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Gonadotropin-releasing hormone neuron development in vertebrates

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ABSTRACT

Gonadotropin-releasing hormone (GnRH) neurons are master regulators of the reproductive axis in vertebrates. During early mammalian embryogenesis, GnRH1 neurons emerge in the nasal/olfactory placode. These neurons undertake a long-distance migration, moving from the nose to the preoptic area and hypothalamus. While significant advances have been made in understanding the functional importance of the GnRH1 neurons in reproduction, where GnRH1 neurons come from and how are they specified during early development is still under debate. In addition to the GnRH1 gene, most vertebrate species including humans have one or two additional GnRH genes. Compared to the GnRH1 neurons, much less is known about the development and regulation of GnRH2 neuron and GnRH3 neurons. The objective of this article is to review what is currently known about GnRH neuron development. We will survey various cell autonomous and non-autonomous factors implicated in the regulation of GnRH neuron development. Finally, we will discuss emerging tools and new approaches to resolve open questions pertaining to GnRH neuron development.

1. Introduction

In humans and the other vertebrates, reproduction is under the regulation of the hypothalamus-pituitary-gonadal (HPG) axis. This third order neuroendocrine axis is conserved in all vertebrate species studied to date (Forni and Wray, 2015; Freamat and Sower, 2013; Roch et al., 2014; Sower et al., 2009; Uchida et al., 2010; Zohar et al., 2010). At the top of the HPG axis are GnRH neurons. These neurons secrete GnRH decapeptides into the median eminence. The GnRH peptides are transported to the anterior pituitary gland, where they stimulate the biosynthesis and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). In both males and females, FSH stimulates maturation of germ cells and sex steroid production (Duan and Liu, 2015).

Since the discovery of the first GnRH decapeptide (GnRH1) in the mammalian hypothalamus in 1971 (Schally et al., 1971), many isoforms of GnRH decapeptides have been identified in a wide range of vertebrates ranging from agnathans to humans. Since many vertebrate species will be discussed, we will use GnRH throughout this article and the species name will be given to avoid any confusion. Phylogenetic analyses have grouped these peptides into 3 main clades (Roch et al., 2014). It is now accepted that three distinct types of GnRH genes exist in the vertebrate class: GnRH1, 2, and 3 (Table 1). The three GnRH genes are thought to have arisen from two rounds of genome wide duplication (Roch et al., 2014). All 3 GnRH genes are present in seabream, medaka, lamprey (an agnathan), and skate (a cartilaginous fish) (Bassi et al., 2016; Oka, 2009; Powell et al., 1994; Roch et al., 2014). Most vertebrates, however, have two GnRH genes due to various gene loss events (Bassi et al., 2016; Oka, 2009; Roch et al., 2014). Amphibian, reptile, birds, and some mammals (including human and primates) have the hypophysiotropic GnRH1 gene and the GnRH2 gene (Table 1). Interestingly, both the GnRH2 and GnRH3 genes were lost in rodents. Therefore, although it is the most widely used animal model, mouse is unusual among the vertebrates in that it only has a single GnRH gene (Table 1). While the GnRH1 gene is present in seabream, medaka and other teleosts, this gene has been lost in some other teleost fish including zebrafish (Bassi et al., 2016; Palevitch et al., 2010; Whitlock et al., 2019; Zohar et al., 2010) (Table 1). In these teleost species, GnRH3 is believed to have adopted the hypophysiotropic role of GnRH1 (Abraham et al., 2010; Palevitch et al., 2007), but this role may not be necessary for fertility in all of these species (Whitlock et al., 2019).

In this short article, we will review recent progress in our current understanding of GnRH neuron development and survey various cell autonomous and non-autonomous factors involved. We will highlight major unresolved questions pertaining to GnRH neuron development and the emerging new tools and new approaches to resolve these issues. Readers are referred to other excellent reviews for a more comprehensive discussion of the migration of GnRH neurons and their important roles in reproductive physiology (Zohar et al., 2010; Freamat

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Table 1
GnRH genes present in a range of vertebrate species.

GnRH genes			
	GnRH1	GnRH2	GnRH3
Lamprey	✓	✓	✓
Skate	✓	✓	✓
Seabream	✓	✓	✓
Medaka	✓	✓	✓
Zebrafish		✓	✓
Stickleback		✓	✓
Xenopus	✓	✓	
Chicken	✓		
Mouse	✓		
Human	✓	✓	

and Sower, 2013; Roch et al., 2014; Forni and Wray, 2015; Bassi et al., 2016; Cho et al., 2019; Chung and Tsai, 2010; Whitlock et al., 2019).

2. Most vertebrates have multiple GnRH genes and different GnRH neurons

Of the 3 types of GnRH neurons, the development of the mammalian GnRH (now known as GnRH1) neurons is arguably the best studied. Early landmark studies in the mouse model revealed that GnRH1 neurons emerge in the nasal/olfactory placode around mid-gestation (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989). GnRH1 neurons then undertake a long-distance migration, moving to the hypothalamus in the brain (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989). Further studies indicated that the GnRH cells migrated along a pathway that is composed of a sub-set of putative vomeronasal/terminal nerve fibers (Wray et al., 1994; Yoshida et al., 1995). It is well accepted that that mammalian GnRH1 neurons migrate from the nasal area to the brain using axons of the terminal nerve/olfactory pathways to reach their final destination (Casoni et al., 2012; Hutchins et al., 2013).

Following these landmark studies in mammals, further investigations in birds, reptiles, amphibians, and some teleost fishes (Medaka) have shown that GnRH1 neurons are born in the nose/olfactory placode and migrate along subsets of fibers to the preoptic area and hypothalamus, suggesting that this migration route is well conserved across species (Forni and Wray, 2015). In these species, GnRH1 is the hypophysiotropic GnRH peptide regulating the HPG axis. In medaka, which is a teleost fish that possess all 3 GnRH genes, the development of GnRH1 neurons and GnRH3 neurons has been analyzed extensively using transgenic reporter lines (Okubo et al., 2006; Takahashi et al., 2016). Takahashi et al. (2016) found that GnRH1 neurons are mainly divided into two populations: the hypophysiotropic innervation of GnRH1 neurons and another population located in the ventral preoptic area (vPOA) with retinopetal projections. In comparison, GnRH3 neurons are divided into three populations: the terminal nerve (TN) population originating from the olfactory placode, the thalamic population originating from the olfactory placode or thalamus, and the trigeminal ganglion (TG) population (Takahashi et al., 2016). There has also been considerable progress in expanding our understanding of GnRH3 neuron development and function in zebrafish, which lacks the GnRH1 gene. Zebrafish GnRH3 neurons are located in the preoptic area–hypothalamus in the adult brain (Palevitch et al., 2007; Steven et al., 2003). Using Tg(GnRH3:EGFP) embryos, a reporter fish line expressing EGFP under the control of the GnRH3 gene promoter, Zohar and colleagues (Abraham et al., 2008) reported that GnRH3 neurons emerge in the nose/olfactory placode area and migrate to the preoptic area-hypothalamus. They further showed that ablation of nasal/olfactory placode GnRH3 neurons resulted in complete lack of preoptic area and hypothalamic GnRH3 neurons in 12-week-old animals. Adult fish lacking GnRH3 neurons exhibited arrested oocyte development and reduced average oocyte diameter. These findings suggest that the hypophysiotropic GnRH3 neurons are critical for normal oocyte development and reproduction (Abraham et al., 2010). This study and others (Palevitch et al., 2007) suggest that GnRH3 is the hypophysiotropic GnRH regulating the HPG axis in species lacking the GnRH1 gene such as zebrafish. A recent study by Feng et al. (2020) reported that zebrafish GnRH3 regulates early sex differentiation by promoting primordial germ cell proliferation via an Erk-dependent mechanism.

Despite the fact that ablation of GnRH3 neurons in development causes infertility in adult zebrafish (Abraham et al., 2010), it was later found that zebrafish with a null mutation in the GnRH3 gene are fertile and show normal reproduction in both males and females (Spicer et al., 2016). This suggests that other peptides may be necessary in fertility, and/or that a compensatory mechanism may be activated when the GnRH3 gene is lost. GnRH2 was an obvious candidate to compensate for the loss of hypophysiotropic GnRH3. However, GnRH2 and GnRH3 double knockout zebrafish were also reproductively normal, although they exhibited changes in a number of genes, suggesting that an unknown compensatory mechanism exits (Marvel et al., 2018). Similar discrepancies in phenotypes between permanent gene knockout and transient knockdowns have been reported for other genes in zebrafish (Anderson et al., 2017; Kok et al., 2015; Rossi et al., 2015; Zhang et al., 2016). In these cases, the lack of major phenotypic changes in the permanent genetic mutants was attributed to genetic compensation and/or transcriptional adaptation, nonsense-mediated decay, and altered mRNA processing (Anderson et al., 2017; El-Brolosy and Stainier, 2017). Whether similar mechanisms underlie the lack of phenotypes in GnRH2 and GnRH3 knockout zebrafish needs to be addressed.

GnRH2 was first discovered in birds and formerly known as chicken GnRH-II. The GnRH2 gene has since been found in a wide range of vertebrate species, including primates and humans (Millar, 2003). In fact, the GnRH2 gene is now considered the most widespread and most conserved of the three GnRH genes (Kauffman, 2004; Millar, 2003). Gene/peptide expression analyses and physiological studies showed that GnRH2 mRNA and/or peptide are expressed in the brain and many peripheral tissues (Kauffman, 2004). In the mammalian brain, the GnRH2 neuron bodies are found most abundantly in the midbrain, but are also detected in hindbrain, and extra-hypothalamic regions (Kauffman, 2004). The most conserved location of GnRH2 expression among other vertebrates is the midbrain tegmentum, from which projections carry it throughout the brain (Umatani and Oka, 2019). GnRH2 mRNA and/or peptide are detected in many non-neural tissues, including placenta, ovary, kidney, breast, bone, and prostate (Millar, 2003). *In vitro* studies suggest that GnRH2 has anti-proliferative activity in normal and cancer cells but it is unclear whether this represents a physiological role of the endogenous GnRH2 peptide (Kauffman, 2004). Physiological studies suggested that GnRH2 is unlikely to be a key regulator of gonadotropin release. Instead, GnRH2 has been implicated in the central control of reproductive behavior and feeding in mammals. In the musk shrew, intracerebroventricular (ICV) administration of GnRH2 decreased food intake, suggesting that GnRH2 may regulate reproductive behavior and energy balance (Kauffman and Rissman, 2004). Furthermore, food restriction decreased and re-feeding restored GnRH2 levels in the brain (Kauffman et al., 2006). This action appeared to be conserved in fish because ICV injection of GnRH2 peptide has anorexigenic effects in goldfish and zebrafish (Hoskins et al., 2008; Matsuda et al., 2008; Nishiguchi et al., 2012). While one study showed that excessive feeding increased GnRH2 mRNA levels in the zebrafish brain (Nishiguchi et al., 2012), another reported fasting of zebrafish increased GnRH2 neuron projection length into the pituitary (Xia et al., 2014). Studies in fish suggest that GnRH2 may also act as a neuromodulator in the auditory system (Kanda et al., 2010; Maruska and Tricas, 2011; Oka, 2009) and a melatonin-releasing factor in the pineal gland, participating in sleep/wake cycles (Servili et al., 2010). Using a Tg (GnRH2:EGFP) reporter zebrafish line, Zohar and colleagues showed that the major site of GnRH2 somas is the midbrain tegmentum but there are also some reticulospinal GnRH2 cells in the hindbrain (Xia

et al., 2014).

3. Regulators of GnRH neuron development

To date, a number of cell autonomous and non-autonomous factors have been suggested to be involved in GnRH neuron development. Many were revealed by studies of human Kallmann syndrome (KS) patients. KS is a rare genetic disease that encompasses a spectrum of isolated hypogonadotropic hypogonadism accompanied by either anosmia or hyponosmia (Hardelin and Dode, 2008; Kallmann et al., 1944). The genetic basis of this condition is complex and a number of mutations have been identified (Cho et al., 2019; Silveira et al., 2010a; Stevenson et al., 2013). These mutations can be divided into several categories: a) mutations in genes that are associated with defects in GnRH1 neuron emergence. Genes in this category include fibroblast growth factor 8 (FGF8), FGF receptor 1 (FGFR1), the so-called "Fgf8 synexpression genes", Pax6, and the chromodomain helicase DNA-binding protein 7 gene; b) genes involved in cell adhesion, neuronal path finding, and cell migration. This group includes anosmin-1 (KAL-1), nasal embryonic LHRH factor NELF, SEMA7A, CHD7, SEMA3A, and SOX10. c) genes that have been shown to influence the GnRH1 neuron migration. This group includes Neuron-derived neurotrophic factor (NDNF), stromal cell-derived factor 1 (SDF1)/chemokine receptor (CXCR-4), GABA, Hepatocyte growth factor (HGF)/Met receptor, PlexinB1, and CCK. These studies have been instrumental in providing candidate genes for possible regulators of GnRH cell fate specification, development, migration, survival, and function (Silveira et al., 2010a; Stevenson et al., 2013). The roles of some of these genes have been elucidated experimentally using molecular genetics (Fig. 1). Some examples are discussed below:

a) Fibroblast growth factor and receptor (FGF8/FGF receptor 1). Tsai and colleagues have discovered that the number of newborn GnRH1 neurons was greatly reduced or completely absent in homozygous *Fgfr1* and *Fgf8* hypomorphic newborn mice (Chung et al., 2008; Gill et al., 2004; Tsai et al., 2005). These findings, together with the fact that human KS patients with defects in GnRH1 neuron emergence harbor loss-of-function mutations in the *FGF8* or *FGFR1* gene (Dode et al., 2007; Falardeau et al., 2008), provide compelling evidence for a critical role of FGF8/FGFR1 signaling in regulating GnRH neuron development, likely at the step of cell fate specification (Fig. 1). Further studies using Fgf1r knockout mice, transgenic mice expressing dominant-negative Fgf1R or *Fgf8* hypomorphic mice suggest that the FGF8/FGFR1 signaling is also critically important for the maintenance of the postnatal GnRH1 neuron system but that it only plays a minor role in GnRH1 neuron migration and axon targeting (Chung and Tsai, 2010). By treating human neural progenitor cells with FGF8 ligand followed by a notch inhibitor, Lund et al. (2016) were able to differentiate them into GnRH expressing neurons that processed and secreted GnRH1 into the medium, further demonstrating the key role of FGF8 signaling in the specification of GnRH neurons. Another gene acting in an FGF signaling-related manner is the Kal-1 gene (Fig. 1). This gene encodes a secreted heparin-binding protein (anosmin-1) that interacts with multiple heparan sulfate proteoglycans and modulates FGF8 action (Hudson et al., 2006; Maggi et al., 2005). Consistent with the notion that FGF8 signaling is important in the regulation of GnRH neuron development, a zebrafish genetic mutant showing that FGF8 is required for the maintenance of midbrain-hindbrain boundary (Reifers et al., 1998). Likewise, knockdown of Kal-1 in zebrafish and medaka affected fasciculation and targeting of olfactory sensory neurons, and disrupted GnRH neuronal migration (Okubo et al., 2006; Whitlock et al., 2005; Yanicostas et al., 2009).

b) Prokineticin 2 ligand and receptor (PROK2/PROKR2)- PROK2 and its G-protein coupled receptor (PROKR2) were shown to primarily regulate GnRH1 neuron migration (Li et al., 2006; Stevenson et al., 2013). PROK2 and PROKR2 are not localized in GnRH1 neurons (Pitteloud et al., 2007). Instead, PROK2 and PROKR2 expression has been mapped to several nuclei of the hypothalamus in mice (Cheng et al., 2002), suggesting that PROK2/PROKR2 may impact GnRH neuron migration by acting on the fibers that guide them into the forebrain (Wierman et al., 2011) (Fig. 1). In zebrafish, overexpression and genetic deletion of Prok2 both affect sleep and wake behaviors (Chen et al., 2017) Whether deletion or overexpression of Prok2 affects GnRH3 neuron development remains unexplored.

c) SOX proteins: The *Sox* gene family belongs to the high mobility group (HMG) protein superfamily. These proteins bind to the minor groove of DNA in a highly sequence-specific manner. There are more than 20 *SOX* genes in the human genome. It was pointed out that the intron A region in the mouse GnRH1 gene has a putative transcriptional enhancer. Overexpression of SOX-4 and SOX-11 substantially increased the activity of a luciferase reporter under the control of the GnRH1 promoter (Kim et al., 2011). Both SOX-4 and SOX-11 were localized within ~80% of GnRH neurons and found in lower levels in non-GnRH hypothalamic cells (Kim et al., 2011). However, no roles have been reported for SOX-4 or SOX-11 in GnRH neuron development. Instead, several studies have linked mutations in the *SOX10* gene to defective GnRH1 neuron migration. 1/3 of the KS patients with deafness carry a *SOX10* loss-of-function mutation (Pingault et al., 2013). In *Sox10* null mouse embryos, only 20~30% of the total GnRH-1 neuronal population migrated into the brain (Herbarth et al., 1998; Inoue et al., 1999; Pingault et al., 2013). Recent studies also showed that SOX10 plays a key role in defining the identity of several neural crest-derived cell populations (Britsch et al., 2001; Finzsch et al., 2010; Pozniak et al., 2010). These findings suggest a possible role of SOX10 in GnRH1 neuron development.

d) Neuron-derived neurotrophic factor (NDNF): Messina et al. (2020) reported several KS patients harboring mutations in the NDNF gene, which encodes a fibronectin-3 (FN3) domain containing protein. Importantly, NDNF is expressed along the GnRH1 neuron migration routes in mice human fetus. Knockout of NDNF in mice delayed GnRH1 neuron migration. Likewise, knockdown of the zebrafish NDNF ortholog also resulted in defective GnRH3 neuron migration (Messina et al., 2020) (Fig. 1).

e) Immunoglobulin superfamily member 10 (IGSF10). A recent study by Howard et al. (2016) identified mutations in IGSF10 in 6 unrelated families with abnormal puberty onset. These authors provided data suggesting that IGSF10 regulates GnRH1 migration in mice. Likewise, knockdown of Igsf10 in Tg(gnrh3:EGFP) zebrafish perturbed GnRH3 neuron migration (Howard et al., 2016). These findings not only linked IGSF10 mutations to delayed puberty in humans but also support the notion that GnRH3 in zebrafish is critical for puberty and reproduction (Fig. 1).

f) Nasal embryonic LHRH factor (NELF). NELF mutations have been found in KS patients (Xu et al., 2010). Using the Tg(gnrh3:EGFP) zebrafish model, Palevitch et al. (2009) showed that Nelf is expressed in GnRH3 neurons and knockdown of Nelf disrupted GnRH3 neuron migration (Fig. 1).

g) Insulin-like growth factor (IGF) signaling. IGFs are evolutionarily conserved polypeptides that play central roles in regulating development, growth, reproduction, and aging in vertebrates (Duan et al., 2010). IGFs are also major embryonic growth-promoting factors and regulate many aspects of brain development, such as neuron proliferation, differentiation, survival, and migration (Bondy and Cheng, 2004; Joseph D'Ercole and Ye, 2008; Nieto-Estevez et al., 2016; Schlueter et al., 2007). Most, if not all, of the actions of IGFs are mediated by the IGF1 receptor (IGF1R). The IGF1R belongs to the receptor tyrosine kinase family and activates two major intracellular signaling pathways, the PI3K-Akt-mTOR and Raf-Mek1/2-Erk1/2 cascades (Duan and Xu, 2005).

Currently, there are no IGF-IGF1R mutations that have been

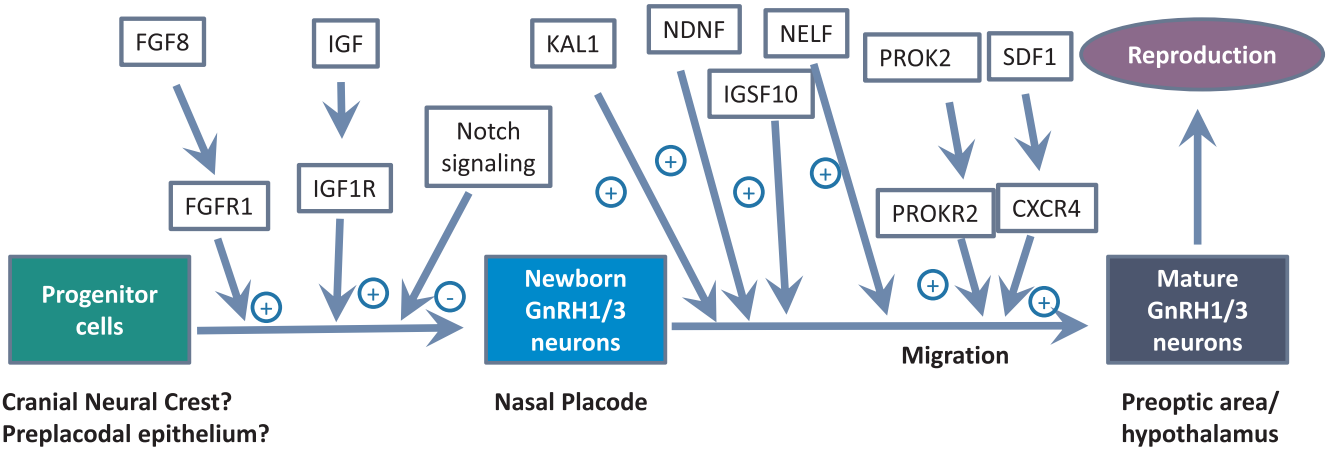

Fig. 1. Cell-autonomous and non-autonomous factors influencing hypophysiotropic GnRH neuron development. FGF8 signaling via the FGFR1 is important for specifying GnRH neurons, and notch inhibition resulted in maturation from a progenitor state. IGF/IGF1R signaling is required for proper spatial patterning of newly emerged GnRH3 neurons. The proper migration of GnRH1/3 neurons to the preoptic area/hypothalamus may require a number of factors, including KAL-1, NDNF, IGSF10, NELF, PROK2/PROKR2, SDF1/CXCR4, etc.

reported in KS patients but mammalian GnRH neurons co-express IGF-1 and the IGF1R in postnatal and adult stages (Daftary and Gore, 2005). IGF-1 stimulates cell proliferation and GnRH gene expression in mammalian GnRH neuronal cell lines (Longo et al., 1998; Zhen et al., 1997) and modulates GnRH activities in cultured pituitary cells isolated from salmonid fish (Ando et al., 2006; Baker et al., 2000; Furukuma et al., 2008; Luckenbach et al., 2010; Weil et al., 1999). IGF-1 has also been shown to regulate the migration of neural crest-derived melanoblasts in chick embryos (Schofer et al., 2001). In young rats, pharmacological inhibition IGF signaling in the brain impairs estrous cyclicity (Todd et al., 2007). Reduced brain IGF signaling in middle-aged female rats leads to luteinizing hormone surge dysfunction by affecting estrogen-dependent processes that influence GnRH neuron activation and/or GnRH release (Todd et al., 2010).

Onuma et al. investigated the possible role of IGF signaling in GnRH neuron development in zebrafish using two complimentary approaches (Onuma et al., 2011). First, Tg(*hsp70:dnIGF1R-GFP*), a stable transgenic fish line expressing a dominant-negative form of the IGF1Ra under the control of the heat shock-inducible *hsp70* promoter (Kamei et al., 2011), was used to genetically block IGF1R-mediated signaling. As an independent approach, two specific and structurally distinct IGF1R kinase inhibitors, NVP-AEW541 and BMS-754807 (Garcia-Echeverria et al., 2004; Wittman et al., 2009), were used to block IGF signaling pharmacologically. GnRH3 neurons normally emerge in two bilateral clusters in the olfactory bulb region at 26 hpf. At 32 hpf, these neurons are clearly observed in these two normal locations. Blocking IGF signaling by dnIGF1R expression or pharmacological inhibition of the IGF1R abolished the emergence of GnRH3 neurons in embryos at 26 hpf (Onuma et al., 2011). Furthermore, these GnRH3 neurons were detected in ectopic positions outside of the olfactory region in the IGF deficient embryos (Onuma et al., 2011). These findings suggest that IGF signaling regulates the emergence of GnRH3 neurons, likely by acting on their progenitor cells (Fig. 1). Further analyses showed that IGFs regulate GnRH3 neuron development via the PI3K pathway but not the MAPK pathway. In addition to GnRH3 neurons, IGF signaling also regulates the timing of GnRH2 neuron emergence (Onuma et al., 2011). In zebrafish, GnRH2 neurons emerge in the midbrain at ~26 hpf. Genetic blockade of IGF signaling resulted in a major reduction in GnRH2 mRNA levels at 26 hpf. Addition of the IGF1R kinase inhibitors NVP-AEW541 and BMS-754807 had similar effects (Onuma et al., 2011). However, no ectopic GnRH2 neurons were found in the IGF signaling deficient zebrafish. These data suggest that IGF signaling is important for the timing of GnRH2 neuron development but it does not affect GnRH2 spatial organization. The fact that perturbation of IGF signaling disrupted the emergence of GnRH3 and GnRH2 neurons led to the speculation that IGF signaling may regulate GnRH3 and GnRH2 neuron development by acting on their progenitor cells (Fig. 1).

h) Kisspeptin and receptor (KISS-KISSR). The kisspeptin receptor (KISS1R), originally named as GPR54, was discovered based on its structural homology to the galanin receptor (Lee et al., 1999). The human kisspeptin (KISS1) gene was discovered from non-metastatic melanoma cells as a possible metastasis suppressor and initially called metastin (Lee et al., 1996). Subsequent studies have shown that metastin (KISS1) is the ligand of GPR54 (KISS1R) (Kotani et al., 2001; Ohtaki et al., 2001). In 2003, de Roux et al. (2003) and Seminara et al. (2003) reported that humans with loss-of-function mutations in the *KISS1R* gene show impaired puberty, small gonads, and infertility. Subsequently, gain-of-function mutations in *KISS1* and *KISS1R* have been linked to GnRH-dependent precocious puberty in humans (Luan et al., 2007; Silveira et al., 2010b; Teles et al., 2008). Deletion of either the *Kiss1* gene or the *Kissr* gene impaired puberty and reproduction in mice (d'Anglemont de Tassigny et al., 2007; Funes et al., 2003; Seminara et al., 2003). Administration of KISS1 peptide increases GnRH secretion and advances puberty onset in rodents (Irwig et al., 2004). These studies have convincingly shown that the KISS1/KISSR system plays essential roles in regulating the hypothalamic-pituitary-gonadal (HPG) axis and reproduction in mammals. Zebrafish has two kiss ligand genes and 2 kiss receptor genes (Biran et al., 2008; Kitahashi et al., 2009; Onuma and Duan, 2012). Zhao et al. (2013) reported that Kiss1 is more important for GnRH3 neuron development. A surprising finding is that permanent deletion of one or both Kiss1r genes resulted in no notable phenotypic changes in zebrafish (Tang et al., 2015). It is possible that there are compensatory pathways mediated by different neuropeptides (Tang et al., 2015). Other possible reasons for the lack of phenotype include transcriptional adaptation, nonsense-mediated decay, altered mRNA processing, and/or physiological context (Anderson et al., 2017; El-Brolosy and Stainier, 2017; Liu et al., 2018).

4. Major unresolved questions in GnRH neuron development and regulation

We now understand that there are three different GnRH genes and distinct populations of GnRH neurons. The “birth” place and migration

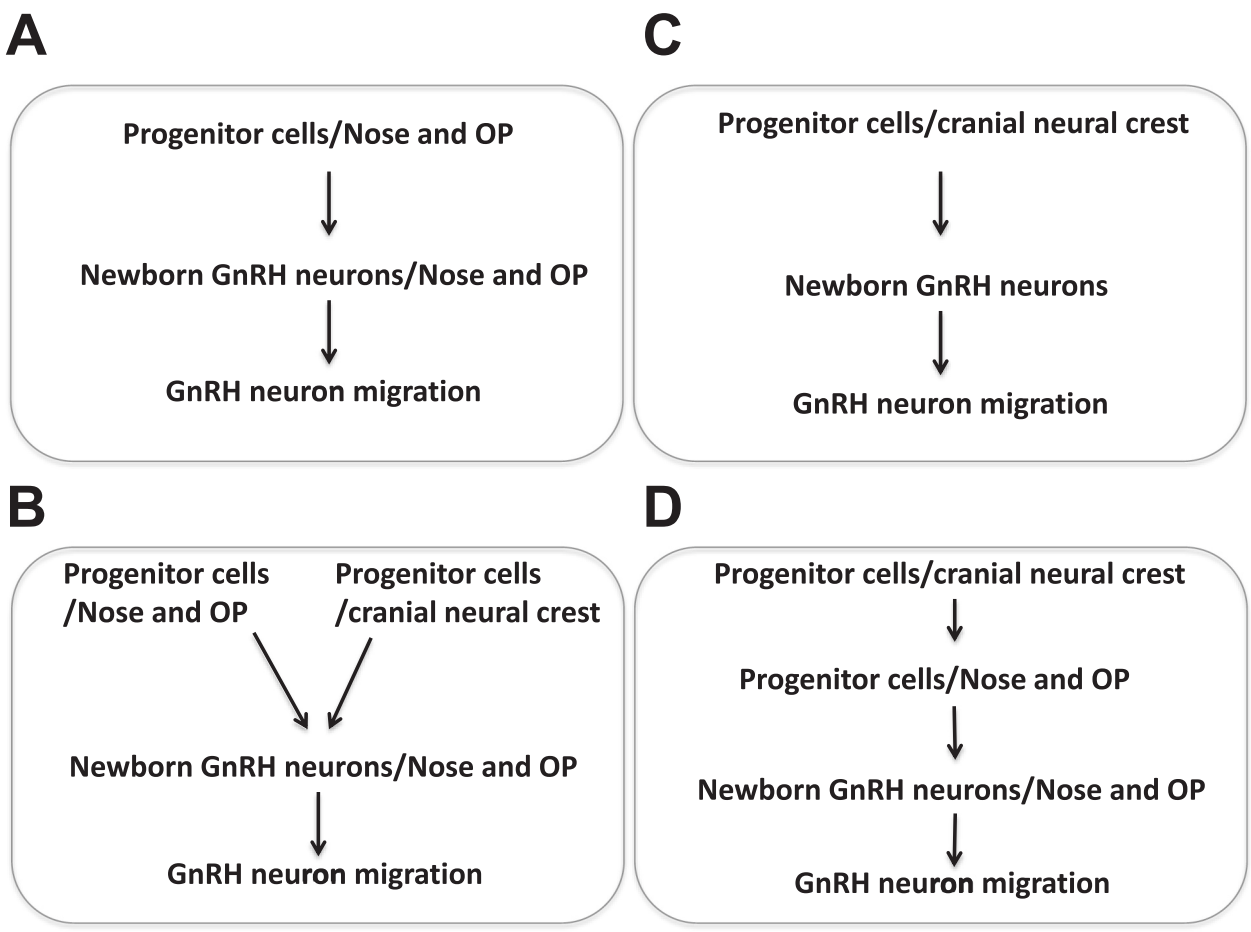

Fig. 2. Competing hypotheses on the embryonic origin(s) of GnRH neurons. (A) GnRH neurons are derived from precursor cells residing in the olfactory placode (OP). (B) Both OP cells and cranial neural crest cells contribute to the birth of GnRH neurons; (C) GnRH neurons are specified from precursor cells in the cranial neural crests; and (D) a single population of progenitor cells moves from the cranial neural crests to the OP initially and then to gives rise to GnRH neurons.

routes of these GnRH neurons are becoming clear and several regulators have been identified. Nevertheless, several important questions remain unresolved.

a) The embryonic origin(s) of the hypophysiotropic GnRH neurons: A prevailing view is that hypophysiotropic GnRH1/3 neurons are derived from progenitor cells in the nose-olfactory placode region (Fig. 2A). This notion is supported by studies using mutant mice lacking olfactory placode (Dellovade et al., 1998) and by ablation experiments in the newt (Murakami et al., 1992). However, ablation of olfactory placode in rat and chick embryos resulted in only a partial reduction of GnRH1 neurons (Daikoku and Koide, 1998; Daikoku-Ishido et al., 1990). These results can be interpreted in several ways. It is possible that the ablation may have left a few olfactory placode cells to survive, which then gave rise to the small number of GnRH1 neurons. It is also plausible that not all GnRH1 neurons are derived from olfactory placode in these species. Indeed, two studies indicated that progenitor cells originating from both neural crest and olfactory placode might contribute to the GnRH1 neuron cell lineage in mice (Forni et al., 2011; Forni and Wray, 2012) (Fig. 2B). Lineage tracing studies in chick and mouse embryos showed that GnRH1 neurons originated from cells that resided in the olfactory placode (Forni et al., 2011). However, it is still possible, as some have argued, that these precursor cells giving rise to the "newborn" GnRH cells may have migrated into the olfactory placode from some other point of origin (Whitlock et al., 2005). In support of this view, several independent reports suggest a neural crest contribution to the cells of the mammalian olfactory placode (Harden et al., 2012; Saxena et al., 2013; Suzuki et al., 2013). Thus, more than 30 years after the landmark studies that traced the appearance of GnRH neurons to the olfactory placode (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989), the embryonic origin(s) and possible heterogeneity of the hypophysiotropic GnRH1 neurons are still being debated (Cho et al., 2019; Forni and Wray, 2015; Patthey et al., 2014; Stevenson et al., 2013).

Studies in zebrafish have added additional complexities to this debate. Cell fate and lineage tracking studies suggested that zebrafish GnRH3 neurons might originate from cranial neural crest cells (Whitlock et al., 2005, 2003) (Fig. 2C). Two studies using reporter zebrafish lines expressing reporter genes under the control of the GnRH3 promoter obtained different results. Abraham et al. (2010, 2008) reported that laser ablation of the GnRH3 soma in the nasal area in an early developmental stage resulted in a loss of olfactory, terminal nerve, preoptic area, and hypothalamic GnRH3, indicating that that the GnRH3 neurons originate from the olfactory region and migrate to the brain in zebrafish. Another study using a different transgenic zebrafish line (GnRH3:EMP) indicated that different GnRH3 neurons may originate from different populations of progenitor cells (Zhao et al., 2013). GnRH3 neurons in the terminal nerve, which play a role in mating behavior in male zebrafish (Li et al., 2017), may originate from cranial neural crest cells, while the hypophysiotropic GnRH3 neurons that are found in the hypothalamus and preoptic area apparently originate from the adenohypophyseal placode (Zhao et al., 2013). The discrepancies among these different studies regarding the embryonic origin(s) of GnRH3 neurons may be in part due to different methodologies. It is also

conceivable that the development of GnRH neurons is more heterogenous and more dynamic than previously thought. In the case of medaka, GnRH3 neurons located in TN are thought to originate from the olfactory placode, while the thalamic GnRH3 neurons may originate from the olfactory placode or thalamus, and the TG GnRH neuron population from thalamus (Takahashi et al., 2016). A recent zebrafish study using the photoconvertible fate mapping technique found that some sox10-expressing cranial neural crest cells migrated to the olfactory placode and formed a capsule surrounding the placode during the first day of development. In day two, these cells moved into the olfactory epithelium to become microvillous neurons (Saxena et al., 2013). This study has raised the possibility that some cranial neural crest cells may travel to the vicinity of the olfactory placode first and then give rise to GnRH neurons (Fig. 2D), thus explaining the different results reported by Whitlock's and Abraham's studies. However, a more recent study by Aguillon et al. (2018) conducted linage reconstructions from time-lapse confocal movies of developing zebrafish embryos and concluded that the GnRH3 expressing neurons in the olfactory epithelium are mostly or entirely derived from the anterior preplacodal ectoderm. These authors also found that the number of GnRH3 expressing cells in the olfactory epithelium was unchanged in *sox10* mutants (Aguillon et al., 2018).

b) The embryonic origin(s) of GnRH2 neurons: GnRH2 is the most conserved GnRH gene among the three GnRH genes and has been identified in every extant vertebrate group (Kauffman, 2004; Millar, 2003). Because mouse and chicken lack the GnRH2 gene, the development of GnRH2 neurons cannot be studied in these animal models. This makes zebrafish and medaka ideal models to study the functional roles of GnRH2, as well as GnRH2 neuron development. As mentioned above, while early lineage tracking studies in zebrafish suggested that GnRH2 neurons may also originate from the cranial neural crest cells (Whitlock et al., 2005), the precise origins of the GnRH2 progenitor cells and their relationship to GnRH3 precursor cells are still not clear.

c) Regulation of GnRH progenitor cells - At present, the only way to define a GnRH neuron is the detected expression the GnRH mRNA/peptide. Therefore, those progenitor cells that are destined to become GnRH neurons cannot be detected. As a consequence, virtually nothing is known about how these progenitor cells are specified to give rise to the birth of new GnRH neurons. By investigating the emergence of newborn GnRH1 neurons in the mouse brain, Tsai and colleagues demonstrated that GnRH1 neurons were absent in FGF8 hypomorphic mutant mice at E11.5, while they were detected in their wild type siblings at the same stage (Chung et al., 2008). These results suggest that FGF8 signaling is critical for GnRH1 neuron fate specification in mice. Likewise, Onuma et al. (2011) found that genetic and pharmacological blockade of IGF signaling delayed the timing of GnRH2 neuron and GnRH3 neuron emergence in zebrafish embryos (Onuma et al., 2011), suggesting that IGF signaling regulates GnRH2 and GnRH3 neuron emergence by acting on their precursor/progenitor cells. Because the progenitors cannot be detected, it is unclear whether FGF8 and IGF signaling regulate the GnRH progenitors' proliferation, migration, differentiation, and/or survival (Fig. 1).

5. Perspectives – overcoming the challenges with new models, new tools, and new approaches

While significant advances have been made in understanding the central importance of the GnRH neurons in reproductive physiology and their developmental processes after emerging in the nasal/olfactory placode or mid-brain, many important questions remain. More than 30 years after publication of the initial studies that demonstrated the birth and migration of GnRH neurons (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989), the precise embryonic origin(s) of the GnRH1 neuron progenitor cells are still under debate, even in the most extensively studied mouse model (Forni and Wray, 2015). Because there are no markers to identify the progenitor cells that are destined to become GnRH neurons, little is known about how these cells are specified to give rise to GnRH cells. Aguillon et al. (2018) have recently shown that immunoreactivity to an Islet1/2 monoclonal antibody in the olfactory epithelium is exactly coincident with GnRH3 promoter-driven GFP expression in transgenic zebrafish embryos. If the Islet-1 or Islet-2 transcription factors are involved in regulating the differentiation of GnRH3 neurons, this may provide an earlier marker for these cells than GnRH expression itself (Aguillon et al., 2018). Compared to the hypophysiotropic GnRH neurons (GnRH1 or GnRH3), much less is known about GnRH2 neuron development and regulation. One of the reasons is that mouse and other rodents only have a single GnRH gene, GnRH1, making it impossible to study GnRH2 neurons in these conventional models. Zebrafish embryos, which are free-living and transparent, are ideal for investigation of the embryonic origin(s) of GnRH neurons and the regulation of their development. Like most vertebrates, zebrafish has a 2-GnRH gene system. The development of transgenic GnRH2 and GnRH3 reporter zebrafish lines, in which GnRH 2 and/or 3 neurons express EGFP or mRFP, makes it possible to visualize the emergence of newborn neurons and follow their development and migration in real time at single cell resolution and to perform laser ablation experiments (Abraham et al., 2008; Xia et al., 2014; Zhao et al., 2013). Likewise, the availability of the Tg(sox10:EGFP)/RFP reporter lines makes it feasible to perform live cell tracing and laser ablation experiments. Several new technical innovations/tools have become available in recent years. One is CRISPR/Cas9-mediated genome editing (Ablain et al., 2015; Jao et al., 2013). Another is the Tg(*sox10*:kaede) transgenic zebrafish line, in which the kaede protein is expressed in cranial neural crest cells (Dougherty et al., 2012; Gfrerer et al., 2013). Kaede is a photo-convertible protein that turns from green to red after photo activation. This makes it possible to "mark" individual cranial neural crest cells by photoconversion and track these cells during development in the transparent zebrafish brain. This approach has been used to perform lineage analysis to delineate a population of cranial neural crest cells that give rise to maxillary versus mandibular elements (Gfrerer et al., 2013). This technique, coupled with crossing with the GnRH:EGFP/RFP lines and with laser ablation experiments, should be able to unequivocally determine whether cranial neural crest cells give rise to newborn GnRH neurons.

Resolving the open questions surrounding the embryonic origins of the hypophysiotropic GnRH1/3 neurons and neuromodulatory GnRH2 neurons will give us a more complete understanding of an evolutionarily ancient neurodevelopmental pathway. The differentiation and migration of GnRH neurons provides an excellent model for studying the mechanisms of neurodevelopment more generally. IGF signaling is known to act in many areas of the developing brain (Nieto-Estevez et al., 2016), but few of its precise roles are fully understood. The involvement of IGF in the spaciotemporal patterning of GnRH neurons provides an opportunity to study its mechanisms of action in neurodevelopment within the context of a well characterized exemplar of a developmental pathway. The initiation of puberty and the function of the reproductive system depend on the proper development of the GnRH neuron system. Filling in the remaining gaps in our knowledge of GnRH neuron development will have important implications for our understanding of the etiology of human reproductive disorders.

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Appendix A. Supplementary data

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