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Novel discoveries in acid-base regulation and osmoregulation: A review of selected hormonal actions in zebrafish and medaka

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ABSTRACT

Maintenance of internal ionic and acid-base homeostasis is critical for survival in all biological systems. Similar to mammals, aquatic fishes have developed sophisticated homeostatic mechanisms to mitigate metabolic or environmental disruptions in ionic and acid-base status of systemic body fluids via hormone-controlled transport of ions or acid equivalents. The present review summarizes newly discovered actions of several hormones in zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*) that have greatly contributed to our overall understanding of ionic/acid-base regulation. For example, isotocin and cortisol were reported to enhance transport of various ions by stimulating the proliferation and/or differentiation of ionocyte progenitors. Meanwhile, stanniocalcin-1, a well-documented hypocalcemic hormone, was found to suppress ionocyte differentiation and thus downregulate secretion of H^+ and uptake of Na^+ and Cl^-. Estrogen-related receptor and calcitonin gene-related peptide also regulate the differentiation of certain types of ionocytes to either stimulate or suppress H^+ secretion and Cl^- uptake. On the other hand, endothelin and insulin-like growth factor 1 activate the respective secretion of H^+ and Na^+/Cl through fast actions. These new findings enhance our understanding of how hormones regulate fish ionic and acid-base regulation while further providing new insights into vertebrate evolution, mammalian endocrinology and human disease-related therapeutics.

1. Introduction

Body fluid ionic and acid-base homeostasis is essential for normal operation of cellular activities and physiological processes in vertebrates, and the underlying epithelial ion transport pathways are tightly controlled by hormones. Knowledge of how hormones act to control ion transport is therefore critical for understanding the basic physiology of vertebrate body fluid homeostasis and also provides valuable information for treatment of human diseases.

Aquatic fish and mammals have developed similar sophisticated homeostatic mechanisms for the transport of various ions or acid equivalents, which generally involve hormonal control of body fluid homeostasis when systemic ionic and acid-base status is disturbed by metabolic or environmental stressors. Aquatic environments are much more diverse than terrestrial environments in terms of ion composition and pH levels. To cope with such environmental diversity, fish have developed iono/osmoregulation mechanisms that exhibit higher plasticity than those in mammals, making fish better models to study the capacity and functional regulation of iono/osmoregulation under stressful or harsh conditions. To overcome the research limitations of traditional model species, zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*) have recently become emerging models to study the molecular physiology of ionic and acid-base regulation. Instead of the kidney, the gills or embryonic skin of fish are the major site of transepithelial ion transport for body fluid ionic/acid-base homeostasis. In zebrafish and medaka, different types of ionocytes were found to transport ions through respective sets of ion transporters, and the molecular mechanisms of ionocyte proliferation and differentiation have also been dissected, providing a competent platform to precisely study the ion transport pathways and ionocytes targeted by hormones. Several hormones have been demonstrated to positively or negatively regulate ion transport through specific receptors at transcriptional, translational or posttranslational levels, and at different stages of ionocyte development (i.e., proliferation or differentiation). These actions may be conserved in mammals because the major principles and players of mammalian and zebrafish endocrine systems are similar (Lohr and Hammerschmidt, 2011). Several recent reviews have summarized current progress in describing the hormonal actions in zebrafish that regulate body fluid ionic and acid-base balance (Hwang and Chou, 2013; Guh et al., 2015, Lin and Hwang 2016, Guh and Hwang 2017, Lewis and Kwong 2018). For some hormones, novel actions have been identified, which are unknown in other vertebrates. In this review, we highlight some prominent examples of these novel hormonal actions, describing how they have enhanced our understanding of hormonal control of fish acid-base

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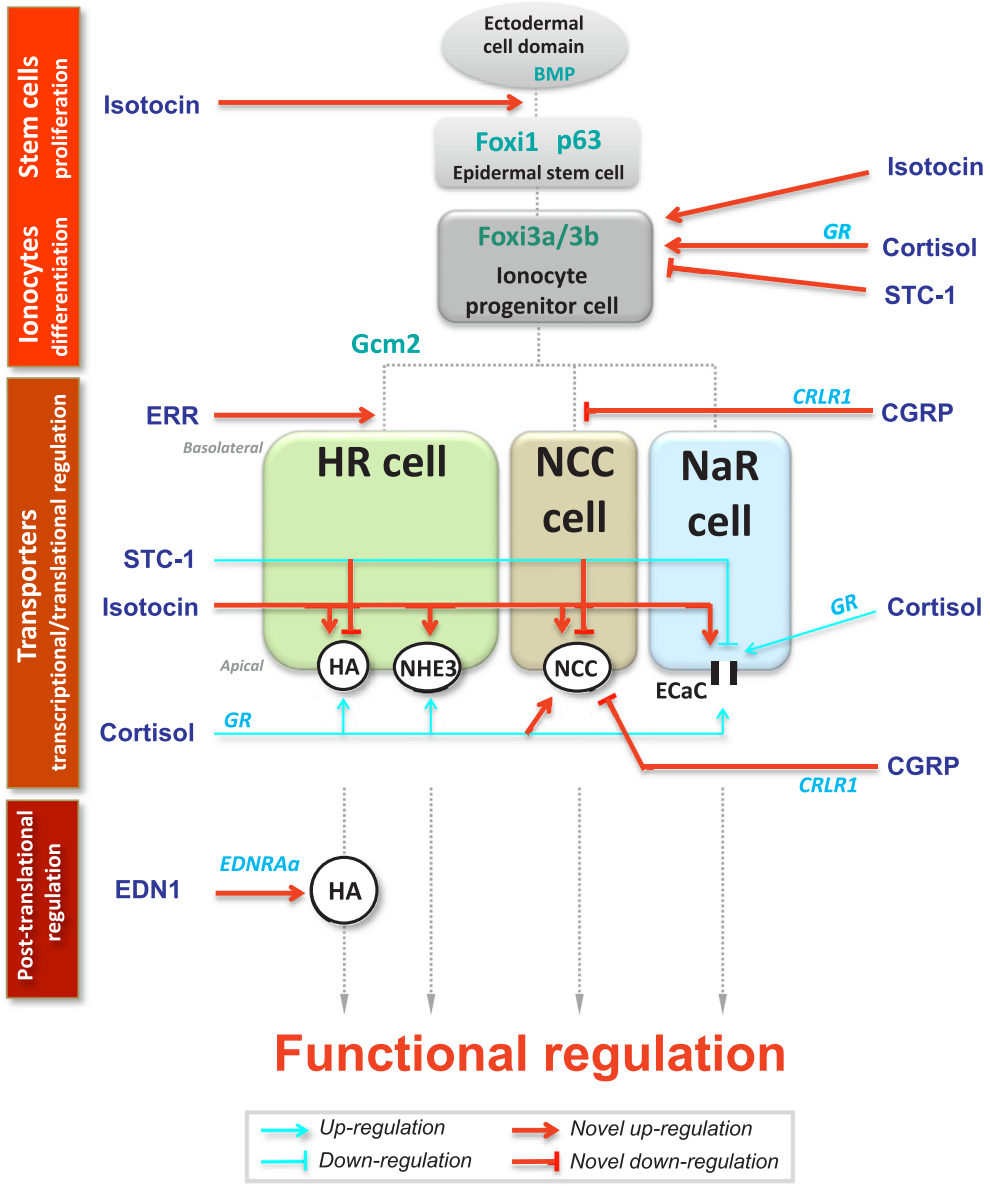

Fig. 1. Novel actions of several hormones identified in zebrafish. Hormones exert newly identified actions on ion transport function by modulating different ion transporters at transcriptional, translational or post-translational levels in various cell stages of multiple types of ionocytes (modified from Guh and Hwang, 2017). For details, please refer to the text. CGRP, calcitonin gene-related peptide; CRLR1, calcitonin receptor-like receptor 1; EDN1, endothelin-1; EDNRAa, endothelin receptor Aa; GR, glucocorticoid receptor; HA, H^+-ATPase; HR, H^+-ATPase rich; NaR, Na^+-K^+-ATPase rich; NCC, Na^+-Cl^-cotransporter; STC-1, stanniocalcin-1.

and osmotic regulation (Fig. 1) and also provided new insights into vertebrate endocrinology.

2. Ion transporters, ionocytes and ion transport functions

Different types of ionocytes have been functionally identified in the gills (or skin during embryonic stages) of zebrafish and medaka using a variety of approaches, including double/triple *in situ* hybridization/immunocytochemistry, loss- and gain-of-function experiments, and ion flux measurements by electrophysiology or radioisotope tracers. Zebrafish develop several types of ionocytes, such as K^+-secreting (KS) cells, solute carrier 26 (SLC26) cells, Na^+-Cl^- cotransporter (NCC) cells, Na^+-K^+-ATPase-rich (NaR) cells, and H^+-ATPase-rich (HR) cells (Fig. 2). The individual functions of HR cells (Na^+ uptake/H^+ secretion/NH_4^+ excretion), NaR cells (Ca^{2+} uptake), NCC cells (Na^+/Cl^- uptake), SLC26 cells (HCO_3^- secretion/Cl^- uptake) and KS cells (K^+ excretion) were demonstrated to be mediated by distinct sets of ion transporters (Fig. 1). In freshwater (FW) medaka, Na^+/H^+ exchanger (NHE) cells are responsible for acid secretion/NH_4^+ excretion/Na^+ uptake/K^+ secretion, epithelial Ca^{2+} channel (ECaC) cells absorb Ca^{2+}, NCC cells absorb Na^+ and Cl^-, and the functions of HR cells are unknown. In seawater (SW) medaka, SW ionocytes carry out acid secretion, NH_4^+ excretion, K^+ secretion, secretion of Na^+ (through the paracellular pathway between ionocytes and accessory cells) and Cl^-, while the function of accessory (AC) cells are still unknown. The ion transport functions and transporter proteins are highly similar between ionocytes in fish gills (and embryonic skin) and the tubular cells of mammalian kidney. For example, zebrafish HR cells and medaka NHE cells are analogous to proximal tubular cells and collecting duct α-intercalated cells in mammalian kidney in terms of Na^+ uptake/H^+ secretion/ammonia excretion. Additionally, zebrafish and medaka NCC cells analogous to mammalian distal convoluted cells in uptake of Na^+ and Cl^-, and zebrafish NaR cells and medaka ECaC cells exhibit similar Ca^{2+} reabsorption functions to mammalian renal cells. A recent review

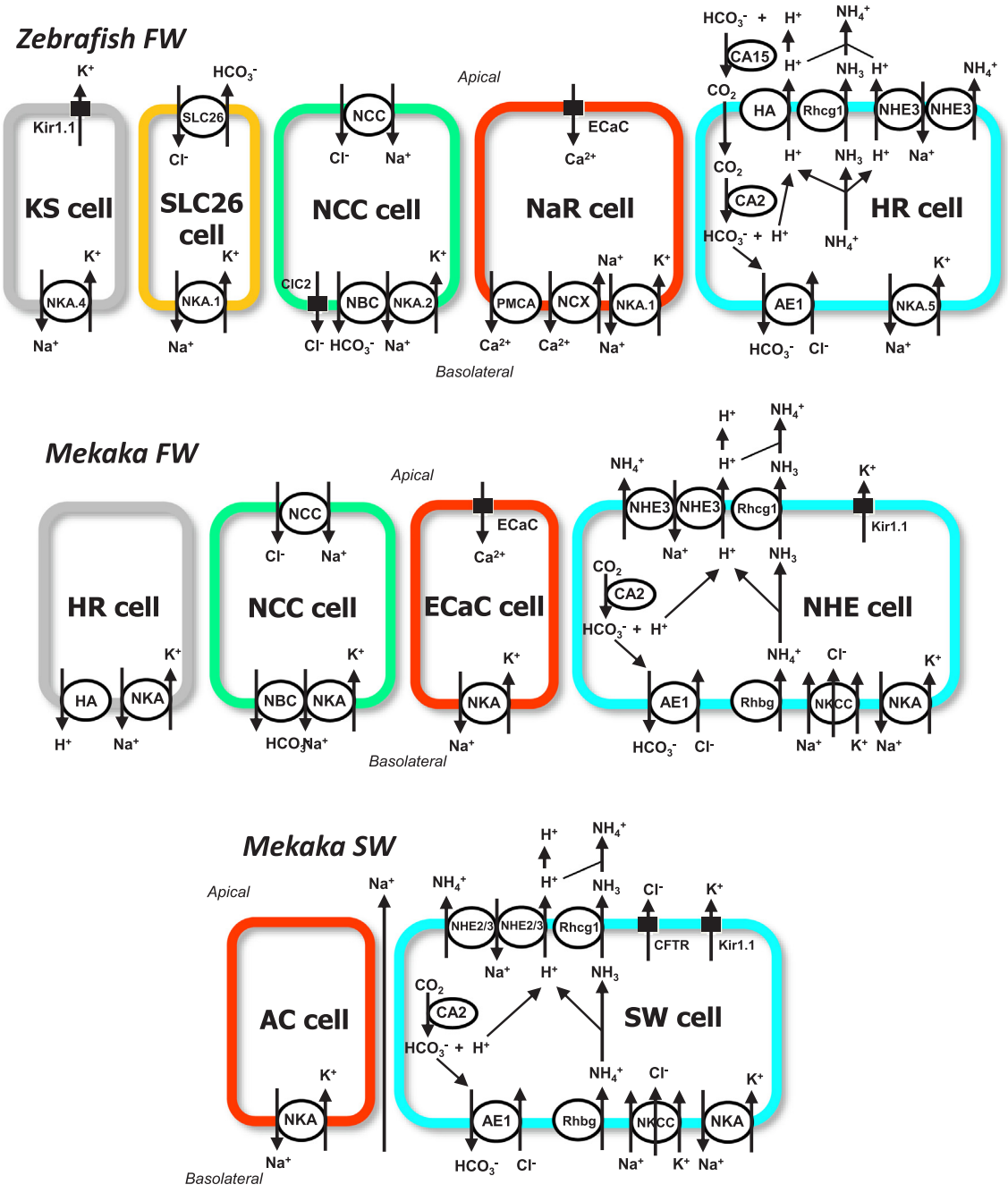

Fig. 2. Ion transport functions, ion transporters, and ionocytes in the model species, zebrafish and medaka, in freshwater (FW) or seawater (SW). Various types of ionocytes are responsible for transport of different ions using distinct sets of ion transporters. In zebrafish, H^+-ATPase rich (HR) cells are responsible for acid secretion/NH_4^+ excretion and Na^+ uptake; Na^+-K^+-ATPase rich (NaR) cells are responsible for Ca^{2+} uptake; Na^+-Cl^-cotransporter (NCC) cells are responsible for uptake of Na^+ and Cl^-; solute carrier 26 (SLC 26) cells are responsible for HCO_3^- excretion/ Cl^-; K^+ secreting (KS) cells are responsible for K^+ secretion. In FW medaka, Na^+/H^+ exchanger (NHE) cells are responsible for acid secretion/NH_4^+ excretion and Na^+ uptake; NCC cells are responsible for uptake of Na^+ and Cl^-. In SW medaka, SW cells are responsible for acid secretion/NH_4^+ excretion and secretion of Na^+ and Cl^-; accessory (AC) cells function is unknown. AE1, anion exchanger 1b; CA2 (−1 5), carbonic anhydrase 2-like a (-15a); ClC2, Cl^- channel 2c; CFTR, cystic fibrosis transmembrane conductance regulator; ECaC, epithelial Ca^{2+}channel; Kir1.1, K^+ channel; NAK.1 ~ 5, Na^+-K^+-ATPase α1 subunit subtypes (atp1a1a.1 ~ 5); NBC, electrogenic Na^+–HCO_3^- cotransporter 1b; NCX, Na^+/Ca^{2+} exchanger; NHE2/3, Na^+/H^+ exchanger 2 or 3; NKCC, Na^+-K^+-Cl^- cotransporter; PMCA, plasma membrane Ca^{2+}-ATPase; Rhcg1/Rhbg, ammonia transporter; SLC26, SLC26A3, −4 and −6.

provided a critical assessment of the conservation between human renal transporters and ion transport functions in zebrafish and highlighted some areas of research that present special potential or difficulties in using zebrafish as a model for human renal ion transport and related diseases (Kersten and Arjona 2017). For example, only a very limited number of transporters, such as Kcnj1a1 (K^+ channel) and SLC4A4 (electrogenic Na^+–HCO_3^- cotransporter) have been functionally validated in a Xenopus oocyte overexpression system, and most ion transporters have only been assayed to confirm expression without functional verification. This lack of information is mainly the result of a paucity of convincing and direct approaches to measure ion transport activity, aside from performing electrophysiology in Xenopus over-expression systems. The gills (or the embryonic skin) are responsible for over 90% of ionic and acid-base regulation activities, and express either

the same (ATP2B2, ATP6V1A, Kcnj1, SLC8A1, SLC12A1, SLC26A3/-4/-6, TRPV5) or paralogous (SLC2A1/-6/-13 vs SLC2A2, SLC9A3.2 vs SLC9A3.1, SLC12A10 vs SLC12A10) transporters compared to kidney (Pan et al., 2005; Liao et al., 2007; Yan et al., 2007; Tseng et al., 2009a, Wang et al., 2009, Lin et al., 2012; Hsu et al., 2014; Wang et al., 2016; Horng et al., 2017). Ion transport functions in ionocytes of zebrafish or medaka can be examined by different approaches, and therefore, these species may be more convenient and efficient models to study epithelial ion transport functions and hormonal control, providing important information and new insights into the transport physiology of zebrafish and mammals.

3. Oxytocin/isotocin

Oxytocin is involved in the regulation of several behavioral and physiological processes, such as social, sexual and maternal behaviors, as well as learning, memory and parturition in mammals (Anderson-Hunt and Dennerstein 1995; Ferguson et al., 2002, Marazziti and Catena Dell'osso, 2008). In addition to these varied functions, oxytocin is also known to regulate body fluids. Dehydration or salt-loading may increase oxytocin expression (Meister et al., 1990). Upregulated oxytocin may then reduce blood pressure by directly acting on the right atrium to stimulate atrial natriuretic peptide release and induce natriuresis and diuresis in the kidney (Haanwinckel et al., 1995). Moreover, oxytocin receptors are expressed in mammalian kidney and this expression responds to estrogen treatment or certain physiological states (Gimpl and Fahrenholz, 2001), suggesting the possibility that oxytocin directly acts on the kidney. In mammals, oxytocin was proposed to be a cardiomyogenic factor that promotes the production of cardiomyocytes from stem cells and thus serves in a cardioprotective role (Gutkowska, Jankowski et al., 2014). Oxytocin was demonstrated to promote hippocampal cell proliferation and dendritic maturation, thereby affecting behavior (Sanchez-Vidana et al., 2016). Another action of oxytocin is to modulate the proliferation of dermal fibroblasts and keratinocytes and thus it is clinically related to stressful conditions in human skin (Deing et al., 2013). These studies illustrate the highly varied actions of oxytocin and imply that it also has the potential to regulate other physiological functions (e.g., body fluid hydro-mineral homeostasis) through actions on target cells (e.g., kidney cells) in mammals. A limited number of studies have proposed possible roles for isotocin, the teleost homolog of oxytocin, in fish osmoregulation. Most of these studies examined the expression of isotocin or isotocin receptors in fishes exposed to different salinities; however, the inconsistent and species-dependent results could not provide a conclusive generalizable role for isotocin in hypo- or hyper-osmoregulation (Motohashi et al., 2009, Martos-Sitcha et al., 2013, Martos-Sitcha et al., 2014, Cao et al., 2018). Our study on zebrafish isotocin provides some evidence to support this notion (Fig. 1). In zebrafish, isotocin expression was stimulated by ion-deficient or low-pH environments, which then led to compensatory enhancement of ion uptake and acid secretion (Chou et al., 2011). This action of isotocin appears to be exerted by stimulating the proliferation of epidermal stem cells and differentiation of ionocyte progenitors via the p63 and Foxi3a (transcription factors for differentiation of ionocytes); activation of p63 and Foxi3a subsequently enhances the differentiation of transporter expressing cells, including H^+-ATPase (HA), epithelial Ca^{2+} channel (ECaC) and Na^+-Cl^--cotransporter (NCC), and their functional activities (H^+ secretion, Ca^{2+} uptake, Na^+ uptake, and Cl^- uptake) in ionocytes (Chou et al., 2011). Thus, the zebrafish study provides a rationale to test whether oxytocin also controls epithelial ion transport functions through the regulation of ion transporter expression during tubular cell differentiation in mammalian kidney to affect body fluid ionic or acid-base homeostasis.

4. Corticosteroids: aldosterone/cortisol

Corticosteroids have two major functions in vertebrates: glucocorticoids affect metabolism and growth, while mineralocorticoids regulate body fluid water and ion homeostasis. In mammals and many other vertebrates, cortisol binding to the glucocorticoid receptor (GR) and aldosterone binding to the mineralocorticoid receptor (MR) are the two main events that stimulate metabolism/growth and water/ion homeostasis ((Baker et al., 2013, Takahashi and Sakamoto, 2013). Aldosterone-MR is involved in salt reabsorption, water conservation, potassium homeostasis and acid-base regulation; MR activation regulates the transport of Na^+, Cl^-, H^+, HCO_3^- through direct actions on various transporters, including epithelial Na^+ channel (ENaC), Na^+-K^+-ATPase (NKA), HA, and pendrin (Wagner, 2014, Rossier et al., 2015, Roy et al., 2015) in mammalian aldosterone-sensitive distal nephron cells. In teleost fishes, aldosterone is not present, and cortisol has long been thought to perform both glucocorticoid and mineralocorticoid actions. Indeed, accumulated evidence has demonstrated a predominant role for cortisol-GR signaling in fishes iono/osmoregulation (Takahashi and Sakamoto 2013). Cortisol-GR signaling promotes both hyper- and hypo-osmoregulation mechanisms in the gills (kidney and/or digestive tract) of FW and SW fishes, respectively (Evans, Piermarini et al. 2005, McCormick and Bradshaw 2006, Takei, Hiroi et al. 2014). Cortisol was also demonstrated to stimulate Na^+/Cl^- uptake and ionocyte differentiation in FW fish gills; it also enhances ionocyte differentiation and the expression of NKA, Na^+-K^+-$2Cl^-$-cotransporter (NKCC) and cystic fibrosis transmembrane conductance regulator (CFTR) in SW gills (McCormick 2001, Evans, Piermarini et al. 2005, Takei, Hiroi et al. 2014). In recent studies on zebrafish, these actions of cortisol were revisited with further in-depth experimentation (Fig. 1). Based on loss- and gain-of-function experiments on GR (injection of morpholinos or mRNA; incubation with GR inhibitors and/or supplementation with exogenous cortisol), cortisol-GR signaling promoted acid secretion by stimulating expression of HA and stimulated Na^+ uptake via elevated Na^+/H^+ exchanger (NHE3)/NCC expression (Kumai, Nesan et al. 2012, Lin, Shih et al. 2015, Lin, Hu et al. 2016). Cortisol-GR signal also stimulated Ca^{2+} uptake through a mechanism mediated by vitamin D_3. (Lin, Tsai et al. 2011). In recent studies on medaka, exogenous cortisol was reported to stimulate the mRNA expression of both CFTR and NCC in the gills (Bossus, Bollinger et al. 2017), and MR-knockout medaka reinforced the major role of GR in fish osmoregulation (Sakamoto, Yoshiki et al. 2016). Thus, the corticoid-mediated promotion of acid-base and ionic regulation appears to be conserved in fishes and mammals.

Corticoids exert their actions through both genomic and non-genomic effects, which include transcription, translation and post-translational modulation of targets (Thomas, Dooley et al. 2010). In fishes, cortisol has been proposed to functionally enhance salt secretion by stimulating cell differentiation of the gill ionocytes, mainly based on data showing increased cell number after SW treatment (McCormick 2001, Evans, Piermarini et al. 2005). In zebrafish, cortisol stimulates the expression of foxi3a/-b (two major transcription factors for differentiation of ionocytes), and thus, the number of ionocytes and ion transport function were upregulated in both *in vivo* and *in vitro* experiments (Cruz, Chao et al. 2012, Cruz, Lin et al. 2013). However, it is unclear whether aldosterone-MR stimulates cellular actions that functionally regulate the salt absorption and acid-base homeostasis in mammalian kidney. Aldosterone is a modulator of renal cell proliferation and differentiation during normal kidney development, and this regulation of renal cell growth is mediated by protein kinase cascades (Thomas, Dooley et al. 2010, Dooley, Harvey et al. 2011). The signaling-mediated actions of aldosterone can also lead to deleterious changes in tissue structure by inducing hypertrophy or dysregulating proliferation and apoptosis, a sequence that is important in chronic kidney disease etiology (Thomas, Dooley et al. 2010, Dooley, Harvey et al. 2011). Interestingly, zebrafish ionocytes and mammalian intercalated cells exhibit similar cell differentiation pathways, which appear to be mediated by similar signaling components (i.e., forkhead transcription factors and Notch) (Hsiao, You et al. 2007, Al-Awqati and Gao

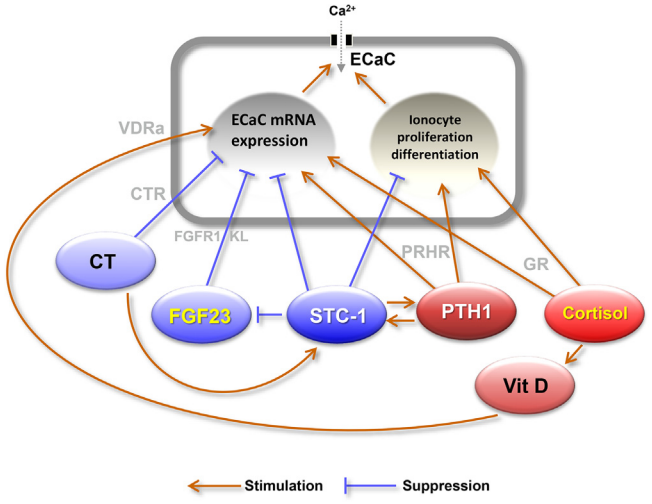

Fig. 3. Interplay between various hormones in the regulation of Ca^{2+} uptake in zebrafish. A proposed model for the actions of calcitropic hormones in zebrafish NaRCs. Calciotropic hormones directly regulate (via the hormone itself or its receptors) ECaC mRNA in ionocytes or indirectly regulate (via effector hormones) ECaC activity by affecting cell proliferation/differentiation to modulate mRNA expression or activity of ECaC. CT, calcitonin; CTR, calcitonin receptor; ECaC, epithelial Ca^{2+} channel; GR, glucocorticoid receptor; PTH1, parathyroid hormone 1; PTHR, parathyroid hormone receptor; STC-1, stanniocalcin 1; Vit D, vitamin D; VDRa, vitamin D receptor A.

2011). α- and β-intercalated cells represent different states of differentiation, and the conversion between the two types of cells can be induced by internal acidosis (Al-Awqati and Gao 2011, Roy et al. 2015), suggesting that differentiation plasticity of renal cells is important to regulate acid secretion function in response to body fluid acid-base disturbances. The zebrafish studies described above (Cruz et al., 2012, Cruz et al. 2013) (Fig. 1) provide some clues to stimulate further mammalian research by raising the hypothesis that corticosteroid may functionally regulate ion transport by adjusting proliferation and/or differentiation of renal cells to cope with body fluid ionic or acid-base disturbance.

5. Stanniocalcin 1

Stanniocalcin 1 (STC-1) was initially found in the corpuscles of Stannius (CS) and showed hypocalcemia action, which inhibited gill calcium uptake in fishes (Fontaine, 1964; Pang et al., 1973, Fenwick and So, 1974, So and Fenwick, 1979, Wagner et al., 1986). The hypocalcemic action of STC-1 is widely recognized in many fish species (Fenwick et al., 1995; Yeung et al., 2012); however, the underlying mechanism of how STC regulates gill Ca^{2+} transport was not clear until the publication of a recent zebrafish study (Yeung et al., 2012). In zebrafish, acclimation to a low-Ca^{2+} FW environment stimulated Ca^{2+} influx and ECaC mRNA expression, while it suppressed STC-1 expression; knockdown of STC-1 with specific morpholinos also resulted in increased Ca^{2+} content, Ca^{2+} influx and ECaC expression. These data suggest that zSTC-1 negatively regulates ECaC gene expression to suppress Ca^{2+} uptake function in fish (Tseng et al., 2009b). STC was also identified in human samples and is expressed in many tissues, including the heart, lung, liver, adrenal gland, kidney, prostate and ovary (Chang et al., 1995). Mammalian STC-1 was shown to exhibit similar actions on transepithelial transport of Ca^{2+} and phosphate (Wagner et al., 1997, Madsen et al., 1998) as those found in fishes (Sundell et al., 1992, Lu et al., 1994, Wagner et al., 1997). On the other hand, loss-of-function studies using STC-1 (−/−) mice did not support its functional role in Ca^{2+} and phosphate homeostasis. Other than STC-1, many hormones such as parathyroid hormone (PTH), calcitonin, vitamin D_3, estrogen, and thyroid hormone have also be shown to control mammalian body fluid Ca^{2+} homeostasis by regulating the expression and function of TRPV5/6, the mammalian homologs of fish ECaC (Hoenderop et al., 2005). As such, hypocalcemic function of STC-1 in fish is thought to have been lost in mammals during evolution (Yeung et al., 2012). Alternatively, STC-1 may play a supporting role by interacting with other hypo- and hypercalcemic hormones in body fluid Ca^{2+} homeostasis after different physiological disturbances. Recent studies on zebrafish provided some insight into this notion. Experiments using overexpression of calcitonin demonstrated that its hypocalcemic action was mediated by suppressing ECaC expression and Ca^{2+} uptake function, and this action appeared to be indirectly derived from stimulation of STC-1 (Lafont et al., 2011). Calcium sensing receptor (CaSR), which responding to high extracellular Ca^{2+}, upregulates the synthesis and function of STC-1 and downregulates PTH1, thus suppressing ECaC expression and Ca^{2+} uptake function. CaSR also has time-dependent effects on the expression of STC-1 and PTH1, providing a possible STC-1/PTH1 counterbalancing mechanism toward body fluid Ca^{2+} homeostasis (Lin et al., 2014). Fibroblast growth factor 23 (FGF23), a hormone required for phosphate metabolism in mammals, acts as a hypocalcemic factor, which regulates body fluid Ca^{2+} homeostasis through the CaSR/STC-1/FGF23 axis in zebrafish (Lin et al., 2017). FGF23 is co-expressed with CaSR and STC-1 in CS, while FGF23 receptor 1 (FGF23R1) and klotho (the coreceptor of FGF23) are co-expressed in ECaC-expressing ionocytes. The activation of CaSR by extracellular Ca^{2+} enhances the expression and/or secretion of STC-1 and FGF23, thereby suppressing ECaC expression and Ca^{2+} uptake. Moreover, increased STC-1 expression inhibits FGF23 expression, showing an interplay between the two hormones (Lin et al., 2017). As such, these hormones form complicated feedback and counterbalancing loops to control zebrafish body fluid Ca^{2+} homeostasis (Lin and Hwang, 2016) (Fig. 3). The knowledge obtained from zebrafish provides many avenues for further studies on STC-1 in mammals and other vertebrates.

Some studies have also implied that STC-1 may modulate the transport of ions other than Ca^{2+}. In early studies on fish CS, cellular degranulation was affected by extracellular NaCl concentration (Aida et al., 1980) or hypotensive stimuli (Butler et al., 2003). Additionally, fish that received a stanniectomy exhibited impaired body fluid K^+ and Ca^{2+} balance (Chan et al., 1967). Interestingly, stanniectomized FW eels also exhibited attenuated hypovolemic hypotension-induced elevations in plasma Angiotensin II concentration (Butler and Brown, 2007). Furthermore, dexamethasone-induced chronic stress resulted in decreased plasma levels of Na^+, Cl^- and Ca^{2+}, and increased STC secretion from the CS in rainbow trout (*Oncorhynchus mykiss*) (Pierson et al., 2004). This result also suggested that STC-1 may be involved in homeostasis of ions other than Ca^{2+}. Reinforcing the fish studies, studies on hypovolemic hypotension in mammals revealed that arginine vasopressin (AVP) modulates renal STC-1 gene expression, or STC-1 may instead counter-regulate the actions of AVP, which modulate the functions of aquaporin, NKCC and ENaC (Law et al., 2012). However, there has been no direct evidence to support this notion until a recent study on zebrafish (Chou et al., 2015) (Fig. 1). STC-1 mRNA expression was stimulated by acclimation to an acidic or ion-deficient medium. Moreover, overexpression of STC-1 downregulated the expression of ECaC, NCC and HA with a concomitant decrease in whole body Ca^{2+}, Na^+, and Cl^- contents and H^+ secretion. Knockdown of STC-1 produced reverse results, and the physiological data were supported by alterations in the number of differentiating and mature ionocytes (Chou et al., 2015). Thus, STC-1 appears to regulate body fluid ionic (Ca^{2+}, Na^+ and Cl^-) and acid-base regulation through negative actions on differentiation and transport functions of ionocytes, without affecting proliferation (Chou et al., 2015). These zebrafish studies may offer an important reference to guide further research on the functions of STC-1 in body ionic and acid-base homeostasis of other vertebrates and mammals.

6. Estrogen-related receptor

The estrogen-related receptors (ERRs) belong to the steroid nuclear receptor superfamily and are thought to be the evolutionary source of estrogen receptor (ER) genes after whole genome duplication (Callard et al., 2011). ERRs, including ERRα (NR3B1), ERRβ (NR3B2), and ERRγ (NR3B3), are the first known orphan nuclear receptors, and no natural ligands have yet been identified (Giguere et al., 1988, Audet-Walsh and Giguere, 2015). ERRs share high sequence homology with ERs. Both have DNA binding domains and ligand binding domains but ERRs do not respond to the same ligands as ERs (Horard and Vanacker, 2003, Huss et al., 2015). ERRα and ERRγ are important in the regulation of metabolic genes and cellular energy metabolism, whereas ERRβ is important for the maintenance of embryonic stem cell pluripotency (Huss et al., 2015). In particular, ERRs are known to be essential for response to various environmental challenges and the actions require a sufficient energy supply (Audet-Walsh and Giguere, 2015). ERRα and ERRγ are primarily expressed in the heart, skeletal muscle and kidney, in which ATP production mostly relies on mitochondrial oxidative metabolism (Heard et al., 2000, Huss et al., 2004, Huss et al., 2015). In mice, knockout of ERRα causes hypernatremia and hypokalemia, and expression of the transporters related handling Na^+ and K^+ is affected in the kidney (Tremblay et al., 2010). The actions of ERRs on transport of other ions in mammalian kidney and the underlying mechanisms are still puzzling. To survive in a harsh environment with abrupt and intense changes in salinity, pH, or temperature, fishes need a timely and surplus energy supply for gill ionocytes to modulate or regulate ion transport functions in order to recover from disturbances in body fluid ionic and acid-base homeostasis (Tseng and Hwang, 2008, Hwang et al., 2011). Gill ionocytes, simialr to renal tubular cells, are rich in mitochondria and thus consume a large amount of energy. It is reasonable to infer that ERRs play a role in ion transport fucntions of fish gill ionocytes; however, there has been not any direct demonstration of this link until recently. In zebrafish, ERRα was found to be specifically expressed in HR cells, and the expression of ERRα not only corresponded to H^+ secretion activity but also affected the expression of other H^+ secretion-related transporters, HA, NHE3 and AE1, as well as the number of HR cells in zebrfish embryos (Guh et al., 2016). Moreover, medaka, a euryhaline fish, also shows expression of ERRα in a portion of NKA-positive ionocytes. Additionally, both H^+ secretion activity and the expression of H^+ secretion-related transporters were reduced in ERRα morphant embryos (Guh et al. unpublished). These research results highlight a novel function of ERRα in vertebrate acid-base regulation, a topic that requires further studies on other species such as mammals. On the other hand, the actions of ERRs on body fluid ionic (Na^+, K^+, or others) homeostasis may have also been developed in fishes as in mammals (Tremblay et al. ,2010). As such, studies on zebrafish and medaka may provide a basis to understand and further examine the role of ERRs in human kidney disease.

7. Calcitonin gene related peptides

Calcitonin gene-related peptide (CGRP) is a member of the calcitonin family of peptides and comprises two forms in humans, α-CGRP and β-CGRP. Zebrafish have only one CGRP, which is an orthologue of human α-CGRP. In contrast to its alternatively spliced variant calcitonin (CT, a hypocalcemic hormone), CGRP appears to be unresponsive to environmental Ca^{2+} (Lafont et al., 2011). A few studies on rainbow trout, eel, and stingray have reported that plasma CGRP levels, CGRP binding (with ^{125}I-labelled human CGRP) or CGRP receptor (calcitonin receptor-like receptor, CRLR) mRNA expression were increased in gills of fishes that were maintained in SW conditions compared with those in FW or diluted SW (Najib and Martine, 1996, Lafont et al., 2006, Suzuki et al., 2012), suggesting a role for CGRP in fish osmoregulation. However, the detailed mechanisms underlying CGRP actions on ion transport were completely unknown until recently (Fig. 1). In zebrafish embryos, CGRP and its receptor CRLR1 were shown to respond to changes in environmental Cl^- concentration but not changes in Ca^{2+} or Na^+, implying a specific role in Cl^- regulation. Subsequent gain- and loss-of-function experiments demonstrated that CGRP acts as a hypochloremic hormone by suppressing NCC2b expression and the differentiation of NCC-expressing ionocytes to affect body fluid Cl^- homeostasis (Wang et al., 2016). In mammals, CGRP is well known as a modulator of cardiovascular function through its action as a hypotensive factor on heart and blood vessels (Gennari and Fischer, 1985, van Rossum et al., 1997). Extracellular Na^+/Cl^- concentration is one of the major factors associated with blood pressure (Edwards, 2012, McCallum et al., 2015); however, the role of GCRP in mammalian iono- or osmoregulation is still unknown. CGRP was found to stimulate the function of CFTR (a Cl^- channel) in human airway epithelial cells, an action that is associated with cell proliferation and differentiation in submucosal glands following airway injury (Xie et al., 2011). Extracellular Cl^- is another important factor in blood pressure regulation that is independent of Na^+ concentration (McCallum et al., 2015, Nakajima et al., 2016). Taking the knowledge gained from zebrafish CGRP experiments as a basis, further studies into the regulatory action of CGRP on renal Cl^- transport may provide new insights into the CGRP-dependent molecular mechanisms of blood pressure regulation, an important issue for human physiology and disease. As such, the new knowledge obtained from zebrafish not only identified the action of CGRP on body fluid ionic homeostasis but also gives important clues for further understanding of the related diseases.

8. Endothelin

Endothelin (EDN) is a peptide that contains 21 amino acids and is highly conserved among many species. In mammals, there are three EDN isoforms (EDN-1, -2 and -3) and two EDN receptors (EDNRA and EDNRB). This pathway is responsible for complex regional actions that include paracrine and autocrine signaling in the kidney (Kohan et al., 2011). EDNRs are widely expressed in the kidney, while the expression of EDNRA is mostly in vascular smooth muscle, and EDNRB is predominantly expressed in endothelial cells and renal tubules. Since EDN was discovered in 1988, it has emerged as an important regulator of renal physiology and pathophysiology. This peptide is involved in regulating many renal functions, including sodium transport, water transport and acid/base transport (Kohan et al., 2011). For example, EDN-1 reduces Cl^- uptake through EDNRB by decreasing the activity of NKCC2 in the thick ascending limb (Plato et al., 2000; Kohan et al., 2011). In the collecting duct, EDN-1 also activates EDNRB to inhibit NaCl transport by reducing the activity of NKA and ENaC (Kurokawa et al., 1993; Tomita et al., 1993; Bugaj et al., 2008). During times of systematic acidosis, EDN was shown to stimulate H^+ excretion in the proximal tubule via NHE3, and it also stimulated H^+ secretion by the collecting duct intercalated cells, which perform luminal acidification predominately via HA (Preisig et al., 1987; Weiner et al., 1999; Tsuruoka et al., 2006). Moreover, H^+ excretion activity in the nephron was found to be stimulated by EDN through EDNRB receptor (Licht et al., 2004).

In fishes, endothelin-like immunoreactivity was first probed in medaka and lamprey (*Lampetra japonica*) (Kasuya et al., 1991). Vascular contraction was then shown to be a function of EDN-1 in the trout and catfish (*Ameiurus melas*) through direct injection of mammalian EDN-1 (Olson et al., 1991; Poder et al., 1991). On the other hand, expression of EDNRA in the gills of trout (*Oncorhynchus mykiss*) and EDNRB in the gills of dogfish (*Squalus acanthias*) was demonstrated by pharmacological or immunohistological assays (Lodhi et al., 1995, Evans and Gunderson, 1999). The physiological function of EDN and EDNR in fish gills was hypothesized to be a signal for pillar cells to contract and generate microcirculation through the gill lamellae (Hyndman and Evans, 2007). This function is similar to that of endothelin in mammalian renal microvasculature (Kohan et al., 2011); however,

information regarding the role of endothelin in fish osmoregulation is still limited. In a study of the opercular epithelium of euryhaline killifish (*Fundulus heteroclitus*), an EDN-1-stimulated and NO^-, O_2^-, and prostaglandin E2-mediated signaling axis was found to modify active extrusion of NaCl (Evans, et al. 2004). Other studies showed that the gene expression levels of EDN-1, EDNRA and EDNRB were higher in the gills after transfer from FW to SW, but only EDNRA was observed in NKA-positive gill ionocytes, suggesting that this receptor regulates the salt secretion function in the gills of killifish (Hyndman and Evans, 2007; Hyndman and Evans, 2009). The previously described action of endothelin to inhibit salt uptake in mammalian kidney may have also developed early in teleosts, although direct physiological evidence in fish gills is still lacking. In light of the known conservation of osmoregulatory mechanisms between mammals and teleosts, it can be hypothesized that EDN-EDNR signaling may also be involved in fish acid-base regulation. This hypothesis did not have supporting evidence until recent studies on zebrafish. Acidic challenge was found to upregulate the expression of zebrafish EDN-1 and EDNRAa, and overexpression of EDN-1 enhanced H^+ secretion in zebrafish (Guh et al., 2014). The EDN-mediated enhancement of H^+ secretion was pharmacologically demonstrated to be dependent on the activity of HA but not related to NHE activity; EDN1 does not appear to affect H^+ secretion through either altering the abundance of HA or affecting the cell differentiation of HR ionocytes based on the EDNR knockdown experiments (Guh et al., 2014). Interestingly, EDN-1 was recently shown to stimulate H^+ secretion by regulating NHE3 (but not HA) in medaka (Guh et al., unpublished data). It is notable that stenohaline zebrafish and euryhaline medaka respectively utilize HA and NHE3 as the major apical transporters for H^+ secretion (Lin et al., 2012). EDN-EDNR signaling differentially affects HA and NHE3 in different fish species, and the actions on both transporters are conserved in mammals. These observations further reinforce the notion that EDN effects on osmoregulatory mechanisms may have evolved in early vertebrates and are now conserved in across many species, including mammals.

9. Insulin-like growth factor 1

In 1957, two novel serum factors were identified for their ability to enhance rat cartilage growth; these factors were named Insulin-like growth factor 1 (IGF-1) and IGF-2 (Stewart and Rotwein, 1996, Laron, 2001). Over the next few decades, researchers found that IGFs are essential for normal growth and development, and exhibit functions related to cell proliferation, differentiation, survival, and metabolism in different mammalian tissues (Bach and Hale, 2015). IGF-1 is both a circulating hormone and a tissue growth factor. In circulation, IGF-1 acts as an endocrine factor that is produced by the liver, and the production of hepatic IGF-1 is activated by growth hormone (GH) secreted from the pituitary gland. Interestingly, local tissues may also respond to the release of IGF-1, making the protein both an autocrine and paracrine signal (Feld and Hirschberg, 1996; Allard and Duan, 2018). The action of IGF system is mediated by the binding of ligands (IGF-1 and IGF-2) to the receptor (IGFR). Since IGFs are essential for cell proliferation and differentiation in mammalian kidney (Bach and Hale, 2015), it is unsurprising that IGF-1 also plays a role in fish osmoregulation through effects on gill ionocyte differentiation (McCormick and Bradshaw, 2006; Takei et al., 2014). Treatment with exogenous GH/IGF increased the tolerance of teleosts to a hyper-osmotic SW challenge by increasing the number and size of gill ionocytes as well as the transcription of salt-secreting ion transporters NKA and NKCC (Pelis and McCormick, 2001; Sakamoto and McCormick, 2006; Takei et al., 2014).

On the other hand, IGF-1 has also been shown to acutely stimulate ENaC-mediated Na^+ reabsorption in renal cells of mammals (Gonzalez-Rodriguez et al., 2007; Ilatovskaya, Levchenko et al., 2015) and toad (Blazer-Yost and Cox, 1988; Blazer-Yost et al., 1989). Interestingly, this acute action of IGF-1 on ion transport also appears to be present in

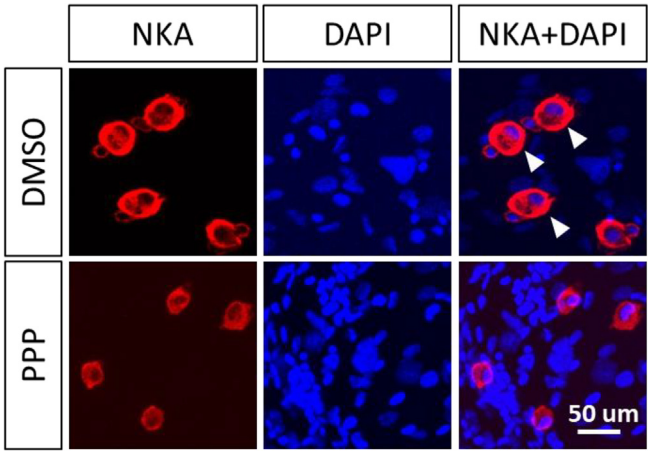

Fig.4. Action of IGF-1 on the reorganization of ionocytes in medaka under acute salinity stress. Ionocytes in embryonic skin were simultaneously stained for Na^+-K^+-ATPase (NKA, red) and DAPI (nuclei, blue). The embryos were incubated with an IGFR antagonist, picropodophyllin (PPP), or DMSO (control) and then transferred from freshwater (FW) to seawater (FW) for 30 min. The NKA-labelled ionocytes transformed from FW-type (single nucleus) to SW-type ionocytes (multicellular complex with multiple nuclei) in the control group, while PPP treatment suppressed this transformation. The multicellular complex of SW-type ionocytes and accessory cells is described in Fig. 2.

fishes. Loss of IGF-1 function by administration of an IGFR antagonist, picropodophyllin (PPP), suppressed the secretion of Na^+ and Cl^- that was normally activated within a couple hours after a direct SW challenge in marine medaka (*Oryzias melastigma*) (Yan et al. unpublished). Supporting these physiological data, PPP treatment also suppressed the transformation of FW ionocytes to SW ionocytes (multicellular complex) that normally occurs within hours during SW challenge (Fig. 4). According to the current model (Fig. 2), the most important responses to salinity stress in teleost gills are the secretion of Cl^- by apical CFTR and basolateral NKCC and NKA (or others), and the secretion of Na^+ through paracellular leaky junctions between SW-type ionocytes and accessory cells (AC) down the Na^+ gradient created by NKA (Evans et al., 2005, Hwang et al., 2011, Hwang and Lin, 2013). These cellular (multicellular complex of SW ionocytes and AC) and physiological (Na^+/Cl^- secretion) events were shown to occur rapidly, within hours after the induction of salinity stress (Shen et al., 2011). These findings in medaka demonstrate for the first time that IGF-1 signaling has acute effects on fish salt secretion mechanisms, in addition to the previously known chronic acclimation responses that are mediated by transcriptional/translational regulation of transporters or differentiation of ionocytes (Takei et al., 2014). Taken together, the action of IGF-1 on body fluid ionic homeostasis may represent an instance of convergent evolution between mammalian kidney for salt reabsorption and fish gills for salt secretion. The validity of this idea will require testing in further studies in other species.

Another group of molecules, IGF-binding proteins (IGFBPs), binds to IGFs to inactivate the ligand activity, thereby titrating the concentration of active ligand in the local tissue or in the circulatory system. (Feld and Hirschberg, 1996, Pollak et al., 2004, Allard and Duan, 2018). Relatively few studies have investigated the role of IGFBPs in fish osmoregulation, and were mainly examined the effects of salinity on IGFBP mRNA or protein expression (Taniyama et al., 2016; Breves et al., 2017). Recent studies in zebrafish reported that IGFBP5a is co-expressed in NaR ionocytes, which are responsible for ECaC-mediated Ca^{2+} uptake (Fig. 2), and IGFBP5a was activated when embryos were acclimated to a low-Ca^{2+} environment (Dai et al., 2014). Further mechanistic analyses clarified that low-Ca^{2+}-induced IGF signaling in fish is similar to the amplification of IGF-induced PI3K-PDK1-Akt signaling in human colon cancer cells, since both occur in an ECaC-dependent

manner (Dai et al., 2014). These results revealed a novel and evolutionarily conserved mechanism of IGF-IGFBP signaling that leads to abnormal epithelial proliferation, and furthermore, the study utilized zebrafish as an alternative model to study this signaling event because mutant mice lacking IGFBP-encoding genes do not exhibit major phenotypes (Liu et al., 2018). As such, these recent studies provide a rationale for further research asking whether IGF-IGFBP signaling is also involved in transport of ions besides Na^+/Cl^- to affect body fluid ionic homeostasis in vertebrates.

10. Conclusions and perspectives

The novel actions of isotocin, cortisol, STC-1, EDN, ERR, CGRP and IGF-1 that were recently identified in zebrafish or medaka have pushed our understanding of iono/osmoregulation beyond the long-held knowledge obtained from traditional model species (Fig. 1). Isotocin, cortisol and STC-1 were found to exert stimulatory or suppressive actions on the transport of several ions by regulating proliferation and/or differentiation of multiple types of ionocytes. This general concept differs from the previous dogma that these actions were limited to effects on certain ions. ERR and CGRP were found for the first time to exert specific actions on H^+ secretion and Cl^- uptake, respectively. These effects on transport of certain ions have not been previously reported in fishes or other vertebrates, including mammals. EDN and IGF-1 show acute functional effects on the respective secretion of H^+ and Na^+/Cl^-, highlighting the evolutionary importance of these actions in vertebrates that must cope with acute environmental stress. Together, these recent findings have greatly enhanced our understanding of hormonal control of body fluid ionic and acid-base regulation in fishes as well as other vertebrates.

These new actions were mostly identified and characterized in embryonic zebrafish and medaka by loss-of-function (mainly morpholino knockdown) or gain-of-function (overexpression) approaches combined with electrophysiological or other physiological analyses. One may question if such hormonal actions are also present in adults. The use of genome editing to generate zebrafish prolactin knockout models was recently employed to verify the results from knockdown morphants and also to study hormonal functions in adult animals (Shu et al., 2016). Another drawback to the current methodology is that researchers are often unable to distinguish between synthesis and release of a hormone due to the difficulty of collecting blood from embryos. Despite these limitations, studies using zebrafish (or medaka) embryos have many advantages. Fast development of fish embryos along with easy and effective methods for loss- and gain-of-function experiments save space and time, facilitating the repeating and scope of experiments. Non-invasive electrophysiology (SIET) and other functional analyses (for ion transport) also allow the fish embryos to serve as a platform for *in vivo* and real-time studies of hormonal actions on body fluid ionic and acid-base homeostasis. Altogether, we suggest taking advantage of the ease of the zebrafish and medaka models, while simultaneously considering their weaknesses. By including these models in larger research efforts, workers may continue to identify thus far unknown endocrine mechanisms that control ionic/acid-base regulation; such mechanisms are relevant not only to the evolution of vertebrates but also to endocrinology and related disease etiologies in humans.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygcen.2019.03.007.

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