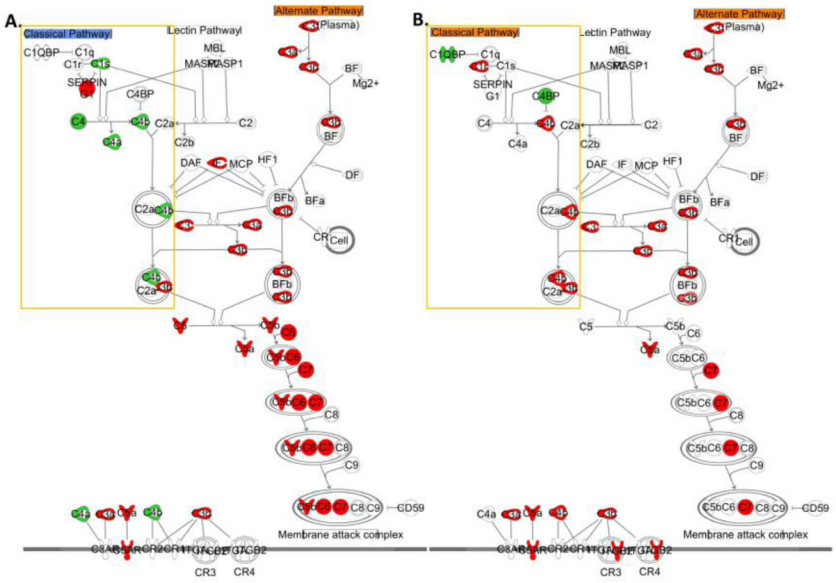

Figure 10.

Both medaka (A) and zebrafish (B) up-modulate the complement signaling pathway (IPA z-score 2.4 in medaka and 2.0 in zebrafish) in skin following FL exposure; however, only zebrafish induce both the classical complement pathway (yellow box) and the alternate pathway whereas medaka only utilizes the alternate pathway. In each plot, molecules shaded in green represent down modulated transcripts and molecules shaded in red represent up-modulated transcripts (Fold Change see Table S9). Functions shaded in blue are predicted to be suppressed and in orange are induced.

Table 1

Read depth and RNA-Seq statistics for FL exposed and unexposed samples.

Species	Treatment	Filtered Reads (x10^7)	Read Length (x10^9)	Reads Mapped (x10^7)	Reads Mapped (%)
Platyfish	FL	4.01	4.60	3.62	90.2
		3.64	4.21	3.24	89.1
		4.24	4.89	3.80	89.5
	Untreated	3.79	4.36	3.35	88.5
		4.25	4.89	3.80	89.4
		3.52	3.97	3.17	90.1
Medaka	FL	4.83	5.36	4.07	84.2
		4.74	5.13	4.02	84.8
		4.45	4.90	3.76	84.6
	Untreated	4.60	5.00	3.90	84.7
		4.96	5.43	4.19	84.6
		4.90	5.43	4.11	84.0
Zebrafish	FL	6.70	7.31	5.46	81.5
		7.15	7.83	5.81	81.2
		6.41	7.17	5.18	80.8
	Untreated	6.12	6.83	4.99	81.5
		6.00	6.46	4.94	82.3
		7.81	8.46	6.37	81.5

Table 2

Differentially expressed genes for FL exposed samples. Total modulated genes are the output file from EdgeR (column 2) that had a $\log_2$(fold change) ≥ | 2.0| and a *p-adj* < 0.05). All fish Ensebl IDs were converted to HUGO IDs (column 5) for IPA analysis and direct comparison of the three fish species. HUGO IDs were then imported for each species mapped by Qiagen's IPA software for functional and pathway analysis (column 6).

Species	Total Modulated	Up-Modulated	Down-Modulated	HUGO IDs	Mapped by IPA
Platyfish	2027	1097	930	1766	1757
Medaka	2773	1478	1295	2303	2277
Zebrafish	671	298	373	616	613

Table 3

Shared regulators in platyfish following UVB exposure and zebrafish following FL exposure. The number inside each parenthesis indicates the number of genes controlled by the regulator (Table S10 lists the genes) and the color indicates whether the regulator is up (red) or down (green) modulated.

Zebrafish 35 kJ/m^2 FL	**Platyfish 16 kJ/m^2 UVB**
NKX2-3 (20)	NKX2-3 (20)
AR (20)	AR (51)
CREB1 (19)	CREB1 (71)
EGR1 (11)	EGR1 (29)
EZH2 (7)	EZH2 (26)
IRF5 (8)	IRF5 (6)
KDM5A (12)	KDM5A (10)
NFKB1 (25)	NFKB1 (21)
PGR (13)	PGR (32)
STAT1 (18)	STAT1 (18)