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The great migration: How glial cells could regulate GnRH neuron development and shape adult reproductive life

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ABSTRACT

In mammals, reproductive function is under the control of hypothalamic neurons named Gonadotropin-Releasing Hormone (GnRH) neurons. These neurons migrate from the olfactory placode to the brain, during embryonic development. For the past 40 years, these neurons have been considered an example of tangential migration, i.e., dependent on the olfactory/vomeronasal/terminal nerves. Numerous studies have highlighted the factors involved in the migration of these neurons but thus far overlooked the cellular microenvironment that produces them. Many of these factors are dysregulated in hypogonadotropic hypogonadism, resulting in subfertility/infertility. Nevertheless, over the past ten years, several papers have reported the influence of glial cells (named olfactory ensheathing cells [OECs]) in the migration and differentiation of GnRH neurons. This review will describe the atypical origins, migration, and differentiation of these neurons, focusing on the latest discoveries. There will be a more specific discussion on the involvement of OECs in the development of GnRH neurons, during embryonic and perinatal life; as well as on their potential implication in the development of congenital or idiopathic hypogonadotropic hypogonadism (such as Kallmann syndrome).

1. Birth and origin of GnRH neurons and Olfactory ensheathing cells

The extra-cerebral origin of GnRH neurons was first reported in guinea pigs 40 years ago (Schwanzel-Fukuda and Silverman, 1980). The detection of GnRH neurons in the medial olfactory placode was subsequently detected at an early stage of embryonic development in various species including rodent and human (Table 1) (Schwanzel-Fukuda et al., 1989, 1996; Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989b). In humans, the recent advances in microscopy imaging combined with three-dimensional analysis have allowed researchers to highlight GnRH immunoreactive cells in the medial part of the olfactory placode of optically-cleared whole-mount embryos aged 39 days of gestation (Casoni et al., 2016). Using rodent models, it was proposed that postnatal Luteinizing Hormone-Releasing Hormone (LHRH) neurons originated from a single population of neurons that differentiates from progenitors in a narrow window of time during development (between E10 and E11 in mouse; Table 1), in contrast to the olfactory receptor neurons which present prolonged neurogenesis in the olfactory epithelium, from E10 and maintained throughout adulthood (Murdoch and Roskams, 2007). However, in the Rhesus monkey (*Macaca mulatta*), studies described two populations of GnRH neurons that originate from the medial part of the olfactory pit at E30 and E32 (Table 1) (Quanbeck et al., 1997). These observations raised the question of the existence of two sets of progenitors or a longer period of neurogenesis (Quanbeck et al., 1997). A prolongated neurogenesis period has been indirectly demonstrated in sheep embryos using the *in vitro* culture model of embryonic olfactory placode (Bruneau et al., 2003). Subsequent studies

Abbreviations: ACE2, angiotensin-converting enzyme 2; AMH, anti-Müllerian hormone; αMPT, alpha-methyl para-tyrosine; APBB (FE65), Amyloid precursor protein binding-protein-1; Ascl1, Aachaete-scute bHLH transcription factor 1; bHLH, basichelix-loop-helix; BLBP, Brain lipid-binding protein; Bmp, Bone Morphogenetic Protein; CA, Catecholamines; CCK, Cholecystokinin; Chd, Chromodomain-helicase-DNA-binding protein; DCC, Deleted in colorectal cancer; endoN, Endoneuraminidase N; FEZF1, FEZ Family Zinc Finger 1; GLI3, Glioma-associated oncogene Family Zinc Finger 3; LDCV, Large dense-core vesicles; NELF, Nasal embryonic LHRH factor; Nhlh, Nescient Helix Loop Helix; Nog, Noggin; NRP1, Neuropilin 1; PSA-NCAM, Polysialic acid-rich form of Neural Cell Adhesion Molecule; PTPRZ1, Protein Tyrosine Phosphatase Receptor Type Z1; Slit1, Slit Guidance Ligand 1; Sox, SRY-Box Transcription Factor; TAG-1, Transiently expressed Axonal Surface Glycoprotein-1.

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have demonstrated that GnRH neurons appear in the vomeronasal epithelium of mice, but originate from two sites: 70% of GnRH neurons come from the olfactory placode and 30% come from the neural crest (Forni et al., 2011b). A second study demonstrated two populations of olfactory placode-derived GnRH neurons in embryonic mice supporting the hypothesis of two separate origins of these cells in a mammal (Shan et al., 2020). Thus, it was suggested that either neural crest-derived GnRH cells differentiate earlier than in the preplacodal ectoderm-derived GnRH cells, or different programs are used for cell specification in the neural crest vs. in the preplacodal ectoderm-derived GnRH cells (Shan et al., 2020). However, this was not able to be reproduced in zebrafish (Aguillon et al., 2018).

Precursors originating from the neural crest will also produce special glial cells termed "olfactory ensheathing cells" (OECs) (Barraud et al., 2010; Forni et al., 2011b). OECs and GnRH neurons have been described to form the migratory mass with other neurons types (Barraud et al., 2010). Indeed, the migratory mass is composed of two different sets of precursors that give rise to different neurons, with neuronal precursors located in the center and glial precursors on the periphery (Blanchart et al., 2011; De Carlos et al., 1996; Farbman et al., 1998; Hilal et al., 1996; Key and Wray, 2000; Miller et al., 2010; Tobet et al., 1996a; Valverde et al., 1993, 1992; Verney et al., 1996; Wray et al., 1996, 1989b). The migratory mass and, more specifically the OECs are essential for the extension of olfactory axons, vomeronasal axons, and the formation of terminal nerves (De Carlos et al., 1995). However, OECs have been mainly studied in the context of neural regeneration with some promising results in animals that need to be reproduced in humans (for review Reshamwala et al., 2019). In fact, OECs do not only promote axon growth but are also easily accessible within the nasal cavity (from those lining the olfactory epithelium), making them a good tool for neural repair therapies (Ekberg et al., 2012). As we will discuss below, it is important to note that OECs are not a uniform population of cells in the main and accessory olfactory system (Ekberg et al., 2012; Geller et al., 2013; Geller et al., 2017; Windus et al., 2010). While several molecules are considered to be markers of OECs, they are not necessarily universally expressed by OECs (Fig. 2B-I). The sub-populations of OECs seem to play different roles depending on their anatomical position and/or the markers they express (Ekberg et al., 2012; Geller et al., 2017). The role of these glial cells in GnRH development was proposed and studied only within the last decade.

2. The inductors of GnRH neurogenesis and OECs genesis

Neurogenesis is the result of different cellular events (which are cell proliferation, apoptosis, cell-fate commitment, and differentiation), and implies numerous molecular actors. These last 20 years, the utilization of different knock-in mouse lines and Cre-lox-mediated lineage allowed researchers to demonstrate the involvement of various factors in GnRH neurogenesis (Fig. 1). Decreased Fibrobast growth factor 8 / Fibroblast growth factor receptor 1 (FGF8/Fgfr1) signaling impaired GnRH neurogenesis and seems to be the result of a more general defect in *Bmp / Nog* signaling, which is responsible for craniofacial dysmorphism (Chung et al., 2008; Falardeau et al., 2008; Forni et al., 2013; Kawauchi et al., 2005). As well, the loss of a chromatin-remodeling protein named Cdh7 mainly disrupts GnRH neurogenesis in the mouse models and could be done through transcriptional regulation of Fgfr1, Bmp4 and Oxt (Kim and Layman, 2011; Layman et al., 2011). Genetic mutations of these factors cause human pathologies, such as idiopathic hypogonadotropic hypogonadism and Kallmann syndrome (Falardeau et al., 2008; Goncalves et al., 2019). Using rodent models, it was shown that the absence of a FE65 functional WW domain signaling (also known as APBB), induced a longer proliferative period and generation of an extra number of GnRH neurons (Forni et al., 2011a). GnRH neurogenesis was compromised in Nhlh2 KO and Nhlh1 KO mice, which are both proteins that belong to a subgroup of the bHLH transcription factor family (Schmid et al., 2020). Concomitant knockdown of Nhlh2 and the pheromone receptors VN4/V2Rs (whose expression is controlled by Nhlh1 or β2-microglobulin) prevent GnRH neurogenesis. However, only Nhlh2 mutants show signs of hypogonadal hypogonadism, while mice lacking Nhlh1 are fertile (Cogliati et al., 2007, 2002; Coyle et al., 2002; Good et al., 1997; Kruger and Braun, 2002; Kruger et al., 2004; Nilaweera et al., 2002). Another subgroup of a bHLH transcription factor named Ascl1 has been also involved in the neurogenesis of GnRH neurons as well as olfactory receptor neurons and vomeronasal neurons (Tucker et al., 2010). Although all OECs and 30% of GnRH neurons come from the neural crest, the existence of common factors involved in their respective genesis is not known. For example, while crucial for GnRH neurogenesis, *Ascl-1* is not required for normal OECs development (Taroc et al., 2020). *Gli3* loss-of-function, which compromises the onset of Ascl-1 vomeronasal progenitors, impacts the formation of OECs in the nasal mucosa and results in significant defects in GnRH neuronal migration but does not alter GnRH neurogenesis. Thus, the existence of common factors involved in both OEC and GnRH genesis has yet to be further explored. Using transcriptional approaches, recent studies identified 25 novels OECs markers, as well molecular mechanisms which could be involved in both OEC development and GnRH neurogenesis (Perera et al., 2020).

3. The migration of GnRH neurons involves OECs

During the past 30 years, the migration pathway of GnRH neurons has been well described, initially in rodents and later in humans (Fig. 1). The description was first proposed using immunohistochemistry (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989b) and afterward by using time-lapse imaging in embryonic slices or nasal explants (Bless et al., 2005; Casoni et al., 2012; Tobet et al., 1996b). There are now abundant reviews that describe it: according to PubMed, 141 reviews mention this atypical development and migration (Wierman et al., 2011; Wray, 2002). We will therefore present the phases of migration of GnRH neurons before considering the role of OECs in this process.

In vivo, GnRH neurons migrate from the vomeronasal organ to the preoptic area in the diencephalon (about 0.5–1 mm) between E11.5 and E13.5 in mice and 32 days and 20 weeks in humans (Casoni et al., 2016; Schwanzel-Fukuda et al., 1989, 1996; Wray et al., 1994). This migration can be divided into four different steps (Figs. 1, 2A):

(1) migration into the nasal septum, which requires GnRH neurons

Table 1
Summary of GnRH neuronal development in various mammalian species.

	Birth date (first detection of GnRH)	Brain entrance	Final destination	Axons in ME	Gestation (duration in days)	Ref.
Mouse	E10	E13.5	E16.5	E18	20 days	(Schwanzel-Fukuda et al., 1989) (Wray et al., 1989b)
Sheep	E26	E35	E45	E60	145 days	(Caldani et al., 1995)
Human	39 days CS[a] 16	48 days CS19	–	–	285days	(Schwanzel-Fukuda et al., 1996) (Casoni et al., 2016)
Macaque	32 days	38 days	47 days	50 days	166 days	(Ronnekleiv and Resko, 1990) (Quanbeck et al., 1997)
Rat	E13.5	E14.5	E18.5	_	21 days	(Daikoku et al., 1981)

[a] Carnegie stage.

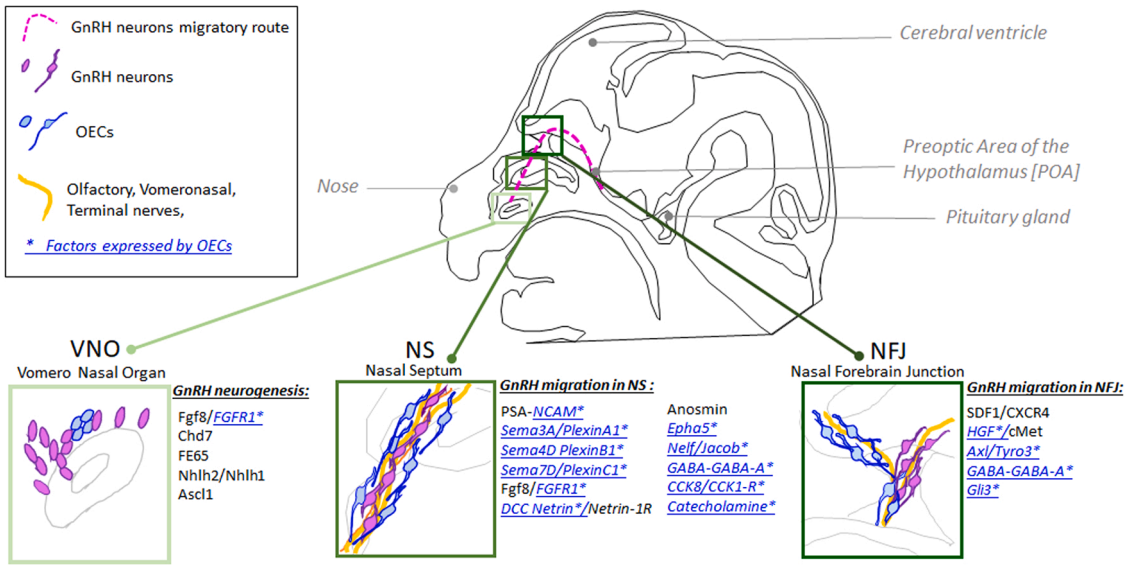

Fig. 1. Graphical Abstract illustrating OECs and GnRH neurons co-migration along the axons/nerves of the accessory olfactory system on a head sagittal section of the mouse embryo. The main factors involve in GnRH ontogenesis and migration are listed and those that are expressed by OECs are underlined in blue.

soma motility and specific factors that promote or inhibit adherence to the terminal and vomeronasal nerve (VNN) axons; (2) crossing the cribriform plate which involves the fasciculation of terminal and VNN nerves; (3) pausing at the nasal-forebrain junction (NFJ) before resuming migration and entering the brain; (4) intracerebral migration follows the projection of the terminal nerve that turns ventro-caudally towards the preoptic and disperses towards their final location through forming a continuum between the preoptic area and the hypothalamus (for review Wierman et al., 2011; Wray, 2002).

For several years, it was considered that the GnRH neurons relied only on olfactory/VNN axons to initiate their tangential migration. However, as described above, OECs and neurons, including GnRH neurons, migrate from the olfactory placode to the telencephalon in the migratory mass (Barraud et al., 2010). In this context, we explored a possible spatiotemporal co-migration of OECs and GnRH neurons a few years ago (Figs. 1, 2A). We demonstrated that OECs are associated with GnRH neurons during nasal and telencephalic migration in mice (Geller et al., 2013, 2017) and raised the question of the role of these glial cells in GnRH migration. It has been shown that axonal migration is necessary but not sufficient for the migration of GnRH neurons suggesting the involvement of another factor(s). In fact, *Semaphorin4D* KO mice presented a normal extension of vomeronasal axons but a lack of GnRH neuron migration (Dacquin et al., 2011; Giacobini et al., 2008). Semaphorin 4D/PlexinB1 is expressed by OECs (Geller et al., 2013; Shyu et al., 2008; Wang et al., 2018). Several regulators of GnRH neuronal migration are expressed by OECs (Fig. 1). We found that the OEC [GFAP-GFP+] associated with GnRH neurons also expressed Nelf/Jacob, a nuclear protein known to regulate GnRH neuronal migration (Fig. 1) (Geller et al., 2013; Xu et al., 2010). The polysialic acid-rich form of Neural Cell Adhesion Molecule (PSA-NCAM) is an adhesion molecule highly described in the regulation of GnRH neuron migration and expressed by OECs, as well by VNN and TN fibers (Franceschini et al., 2010; Franceschini and Barnett, 1996; Oprych et al., 2017). Removal of PSA groups by endoneuraminidase N (endoN) injected in embryos led to a disruption of GnRH neuronal migration in mouse and chick (Murakami and Arai, 2002; Yoshida et al., 1999). Deleted in Colorectal Cancer (DCC), a vertebrate receptor for the guidance molecule netrin-1, is also expressed by OECs, olfactory and vomeronasal axons, and is known to regulate GnRH neuron migration. In $DCC^{-/-}$ mice, nasal migration of GnRH neurons is normal, but once they penetrate the brain tend to follow a more dorsal route resulting in an inappropriate destination (Schwarting et al., 2001). Semaphorin 3 A (Sema3A) is also expressed by OECs and GnRH neurons failed to enter the brain in mice lacking Sema3A (Cariboni et al., 2011; Schwarting et al., 2000). Interestingly, Sema3A induced the collapse of OECs and inhibited OEC migration (Wang et al., 2018). The gradient distribution of Sema3A in the olfactory bulb (OB) may stop OEC migration in the olfactory nerves layer at the level of nasal forebrain junction and thus could be one of the factors responsible for the OECs pause at this level.

Specific disruption of OECs development induced a default of GnRH neuron migration. Two independent groups demonstrated that the absence of *Sox10*, which is expressed by [BLBP+] OECs, induced the disruption of OEC differentiation and caused an accumulation of olfactory axons in the ventromedial nerve layer of the embryonic OB, as well as slowed the migration of GnRH neurons into the forebrain (Fig. 1) (Barraud et al., 2013; Pingault et al., 2013). As introduced above, Gli3 loss-of-function leads to an almost complete loss of OECs (which are [Sox10 +] and [BLBP+]) and prevents the entry of GnRH neurons in the forebrain (Fig. 1) (Taroc et al., 2020).

Many other factors expressed by OECs could be involved in GnRH neuron migration. Based on bulk RNA-seq data obtained from developing [Sox10 +] cells isolated *via* laser-micro-dissection and considered as OECs (Perera et al., 2020), we were able to list some factors that could be expressed by these cells during embryonic development and that are known to be involved in GnRH neuronal migration (Fig. 1, Table 2). The development of OMIC approaches combined with transgenic mice models but also single-cell RNAseq offers the opportunity to discover new genes expressed by OECs that could be associated with Idiopathic hypogonadotropic hypogonadism (IHH).

Moreover, OECs could regulate the migration of GnRH neurons also by controlling their activity. We recently demonstrated that OECs regulate the electrical activity and $[Ca^{2+}]$ transients of migrating GnRH neurons and thus could regulate their speed of migration (for review Medvedeva and Pierani, 2020; Pinet-Charvet et al., 2020, 2016). Calcium plays a major role in growth cone formation and in contracting actin filaments and other cytoskeleton components. Blocking or enhancing Ca^{2+} signaling respectively inhibited or increased GnRH neuronal migration (Hutchins and Wray, 2014). Thus, we can hypothesize that calcium signaling regulated by OECs is involved in GnRH migration.

Table 2
Factors expressed by OECs and involved in GnRH neuronal migration and olfactory nerve projection.

Molecule/ receptor	Classification	Target	Location	Human pathology
PSA-**NCAM**	Adhesion molecule	GnRH, Olf	Nasal septum	
Anosmin	Adhesion molecule	GnRH, Olf	Nasal septum	Kallman disease
EphA5/EphA, EphB	Guidance factor (repulsive)	GnRH, Olf	Nasal septum	
Nelf	Guidance factor (attractive)	GnRH, Olf	Nasal septum	Kallman syndrome
Netrin-1/ Netrin-1R	Guidance factor (attractive)	GnRH, Olf	Nasal septum	
Reelin	Guidance factor (attractive)	GnRH	Nasal septum	
Semaphorin 4D/Plexin/ HGF	Guidance factor (attractive)	GnRH	Nasal septum	
Semaphorin 3A/ Neuropilin 2/ **Plexin A1**	Guidance factor (attractive)	GnRH, Olf	Nasal septum	Kallman syndrome
SDF1/**CXCR4**	Growth factor (repulsive)	GnRH, Olf	Cribiform plate, brain	
FGF8/**FGFR1**	Growth factor (attractive)	GnRH, Olf	Nasal septum	Kallman syndrome, HH
HGF/cMet	Growth factor (attractive)	GnRH, Olf	Cribiform plate, brain	
Axl/Tyro3	Growth factor (attractive)	GnRH	Cribiform plate, brain	
GABA / **GABA-A**	Neurotransmitter (repressor)	GnRH, Olf	Septum nasal, Cribiform plate, brain	
CCK8/**CCK-1R**	Neurotransmitter (repressor)	GnRH, Olf	Nasal septum	

HH = hypogonadotropic hypogonadism **Red = expressed by OECs.**

4. Multiple OECs players could be involved in GnRH neurons differentiation

GnRH neurons are differentiated at the early stages of development, 1–2 days after precursors division [at E11.5 in mouse] (Jasoni et al., 2009; Wray et al., 1989a). Several studies explored the role of glial cells in peri-pubertal GnRH maturation and more recently during infancy (Ojeda et al., 2010; Pellegrino et al., 2021; Sharif et al., 2013; Sinchak et al., 2020; Srivastava et al., 2011). However, the role of glial cells in peri-natal GnRH neuron maturation and embryonic development is not well known (Geller et al., 2017).

Migrating GnRH neurons present the first morphological differentiation. In the VNO epithelium, GnRH neurons are round-shaped with no or very short neurites (Fig. 1). During their nasal migration, the soma adopts an ovoid shape and they develop two short neurites (from E11.5-E16.5 in mouse) (Schwanzel-Fukuda et al., 1996; Wray et al., 1989b). At the nasal forebrain junction, GnRH neurons and OECs halt their migration, and GnRH neurons grow long neuritic processes. This morphological transition has been associated with the maturation of the GnRH peptide and its detection in the trans-Golgi network (Wray, 2002). The moment of crossing the nasal forebrain junction is a key period for GnRH neuronal differentiation. Early entry of GnRH neurons into the brain results in decreased GnRH expression. We have recently observed that OECs associated with GnRH neurons exhibit a phenotype change across regions, and specifically at the level of this junction (Fig. 2B-G) (Geller et al., 2017). Mainly GFAP+ OECs are present in the nasal septum and BLBP+ cells in the cribriform plate (Fig. 2B-C). In this context, we explored the role of GFAP+ OECs in GnRH neuronal differentiation. Depletion of GFAP+ OECs caused a decrease in GnRH neurite outgrowth, suggesting that OECs play a key role in the morphological differentiation of GnRH neurons during nasal migration (Geller et al., 2017). The importance of OECs sub-population on GnRH neuron migration at the level of the cribriform plate needs to be further explored, as well as the involvement of OECs molecular heterogeneity in varieties of hypogonadotropic hypogonadism.

During their migration, GnRH neurons also present a functional differentiation. GnRH expression gradually increases between E12.5-E19.5 in mice and the proportion of GnRH neurons expressing the mature form of GnRH increases from E12.5-E14.5 (Livne et al., 1993; Simonian and Herbison, 2001). Large dense core vesicles (LDCV) immunoreactive for GnRH are detected at E14.5 in rat embryos (Zheng et al., 1992). All these findings show that GnRH secretion can occur during GnRH neuronal migration in rodents. However, GnRH neurons in hpg mice are present in normal size and distribution suggesting that GnRH secretion/production is not required for their migration (Gill et al., 2008). GnRH release was demonstrated *in vitro* using E11.5 mouse embryo nasal explants and showed the development of episodic secretions between 3 days *in vitro* (div) and 7 div, reaching a maximum of 14 div (Constantin et al., 2009). Interestingly, GnRH secretion was episodic and correlated with the synchronization of intracellular calcium events between 30% or more GnRH neurons. As described above, OECs regulate GnRH episodic secretion as well as $[Ca^{2+}]$ events in migrating GnRH neurons, suggesting an involvement of these glia cells in the functional differentiation of these neurons (Pinet-Charvet et al., 2020, 2016). Moreover, the existence of a variety of OECs sub-populations (Fig. 2B-I) raises the question of their role(s) in the functional heterogeneity of GnRH neurons observed in the adult brain.

Further studies are required to determine the OEC factors that induce morphologically and functional differentiation of GnRH neurons. According to the presence of BLBP+ OEC-like cells in the mouse diencephalon and their role in the regulation of GnRH neurons activity and secretion, it could be interesting to investigate the localization and role of OECs in the adult hypothalamus (for review Clasadonte and Prévot, 2018; Pinet-Charvet et al., 2020, 2016; Sharif et al., 2013). Common characteristics between OECs and astrocytes are well known, as also between macroglia aldynoglia [which correspond to OECs, tanycytes, and Muller cells] (Gudino-Cabrera and Nieto-Sampedro, 1999; Ramon-Cueto and Avila, 1998).

5. OECs role(s) in default of GnRH development, congenital/ idiopathic hypogonadotropic hypogonadism, and Kallman Syndrome

Defects in neurogenesis and/or migration of GnRH can lead to the development of Kallman Syndrome (KS), a genetic disorder characterized by pubertal failure due to congenital Hypogonadotropic Hypogonadism (HH) and anosmia (impaired sense of smell), or to normosmic idiopathic hypogonadotropic hypogonadism (nIHH). This is a clinically and genetically heterogeneous disease described by many reviews (for review Grinspon, 2021; Louden et al., 2021). In the last three decades, various causal genes for KS have been identified. The disruption of these genetic pathways leads to KS through aberrant development of olfactory placode derivatives and/or impaired migration of GnRH neurons. The prevalence of KS has been estimated at 1 in 8000 males and 1 in 40,000 females (for review Pingault et al., 2013). To date, many genes (*namely KAL1 (ANOS1), NELF, SEMA3A, SEMA7A, AXL, FEZF1, CCDC141, IGS10, FGFR1, FGF8, PROKR2, PROK2, WDR11, HS6ST1*, CHD7*)* have been implicated (Table 2), but mutations in any of these genes have only been identified in approximately 30% of KS individuals (for review Latronico, 2019; Pingault et al., 2013), which indicates that other genes involved in the disease remain to be discovered.

Of the known KS genes, two genes, *SOX10* and anosmin-1 (*ANOS1*), have been recently identified as key factors controlling OEC development (Fig. 1, Table 2) (Barraud et al., 2013; Hu et al., 2019; Pingault et al., 2013). Human *Sox10* mutation was first described to be implicated in the Waardenburg syndrome (characterized by the association

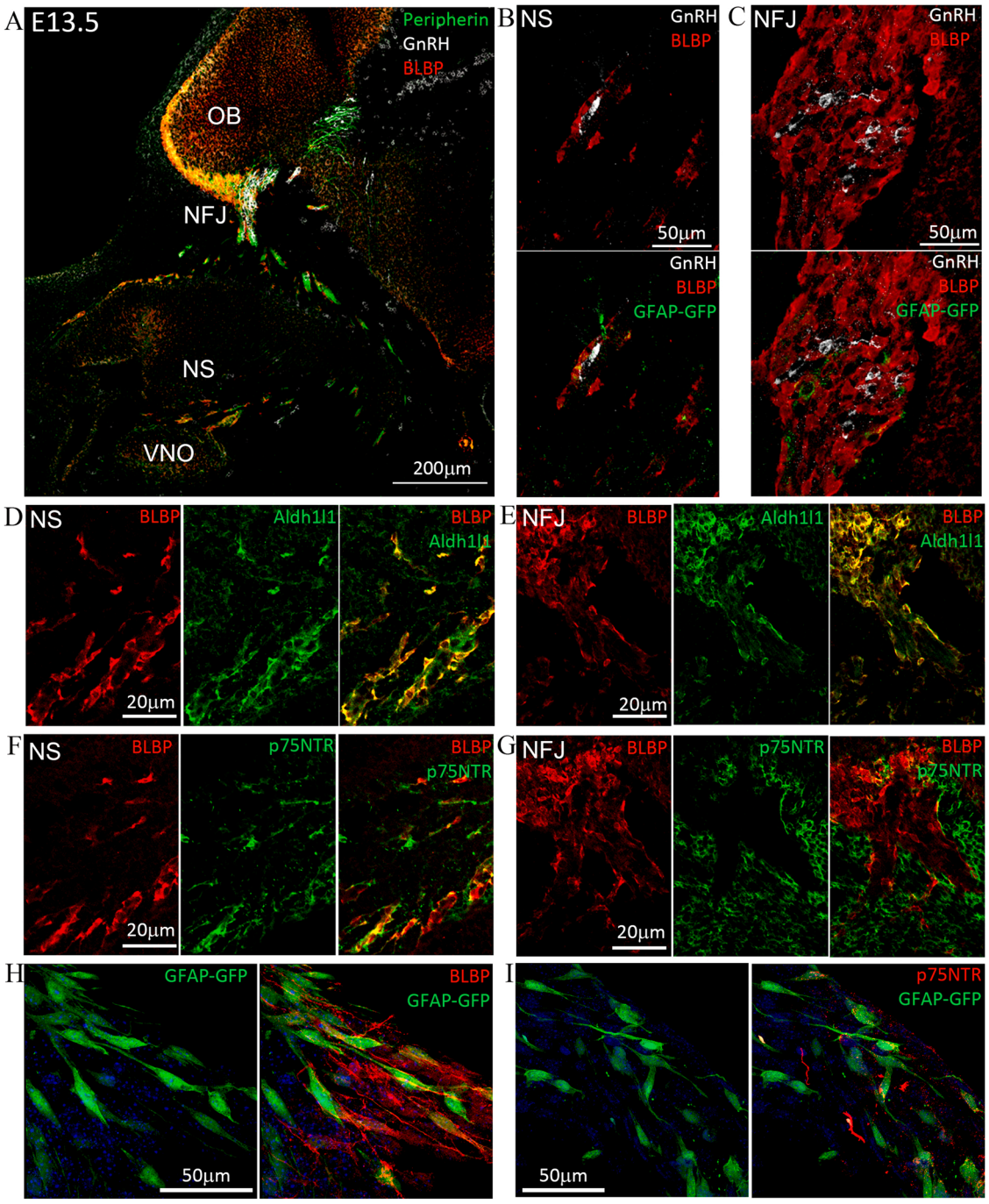

Fig. 2. Molecular heterogeneity of OECs associated with GnRH neurons in migration, A. Para-sagittal mouse embryo head section illustrating the distribution of GnRH neurons and OECs [BLBP+] along [peripherin+] axons at E13.5. B-G. [GFAP-GFP+] OECs and OECs immunoreactive for glial cells markers Aldh1L1, p75NTR, and BLBP in the nasal septum (NS) and nasal forebrain junction (NFJ) along GnRH neurons migratory pathway at E13.5. H-I 3D representation of [GFAP-GFP+] OECs labeled with BLBP or p75NTR in mouse nasal explant cultures after 10 days *in vitro*. VNO: Vomeronasal Organ, OB: Olfactory bulb.
[B-G are adapted from Geller et al. 2017].

between pigmentation abnormalities and deafness) (Barnett et al., 2009; Bondurand et al., 2007) and more recently in the Kallmann syndrome (Pingault et al., 2013). It was shown that a SOX10 loss-of-function mutation appears in approximately one-third of KS individuals with deafness. Interestingly, disruption of OEC differentiation and thus a default of GnRH neuron migration to the forebrain is present in SOX10-null mutant mice (Barraud et al., 2013). Loss of function of the extracellular matrix protein *ANOS1*, encoded by the X-linked *KAL-1* gene, is almost invariably associated with a highly penetrant phenotype of pubertal failure with an abnormal sense of smell, frequently resulting from olfactory dysgenesis. Recent evidence suggests that *ANOS1* may also modulate glial cell development and this may result from its effect on enhancing FGF8 activity while inhibiting BMP5 and Wnt3a signaling (Endo et al., 2012). Furthermore, knock-down of *Anos1* in olfactory placodes of chick embryos resulted in a complete absence of Sox10 + OECs, an emergence of GFAP+ OEC, and poorly organized BLBP+ OEC of outmost OB (Hu et al., 2019). Moreover, these phenotypes are associated with a loss of OB innervation by olfactory axons (Hu et al., 2019). Interestingly, overexpression of *ANOS1* or *FGF2* in immature OECs from embryonic OB inhibits ectopic GFAP expression.

These data demonstrate that the function of the anosmin-1 is to regulate OEC maturation (*via* FGF signaling), thus providing a permissive glial environment for a projection of the axons to the OB (Fig. 1, Table 2). Finally, a *GLI3* loss-of-function variant in a KS individual was recently identified and validated (Taroc et al., 2020). Due to its role in VNO neurogenesis, targeted next-generation sequencing (NGS) identified *GLI3* genetic variants associated with IHH cases (Johnston et al., 2010). As described above, *Gli3* loss-of-function compromises the onset of Ascl-1^{+} vomeronasal progenitors, the formation of OECs in the nasal mucosa, and impairs GnRH neuronal migration to the brain (Fig. 1, Table 2) (Taroc et al., 2020). All these findings not only provide new insights into GnRH neurons and OECs development but also demonstrate that several mutations of OEC expressed genes contribute to KS's etiology (Table 2).

Finally, recent observations raise the question of the role of the OECs in the induction of HH in the inflammatory maternal environment. Inflammatory responses require the activation of immune and inflammatory cells by increased cytokine secretion and cell migration (Lee et al., 2019). A recent study showed that cytokines modulate olfaction through ensheathing glia on drosophila (Cai et al., 2021). OECs express a wide range of cytokine receptors (Lin et al., 2019); and cytokines induce a metabolic reprogramming of ensheathing glia, thus affecting olfactory neurons (Cai et al., 2021). Previous studies have shown that lipopolysaccharide (LPS)-induced maternal inflammation affects GnRH neuronal development in fetal rodents and induces disruptions of the hypothalamic-pituitary-gonadal axis in pre- and post-pubertal periods (Izvolskaia et al., 2016; Sharova et al., 2015). Hence, in an inflammatory maternal environment, the default of GnRH neuron migration could be explained by the modulation of OECs phenotypes by cytokines. On the other hand, OECs can affect LPS-induced microglial activation profiles (Xie et al., 2019). They can also moderate the inflammatory microenvironment (Xie et al., 2019) and thus lessen the harmful effects of inflammation on GnRH neuronal development. Finally, SARS-COV-2 infections during pregnancy are associated with robust inflammatory responses at the maternal-fetal interface (Lu-Culligan et al., 2021). This data raises many questions about OECs and their relation to SARS-COV-2 inflammatory responses. SARS-COV-2 crosses the blood-brain barrier (Zhang et al., 2021). Moreover, it is known that vertical transmission of the SARS-CoV-2 virus from mother to fetus in the third trimester is possible; but it remains unclear whether SARS-CoV-2 directly affects the embryo earlier in the development (Lee, 2021; Weatherbee et al., 2020). If this hypothesis is validated, GnRH neuronal development could be affected by the virus. It is known that angiotensin-converting enzyme 2 (ACE2), the required virus entry receptor, is expressed by the large majority of GnRH-labeled nervus terminalis neurons (Bilinska et al., 2021). Future studies should be performed on the potential effect of inflammation on OECs and GnRH neuron development.

6. Conclusion

During the last 10 years, a growing number of studies have pointed out the importance of crest-derived OECs in both normal and abnormal GnRH neuronal development. OECs seem to be key players in different processes of GnRH neuronal ontogenesis according to their phenotype and/or maturation level. However, mechanisms and factors through which OECs regulate GnRH ontogenesis are still not well known and need additional studies. All these discoveries raise questions about the effects of OECs' molecular diversity on i) GnRH neuronal heterogeneity observed in adult hypothalamus and ii) the diversity of phenotypes observed In HH patients. The role of OECs in the etiology of KS defects and other syndromes exhibiting subfertility is worth being further explored.

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Declarations of interest

The authors declare no financial conflicts of interest.

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