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FROM THE PERIPHERY TO THE BRAIN: WIRING THE OLFACTORY SYSTEM

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Abstract

The olfactory system represents a perfect model to study the interactions between the central and peripheral nervous systems in order to establish a neural circuit during early embryonic development. In addition, another important feature of this system is the capability to integrate new cells generated in two neurogenic zones: the olfactory epithelium in the periphery and the wall of the lateral ventricles in the CNS, both during development and adulthood. In all these processes the combination and sequence of specific molecular signals plays a critical role in the wiring of the olfactory axons, as well as the precise location of the incoming cell populations to the olfactory bulb. The purpose of this review is to summarize recent insights into the cellular and molecular events that dictate cell settling position and axonal trajectories from their origin in the olfactory placode to the formation of synapses in the olfactory bulb to ensure rapid and reliable transmission of olfactory information from the nose to the brain.

Keywords

• Olfactory bulb • Ensheating cells • Olfactory placode • Olfactory epithelium • RT-PCR • Embryo • Mice • Sensory neurons • Molecular signaling • Glomerulus

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Introduction

Chemical signals are likely the most ancient form of communication, and many behavioural responses are based on olfactory information. The olfactory system is composed of two different but complementary structures: the main olfactory system, which detects volatile odorants in the environment [1], and the accessory olfactory system, which mostly detects the non-volatile components of chemical signals, processing reproductive and social behaviours, through the detection of pheromones [2,3]. Nevertheless, this functional classification is not that rigid, since both systems are capable of responding to each other's stimuli [4-7]. Thus, the olfactory system shows an unusual plasticity rarely seen in other structures within the nervous system. The present review focuses on the development of the main olfactory system.

Main olfactory system overview

The structure of the main olfactory system was first described at the turn of the nineteenth century by Golgi [8] and Cajal [9,10], as formed by the olfactory epithelium (OE), olfactory bulb (OB) and olfactory cortex (OC). The OE consists of a pseudostratified columnar epithelium, located at the caudal part of the nasal cavity and formed by supporting cells, globose basal cells and olfactory sensory neurons (OSN). Odorant receptors (OR) are localized on the cilia of the OSN dendrites, directly exposed to the lumen of the nasal cavity. Five million OSN populate the OE, and each one expresses just one gene [11,12] of the about 1300 OR genes, from which about 20% are predicted to be pseudogenes [13-15]. Humans have fewer OR coding genes (640), of which 46% are pseudogenes [16]. Those OR are not spread over the entire OE but are restricted to four zones based on the expression pattern of a few OR [17,18]. OSN expressing the same OR target the same glomeruli [19-21]. Deletion or replacement of an OSN receptor results in an OSN axon misguidance into the glomeruli [21,22]. OSN expressing their receptor coalescence at embryonic day 12 (E12) when the first homotopic axonal segregation takes place through the cribose plate [23]. Then, OSN axons in the olfactory bulb join into glomeruli, establishing stereotypic connections in the glomerular layer with periglomerular cells and dendrites of mitral/tufted (M/T) cells. M/T cells are the primary OB projection neurons and project to different brain areas forming the lateral olfactory tract (LOT) [24-29], relaying odorant-elicited signals to the olfactory cortex. As occurs in the projections from OE to OB, the LOT shows a spatial rearrangement of the axons depending on the projection neurons' position within the OB [30]. This topographical organization is dependent on the neurogenesis of the projection neurons [30,31] and within the LOT, also serves as a spatial rearrangement of the cortical connections.

Unlike other sensory systems, some of the neuronal populations in both OE and OB are replaced throughout the whole life span of the animal [32]. In the OE, newly generated OSN [33] are able to project to the correct glomeruli [34]. In the OB, newly generated interneurons migrate either from the SVZ, in postnatal ages, to repopulate the glomerular and granular layers of the OB [35-39] or, from the lateral ganglionic eminence, at embryonic stages [40]. Interestingly, the percentage of adult-born neurons in the granular layer remains constant at approximately 10%, while the proportion of adult-born neurons in the glomerular layer

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increases over time [41]. In fact, almost all classes of periglomerular interneurons undergo adult neurogenesis, including glutamatergic short axon cells [42]. Thus, the olfactory system shows a solid and well-structured relationship between the central and peripheral nervous systems and, at the same time, a high level of plasticity that allows the integration of new neurons and sensory axons, thus preserving its ability to process the olfactory information.

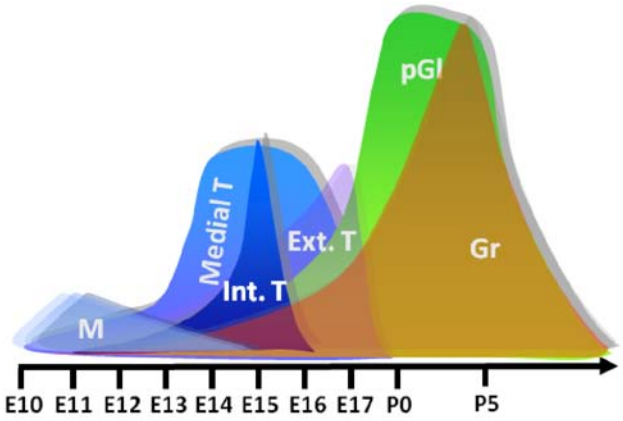
In this work, we will focus on the generation and development of the afferent sensory fibres into the OB, since it constitutes not only the first relay station in the transduction of the olfactory information into the CNS, but also the source of molecules and cell populations implicated in the growth and guidance of the incoming sensory axons into the OB, in both stages, during development and in adulthood.

Early differentiation of the olfactory sensory neurons — how does the connectivity work?

The OE is the first structure that develops during embryogenesis; it arises from the olfactory placode (OP), a thickening of the surface ectoderm, visible at E9 in the rostral prosencephalon of mice. One day later, the placode invaginates to form the olfactory pit from which several cell populations migrate to the telencephalic vesicle, both in rodents [43-47] and chick [48]. These cells form a heterogeneous population expressing a different variety of markers as they migrate towards the CNS (see below). During these early stages, and despite the absence of a fully anatomically differentiated OB, projection neurons have already undergone generation and differentiation processes [49-52]. The close developmental timing between OE and OB raises the question whether the early OE axons play an inductive role in the OB protrusion and projection neurons' generation [53,54]. Nevertheless, in the Pax-6$^{Sey\text{-}Neu}$ mutant mice, where the OE is absent, exists a structure called olfactory bulb-like structure (OBLS) [51,55]. This structure has projection neurons which give rise to a lateral tract where their axons project to cortical caudo-ventral areas. As we will describe in depth, the OSN axons play an important role in the OB development; however, they do not induce the generation of the projection neurons (first OB neurons generated in the development), since they reach to the OB primordium at E12 in mouse [56] when the first projections neurons are already generated (Figure 1).

Role of the migratory mass in olfactory bulb development — ensheathing cells, the pillars of axonal growth

Another striking event that follows the development and differentiation of the OE is the generation and migration of several cell populations towards the rostral telencephalic vesicle (Figure 2A, B). Here we focus on the migratory mass (MM) [44,57], formed by a mix of glia and neuronal migrating cells, closely related to the OSN axons and contributing to the OB development. The nature of these cells remains controversial, since they are mainly identified by the expression of neuronal markers such as GAP-43 [58], β-III-tubulin [47] and the vesicular glutamate transporter type 2 [59]. An elegant and acute analyses of the MM



Celullar types		Generation times
Mitral cells		E11-E15, peak E12[1]
Tufted cells	External	E10-E18, peak E17[1]
	Medial	E10-E18peak E14-E16[1]
	Internal	E11–E16 peak E15[1]
Interneurons	Periglomerular	E12-adult, peak E18-P5[2]
	Granular	E11-adult, peak P5[2]

Figure 1. Generation time curves of the different olfactory bulb cell populations during development. First generated cells are the projection neurons and then the interneurons. Interneuron generation continues through the whole life. [1] [49,51] [2] [49,153-155]

described the existence of a heterogeneous neuronal labelling of DCX, OMP, DNER, GnRH, and Lhx2 [60]. However, we recently recognized that heterogeneous neuronal labelling could also correspond to growing axons [61] and a wide range of glial markers, such as S100β, GFAP or BLBP, are expressed in the MM [62,63]. Moreover, GFP-retrovirus-infected MM cells, colabelled with the neurogenic marker BrdU, revealed the existence of cell proliferation within the MM. In addition, MM-cells coexpress the neural stem cell markers, Sox2 and nestin, which enhances the idea of the MM as a niche of glial and progenitor cells that give rise to different glial cells along the OSN pathway, both in the mesenchyme and in the glomerular layer of the OB. Furthermore, these GFP-infected MM cells express the glial markers GFAP, p75, S100β and BLBP, but none express neuronal marker [61]. In addition, these GFP-infected MM cells were always intimately related to the glomeruli and axons bundles across the mesenchyme, both common features of olfactory ensheathing cells (OEC) [43,64,65]. This fact raises the possibility that MM is a niche of newly generated ensheathing cells at early embryonic stages. This hypothesis supports the in vitro idea that OECs facilitate the growing of the OSN axons through the mesenchyme and their implication in the axonal segregation into the glomeruli [66-75]. Furthermore, activation of Wnt/β-catenin signalling, in Wnt reporter TOPgal transgenic mice, labels a subpopulation of OECs in the most external part of the OB, in a dependent way [76], through its canonical pathway [77], playing an important role in the sorting of OSN axons and glomerulus formation. To sum up, the MM is not just a bulk of cells migrating with the axons, but rather a necessary axonal scaffold to grow towards the OB. Whether the OB sends or produces some type of molecular signal for these migrating cells still remains to be elucidated. So far, possible chemoattractive role of the OB on the migrating olfactory cells

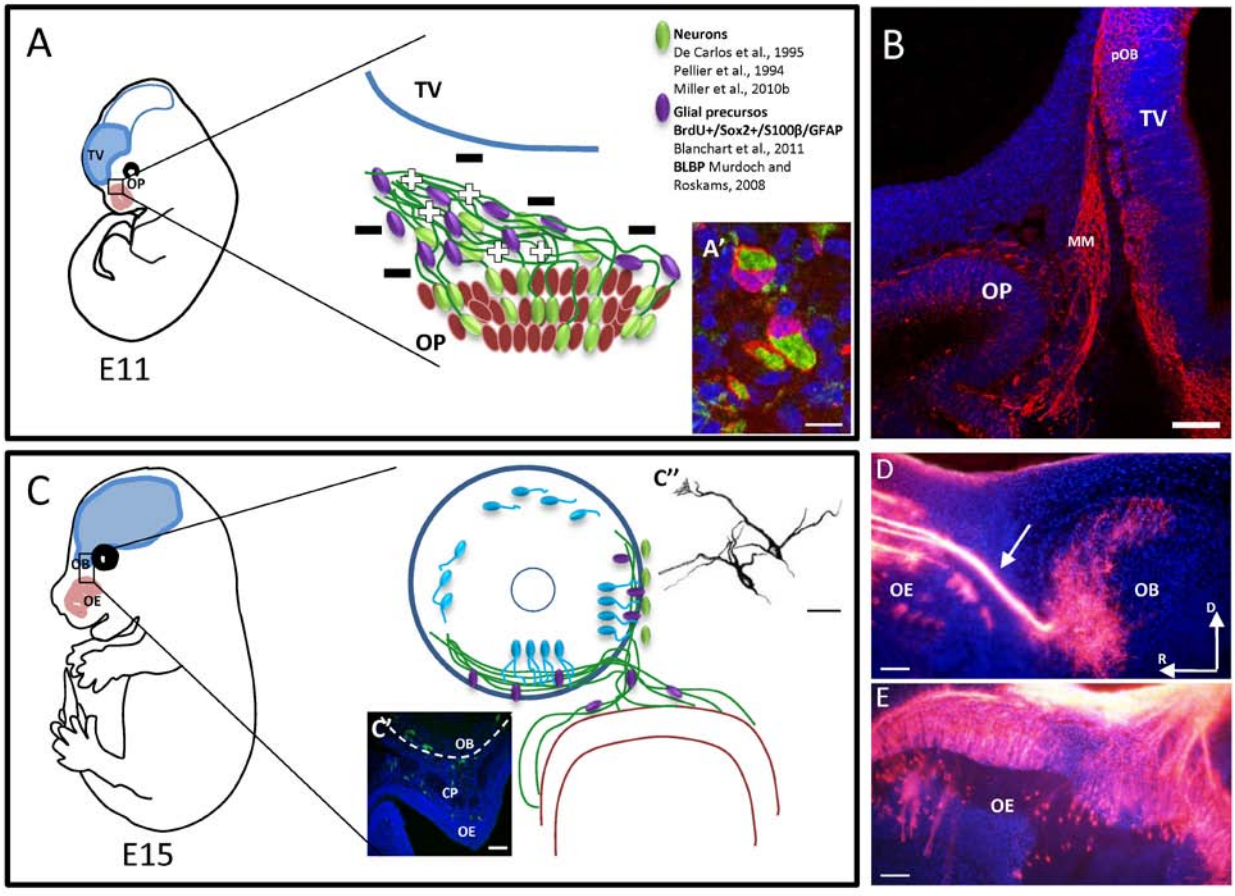


Figure 2. Schematic representation of the earlier stages in the olfactory system development. A. At early stages olfactory placode gives rise to the olfactory pit (OP). From hereafter several cell populations from the OP migrate together with olfactory axons towards the telencephalic vesicle (TV), forming the Migratory Mass (MM). Neurons (green) and glial precursors (purple), follow a pathway defined by the expression of molecular cues from mesenchyme, the MM cells and from target regions in the TV. A'. Many of these glial precursors processed (S100β+ cells, red) envelop the axon bundles (TuJ1, green). B. At E11, TuJ1 expression (red) labels the OP, MM and the prospective OB in the TV. C. At E15, MM cells are still present in both the mesenchyme and the Olfactory Bulb (purple and inset C', GFP cells), while the axons start to innervate the OB from the ventromedial part to the laterodorsal regions. This event will trigger the reorientation of projections neurons achieving its final position (C''). Simultaneously, the number of synaptic contacts will increase following the same innervation pattern. Still, at this age LHRH, GnRH cells are migrating towards diencephalic areas (green). D, E. DiI crystal into the OE (D) shows the OSN axons (D, arrow) reaching the medial and ventral parts OB, while a DiI injection into the OB (E) labels OSN in the OE. E14, sagittal sections. OB, olfactory bulb; CP, cribriform plate; OE, olfactory epithelium; OP, olfactory pit; MM, migratory mass; TV, telencephalic vesi-cle, pOB, prospective OB. Scale bars, A' = 10 μm, B and C' = 100 μm, C'' = 50 μm, D and E= 100 μm.

was described, where OEC migrate along a gradient concentration of soluble factors released by the OB [78]. Nevertheless, this effect seems unlikely to occur at the beginning of the migration since the mesenchyme situated between OB and OE, contains a wide range of clue molecules that affect both the OSN axonal growth and the OE migrating cells. Thus, the possibility of the OB exerting an attractive effect could most likely occur at the final phase of cell migration into the OB.

The sensitive phase is a key component of connectivity — spatiotemporal development of axonal connections and neurons

The MM fuses with the rostral part of the mouse telencephalon at E12/E13. This event will trigger the initial innervation of OSN axons into the OB, although this process does not occur simultaneously. First, in the sensitive phase, olfactory axons innervate the ventromedial part of the OB and, thereafter, extend to lateral and dorsal regions (Figure 2C-E; [52]). During this phase, between E15/E16, the protoglomeruli are formed; while at E14, the OSN axons stay in the ONL without entering into the inner OB layers. Furthermore, this axonal innervation occurs in parallel with the reorientation of the OB projection neurons [79]. But most importantly, these effects seem to be only exerted at E14-E15, corresponding to the reorientation cell process [51]. This process shares some common features with the development of the olfactory system in *Drosophila*, where the projection neurons are differentiated before the arrival of the olfactory axons [80]. This could be due to molecular signals, derived from either the OE [81] or from the mesenchyme, such as retinoic acid, FGF8, BMPs or Sonic [82]. The lack of projection neuron orientation in the OBLS could be due to the absence of retinoic acid in Pax-6$^{Sey\text{-}Neu}$ [83]. Nevertheless, the question whether the OE axons either exert a trophic effect or secrete certain molecular clues, as inducers of neuronal reorientation, remains unclear. Both the first synaptic contact and its spatiotemporal pattern occur simultaneously with the axonal innervation pattern and reorientation of the OB projection neurons

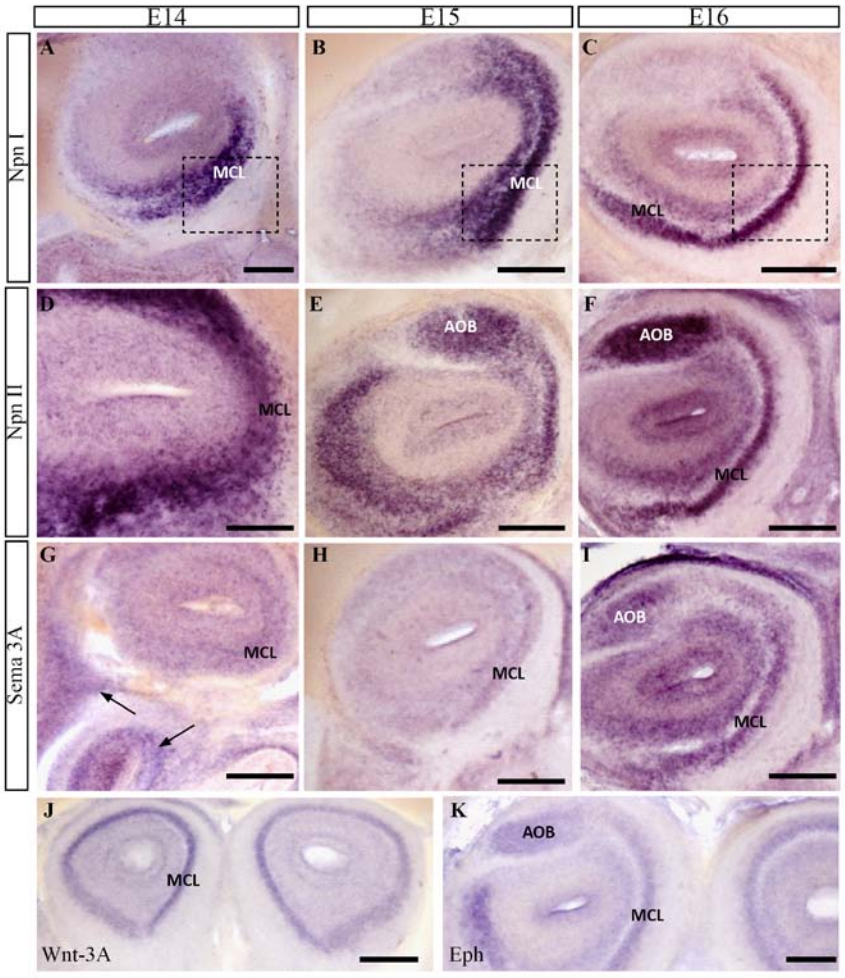


Figure 3. Unchanged expression pattern of several genes implicated in axonal guidance. A-C. ISH for *Npn1* in the OB. *Npn1* expression is mainly restricted to the MCL during the sensitive phase, decreasing the expression intensity level throughout the ages. Boxes represent the OB region selected for the quantitative RT-PCR analyses. D-E. Expression pattern of *Npn2* mRNA. *Npn2* expression is similar to *Npn1*, with the highest expression in the MCL. G-H. *Sema3A*, the Npn receptor, is expressed in both t MCL and mesenchyme (arrows, G). J. At E16, *Wnt-3A* is also expressed in the MCL without any changes during the sensitive phase. K. *Eph* receptor expression is also restricted to the MCL. ISH, in situ hybridization; MCL, mitral cell layer; OB, olfactory bulb. Scale bars, A-C and E- K = 200 µm; D = 100 µm.

[63]. These data raise the question whether these newly established synaptic contacts contribute to the refinement of the dendritic tree of the projection neurons. In fact, dendritic stability is higher within the olfactory glomeruli upon exposure to odor-enriched environment [84]; and the maturation process of the dendritic tree is heavily influenced by excitatory neurotransmission. Moreover, an interaction of Ca^{2+} with some intracellular enzymes has been proposed, as well as the synthesis of trophic factors, or simply the synaptic activity itself contributes [84-90]. Thus, the sensitive phase represents a unique event during OB development, which follows a well-established spatiotemporal pattern by the establishment of synaptic connections and the initial steps towards the differentiation of M/T cells. As those processes turn out to be critical in the information "flow" from the PNS to the CNS, this stage requires the participation of cellular, axonal and chemical clues to set up the right axonal and cellular wiring.

Molecular barriers and spatiotemporal gene expression gradients — a better understanding of the sensitive phase

So far, we focused on the cellular compartments during the sensitive phase, the relationship between mesenchyme, OE/OB and the presence of different molecular clues during the development of the olfactory pathway is conclusive. To investigate the differential profiles of these structures, we performed a quantitative RT-PCR analyses of a list of genes involved in migration, axon guidance and extracellular matrix molecules (Table 1). We used three representative embryonic ages, and the tissue was limited to the ventro-medial part of the OB (Figure 3A-C). That is the place where the first OE axons contact with the telencephalic vesicles and it is also the location for the first synapses [52,63,91].

Comparing gene expression between the three developmental stages of the sensitive phase, 21 out of 99 selected genes showed significant differences (Table 2). Only one of the analyzed genes showed significant differences between E14 and E15; seven genes between E14-E15; and 13 genes between E14-E16. It is noteworthy that the unique gene with a differential expression between E15 and E16 is Neuropilin-2 (Nrp-2). This protein, which constitutes the main receptor of the secretable semaphorin 3B, 3F and 3C proteins [92-94], is one of the main candidates in the guidance of OE axons towards the OB, both in chicken [95] and rodents [94,96,97]. In fact, olfactory axons of the Nrp2-/- mice [98] or of those with expression of dominant negative Nrp1, the Sema3A receptor [99], failed to converge into the correct glomeruli, reaching to the inner OB layers. This suggests that the expression of different semaphorins in the mitral cell layer exerted a barrier effect on the incoming axons, preventing them from growing further into the OB as occurs in the Nrp2 mutant mice. While the expression pattern of the *Nrp-2* mRNA is similar during the three selected ages (Figure 3D-F), RT-PCR analyses revealed different transcript levels. This change could be related to the presence of a ligand in the mitral cell layer, which is important in the targeting of the olfactory axons into specific glomeruli. Furthermore, quantitative RT-PCR analyses also shows significant differences between E14/E15 in the mRNA levels of Sema3C and Sema3E, and between E14/E16 in these two nrp ligands. Sema3C mRNA is localized in the OB [56,98,100,101], but not in the AOB [94,100,102,103] Moreover, although the expression mRNA pattern did not show changes during the sensitive-phase (Figure 3), the mRNA levels decreased from E14 to E15 (Table 2). This suggests the Neuropilin family and their ligands, the semaphorins, as one of the candidates in the OB innervation, and could partially explain the sharp "behaviour" of OSN axons during this phase. Together with these two proteins, significant differences between the selected ages were also detected in the mRNA expression of the following four molecules: i) Aggrecan (*Acan*), a large aggregating proteoglycan or chondroitin sulphate proteoglycan 1, which is the major proteoglycan in the articular cartilage providing a hydrated gel structure, and it also mediates chondrocyte-chondrocyte and chondrocyte-matrix interactions [104]. As a member of a chondroitin sulfate family, *Acan* could be involved in the migration of different cell subtypes and axons within the mesenchyme during the sensitive phase; ii) Brevican (*Bcan*) belongs to the chondroitin sulphate family proteins [105], and it was recently described as one of the ECM proteins produced and released by astrocytes and involved in synapse generation in the hippocampus [106]. Moreover, *Bcan* is also expressed in the astrocytes ensheathing cerebellar glomeruli [107]. Thus, due to the significant increase in synapses during the OB sensitive phase [63], the up-regulation of the Bcan mRNA suggests an active role in the OB synaptogenic process; iii) Collagen A3 (IV) chain, first described in humans [108], both in kidney glomeruli formation [109] and kidney disease Alport syndrome [110]; iv) NRCAM or neuron-glia-CAM-related cell adhesion molecule, implicated in the guidance of thalamocortical axons by the interactions with the *Nrp-2* which is critical for Sema3F-induced guidance [111]. All these proteins are implicated and related to ECM and axonal growth, thus their expression variation or abundance in the OB could trigger changes within the environment, allowing the axon entrance into the external plexiform layer and the formation of the first glomerulus [52,112-115], giving rise to the glomerular layer at E16.

On the other hand, molecules such as neuroligin 1 (Nlgn1), implicated in regulation of synaptogenesis in hippocampal cultures [116] and in presynaptic differentiation [117], could be potential candidates in the OB synaptogenesis, as between E14/E15 the highest increase in the number of synapses. Another potential molecule is Presenilin 1 (Psen1), required for gamma secretase function *in vivo* [118] and neural progenitor cell differentiation in the brain [119]. Finally, between E14-E16, we observed a significant variation of mRNA in the following genes: C-C chemokine receptor type 5 (Ccr5), a member of the beta chemokine receptors family of integral membrane proteins implicated in numerous processes during brain development [120] and inflammation [121]; chemokine (C-X-C motif) ligand 1 (CXCL1), a small cytokine belonging to the CXC chemokine family, described in ovarian cancer [122], inflammation [123], precursor cell proliferation and migration [124-126], and neuronal migration [127]; Deleted in Colorectal Carcinoma (DCC), a transmembrane receptor, first discovered in colorectal cancer [128], and receptor of the netrin molecule and therefore a clue protein for axon guidance [129]. Genetic studies in mice and *C. elegans* showed that DCC is a receptor that mediates netrin1 attraction of commissural axons [130,131]. DCC has both attractive and repulsive effects [132], being also implicated in regulation of cell death [133] and in surveillance of developing retinal cell types [134]. Moreover, its role in cell apoptosis could be related to the presence of apoptotic events when the MM reaches the OB [135]. The neurotrophic tyrosine kinase, receptor type 3 (Ntrk3) is another example of a molecule implicated in the proliferation and differentiation of neurons during development, and in growth and survival in adult [136], playing an important role in survival and cell death [137]. The differential gene expression of both DCC and Ntrk3 during the sensitive phase might partially explain the balance between cell proliferation [61] and apoptosis [135] during the cell migration of the migratory

Table 1. List of all genes analyzed during the sensitive phase. Differential gene expression was analyzed by quantitative RT-PCR of RNA extracted from the ventro-medial part of the olfactory bulb, where the first OSN axons start to innervate the OB [52]. All genes were selected based on their function in development, axon migration, cytoskeleton modifications, apoptotic and/or differentiation effects and ECM protein interactions, including axon guidance, repulsion and attraction.

Gene	Name	Known function	Reference
Acan	Aggrecan, large aggregating proteoglycan, or chondroitin sulfate proteoglycan 1	Major component of extracellular matrix of cartilagenous tissues.	[156]
Adam10	Disintegrin and metalloproteinase domain-containing protein 10, also known as ADAM10 or CDw156 or CD156c	Responsible for the proteolytic release of several other cell-surface proteins, including heparin-binding epidermal growth-like factor, ephrin-A2 and for constitutive and regulated alpha-secretase cleavage of amyloid precursor protein (APP).	
Akt	Protein Kinase B (PKB)	Controls the tempo of the newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation	
Arf6	ADP-ribosylation factor 6	Regulates endocytic recycling and cytoskeleton remodeling	
Arg1	Arginase type I	Possible role in nitric oxide and polyamine metabolism.	
Arg2	Arginase Type II		
Astn1	Astrotactin 1	Neuronal adhesion molecule required for glial-guided migration of young postmitotic neuroblasts in cortical regions of developing brain, including cerebrum, hippocampus, cerebellum and olfactory bulb	[157]
Bcan	Brevican	Major chondrotin sulfate in the adult brain. Mediates interactions with ECM.	[105,106]
Bdnf	Brain-derived neurotrophic factor		
Bgn	Biglycan	ECM	
Bmp7	Bone morphogenetic protein also known as osteogenic protein-1 or OP-1	Transformation of mesenchimal cells	
Boc		Cell surface receptors of the immunoglobulin (Ig)/fibronectin type III	
Ccl5	Chemokine (C-C motif) ligand 5	Chemotactic cytokine or chemokine	
Ccr5	C-C chemokine receptor type 5	Integral membrane proteins	[158]
Ccrl1	C-C chemokine receptor type 11	G protein-coupled receptor family, and is a receptor for C-C type chemokines	
Cdc42	Cell division control protein 42 homolog	GTPase of the Rho-subfamily, which regulates signaling pathways that control diverse cellular functions including cell morphology, migration, endocytosis and cell cycle progression	
Cdh11	Cadherin-11	Integral membrane protein that mediate calcium-dependent cell-cell adhesion	
Cdh13	T-cadherin	Cell–cell contacts, dynamic regulation of morphogenetic processes in embryos and tissue integrity in adult organisms	
Cdh2	Cadherin-2		
Celsr1	Cadherin EGF LAG seven-pass G-type receptor 1	Nonclassic-type cadherins-contact-mediated communication, with cadherin domains acting as homophilic binding regions and the EGF-like domains involved in cell adhesion and receptor-ligand interactions	[159]
Chek1	Serine/threonine-protein kinase Chk1	Phosphatase in cell cycle control, particularly for entry into mitosis	

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Gene	Name	Known function	Reference
Col4a3	Collagen, type IV, alpha 3	Major structural component of basement membranes	
Csnk2b	Casein kinase II subunit beta	Ubiquitous protein kinase which regulates metabolic pathways, signal transduction, transcription, translation, and replication	
Cxcl1	Chemokine (C-X-C motif) ligand 1	Mitogenic properties and it is also implicated in melanoma pathogenesis	[160]
Cxcl12	Chemokine (C-X-C motif) ligand 12	Participates in nervous system development	[161,162]
Cxcr3	Chemokine (C-X-C motif) receptor 3	Induces various cellular responses, most notably integrin activation, cytoskeletal changes and chemotactic migration	
Cxcr4	Chemokine (C-X-C motif) receptor 4	Normal development of the central nervous system, influencing the guidance of both growing axons and migrating neurons	[163,164]
Dab1	Disable homolog-1	Adaptor protein in charge of Reelin signal transduction	[165]
Dcc	Deleted in Colorectal Carcinoma	Bounds to netrin-1, signals are conveyed that can lead to proliferation and cell migration. In the absence of netrin-1, DCC signaling has been shown to induce apoptosis.	[166]
Dcn	Decorin	Small cellular or pericellular matrix proteoglycan closely related in structure to biglycan protein. It is a component of connective tissue, binds to type I collagen fibrils, and plays a role in matrix assembly.	
Fert2	fer (fms/fps related) protein kinase	Required for p38 activation to promote chemotaxis	[167,168]
Fgf2	Basic fibroblast growth factor	Located in basement membranes and in the subendothelial extracellular matrix of blood vessels. Extensively used in stem cell cultures	
Fgfr1	Fibroblast growth factor receptor 1, also known as basic fibroblast growth factor receptor 1, fms-related tyrosine kinase-2 / Pfeiffer syndrome, and CD331	Receptor tyrosine kinase whose ligands are specific members of the fibroblast growth factor family.	
Fgfr3	Fibroblast growth factor receptor 3 or CD333		
Fmod	Fibromodulin	Participates in the assembly of the extracellular matrix: interacts with type I and type II collagen fibrils and inhibits in vitro fibrillogenesis	
Gpc2	Glypican 2, also known cerebroglycan	Integral membrane heparan sulfate proteoglycan found in the developing nervous system. Cerebroglycan participates in cell adhesion and is thought to regulate the growth and guidance of axons. Cerebroglycan has especially high affinity for laminin-1.	[142,169]
Hhip	Hedgehog-interacting protein	Modulates the responses to any Hedgehog signal.	[170]
Igsf8	Immunoglobulin superfamily member 8	Role on integrin-dependent morphology and motility functions. Participate in the regulation of neurite outgrowth and maintenance of the neural network in the adult brain	
Il8rb	Interleukin 8 receptor, beta is a chemokine receptor, is also known as CXCR2	Reported on various cell types, including neurons, astrocytes, microglia, neural progenitor cells, and microvascular endothelial cells. It is related to development of the CNS, neurotransmission, blood-barrier permeability and in several brain pathologies.	[171]
Irf1	Interferon regulatory factor 1	Acts as a tumor suppressor and regulating apoptosis	
Irf8	Interferon regulatory factor 8	Plays a negative regulatory role in cells of the immune system	
Itga3	Integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	Receptor for fibronectin, laminin, collagen, epiligrin, thrombospondin and CSPG4. Alpha-3/β-1 may mediate with LGALS3 the stimulation by CSPG4 of endothelial cells migration	

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Gene	Name	Known function	Reference
Itpr1	Inositol 1,4,5-triphosphate receptor, type 1	Intracellular channel that mediates calcium release from the endoplasmic reticulum following stimulation by inositol 1,4,5-trisphosphate	
Jag2	Protein jagged-2	Putative Notch ligand involved in the mediation of Notch signaling	
Lmx1b	LIM homeobox transcription factor 1-beta	Dorso-ventral patterning of vertebrate limbs, and ventral brain development	[172]
Lrp2	Low density lipoprotein-related protein 2 or megalin	Multiligand binding receptor found in the plasma membrane.	
Lum	Lumican	Lumican is the major keratan sulfate proteoglycan of the cornea but is also distributed in interstitial collagenous matrices throughout the body	
Myh10	Myosin, heavy chain 10, non-muscle	Plays a role in cytokinesis, cell shape, and specialized functions such as secretion and capping	
Ncan	Neurocan	Modulates neuronal adhesion and neurite growth during development by binding to neural cell adhesion molecules (NG-CAM and N-CAM)	[173]
Ngfr	Nerve growth factor receptor	Mediates cell survival as well as cell death of neural cells	
Nisch	Nischarin	Binds numerous imidazoline ligands that induces initiation of cell-signaling cascades triggering to cell survival, growth and migration	
Nlgn1	Neuroligin-1	Neuronal cell surface protein thought to be involved in cell-cell-interactions by forming intercellular junctions through binding to beta-neurexins.	
Nrcam	Neuronal cell adhesion molecule	Cell adhesion, ankyrin-binding protein involved in neuron-neuron adhesion, axon projection and Schwann cell and axon interactions	[111,174]
Npn1	Neuropilin 1	Implicates in cell migration and axonal targeting.	[175,176]
Npn2	Neuropilin 2		
Ntf3	Neurotrophin 3	Controls survival and differentiation of mammalian neurons	
Ntn1	Netrin 1	Controls guidance of CNS commissural axons and peripheral motor axons. Its association with either DCC or some UNC5 receptors will lead to axon attraction or repulsion	[177,178]
Ntn2l	Netrin-2-like protein precursor	(See Netrin)	
Ntrk2	Neurotrophic tyrosine kinase, receptor, type 2	BDNF modulates synaptic transmission and plasticity primarily through the TrkB receptor, but the molecules involved in BDNF-mediated synaptic modulation are largely unknown.	[179,180]
Ntrk3	neurotrophic tyrosine kinase, receptor, type 3	Receptor for neurotrophin-3. Mediates the multiple effects of this neurotrophic factor, which includes neuronal differentiation and survival.	[137]
Pafah1b1	Platelet-activating factor acetylhydrolase IB subunit alpha	Required for proper activation of Rho GTPases and actin polymerization at the leading edge of locomoting cerebellar neurons and postmigratory hippocampal neurons in response to calcium influx triggered via NMDA receptors	
Pcdhb16	Protocadherin beta-16	Potential calcium-dependent cell-adhesion protein	
Pcdhb21	Protocadherin beta 21	Cell-adhesion protein	
Pex5	Peroxisomal biogenesis factor 5	Essential role in peroxisomal protein import	

continued Table 1. List of all genes analyzed during the sensitive phase. Differential gene expression was analyzed by quantitative RT-PCR of RNA extracted from the ventro-medial part of the olfactory bulb, where the first OSN axons start to innervate the OB [52]. All genes were selected based on their function in development, axon migration, cytoskeleton modifications, apoptotic and/or differentiation effects and ECM protein interactions, including axon guidance, repulsion and attraction.

Gene	Name	Known function	Reference
Prrxl1	Paired related homeobox protein-like 1	Required for the formation of spatio-temporally appropriate projections from nociceptive sensory neurons to their central targets in the dorsal horn of the spinal cord.	
Psen1	Presenilin-1	Involved in the cleavage of Notch receptors	
Pten	Phosphatase and tensin homolog	The lipid phosphatase activity is critical for its tumor suppressor function. Antagonizes the PI3K-AKT/PKB signaling pathway by dephosphorylating phosphoinositides Dephosphorylates tyrosine-phosphorylated focal adhesion kinase and inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation.	
Ptk2	Protein tyrosine kinase 2	Implicated in signaling pathways involved in cell motility, proliferation and apoptosis.	
Ptprz1	Protein tyrosine phosphatase, receptor-type, Z polypeptide 1	Expressed in developmental CNS and implicated in glioblastoma cell migration	[181,182]
Pxmp3	Peroxisome biogenesis factor 2	The protein is thought to be involved in peroxisomal matrix protein import	
Pxn	Paxilin	Cytoskeletal protein involved in actin-membrane attachment at sites of cell adhesion to the extracellular matrix (focal adhesion)	
Rhoa	Ras homolog gene family, member A	Regulates a signal transduction pathway linking plasma membrane receptors to the assembly of focal adhesions and actin stress fibers	
Robo1	roundabout, axon guidance receptor, homolog 1 (Drosophila)	Receptors for SLIT1 and SLIT2 which are thought to act as molecular guidance cue in cellular migration, including axonal navigation at the ventral midline of the neural tube and projection of axons to different regions during neuronal development	[145,148,183]
Robo2	roundabout, axon guidance receptor, homolog 2 (Drosophila)		
Robo3	roundabout, axon guidance receptor, homolog 3 (Drosophila)		
Sema3A	Semaphorin 3A	Secreted and membrane proteins that act as axonal growth cone guidance molecules. They primarily act as short-range inhibitory signals and signal through multimeric receptor complexes. They are usually cues to deflect axons from inappropriate regions, especially important in neural system development	[98,184-186]
Sema3B	Semaphorin 3B		
Sema3C	Semaphorin 3C		
Sema3D	Semaphorin 3D		
Sema3E	Semaphorin 3E		
Sema3F	Semaphorin 3F		
Sema4F	Semaphorin 4F		
Sema6b	Semaphorin 6b		
Sema6c	Semaphorin 6c		
Shh	Sonic hedgehog homolog	Intercellular signal essential for a variety of patterning events during development: signal produced by the notochord that induces ventral cell fate in the neural tube and somites, and the polarizing signal for patterning of the anterior-posterior axis of the developing limb bud	

continued Table 1. List of all genes analyzed during the sensitive phase. Differential gene expression was analyzed by quantitative RT-PCR of RNA extracted from the ventro-medial part of the olfactory bulb, where the first OSN axons start to innervate the OB [52]. All genes were selected based on their function in development, axon migration, cytoskeleton modifications, apoptotic and/or differentiation effects and ECM protein interactions, including axon guidance, repulsion and attraction.

Gene	Name	Known function	Reference
Slit1			
Slit2		Acts as molecular guidance cue in cellular migration, and function appears to be mediated by interaction with roundabout homolog receptors. During neural development involved in axonal navigation at the ventral midline of the neural tube and projection of axons to different regions.	[145,187]
Slit3			
Trl1;Trl6	Transfer RNA leucine 1 (anticodon AAG)		
Tlx3	T-cell eukemia homeobox 3	Transcription factor implicated in differentiation processes	[150]
Tnn	Tenascin N	Sited around migrating cells, at sites of epithelium-mesenchyme interactions, at sites of smooth muscle and connective tissue morphogenesis, and throughout the central and peripheral nervous system, and is often induced under pathological conditions Tenascin-X and tenascin-Y are expressed around developing muscle and blood vessels and tenascin-R expression is limited to the nervous system	[188]
Twist1	Twist homolog 1	Acts as a transcriptional regulator	
Unc5c	Unc-5 homolog C	Receptor for netrin required for axon guidance. Mediates axon repulsion of neuronal growth cones in the developing nervous system upon ligand binding. Axon repulsion in growth cones may be caused by its association with DCC that may trigger signaling for repulsion.	[189]
Vax1	Ventral anterior homeobox 1	Genes of this family are involved in the regulation of body development and morphogenesis	
Vldlr	Very low density lipoprotein receptor	Receptor for the extracellular protein reelin, implicated in migration processes.	[190]

mass towards the OB. Outstanding variations in gene expression during the sensitive phase included the Glypican 2 (GPC2), also known as cerebroglycan, a glycophosphatidylinositol-linked integral membrane heparansulfate proteoglycan located on the surface of axons and growth cones [138-141]. GPC2 is also present in the developing nervous system contributing to cell adhesion, growth and guidance of axons [142]. The reported differences may explain the slow, progressive penetration of axons into the developing OB comparing E16 and E14, likely modulated by repulsive effects. Another candidate, the Nischarin (Nsch), is a citoplasmatic protein that binds the citoplasmatic domain of the integrin α5β1, inducing α5β1-dependent migration in several cell types [143,144]. In our analyses, we found a 34 fold down-regulation of its mRNA during the sensitive phase, which could partially explain the cell migration of the MM throughout all the OB regions, fusing with the telencephalic vesicle at E13 [61]. Another secreted protein implicated in axon guidance process is Slit-1, a well-known secreted protein in the olfactory system [145-147], as well as spinal motor axons [148] and midbrain [149], which is responsible for growth cones collapse. Levels of *Slit-1* mRNA decreses from E14 to E16, partially supporting its downregulation, and allowing for the incoming OE axons to penetrate the OB and give rise to the glomeruli by E16. Unlike the previous proteins, the T-cell leukemia homeobox 3 (Tlx3) is a transcription factor implicated in multiple differentiation processes [150] and it also mediates by Wnt activation [151]. As mentioned above, activation of the canonical pathway in a subset of OECs [152] seems to be critical for the guidance of OSN axons during the MM migration towards the rostral telencephalic vesicle [77], although its expression pattern does not change during the sensitive phase (Figure 3K). Altogether, these data indicate that Tlx3 could be implicated in the specification of at least a subpopulation of these migrating cells from the OE, during the early onset of the olfactory connections.In summary, a dynamic balance of multiple attractive and repulsive signal cues during the olfactory development, and specifically during the sensitive phase, are important to allow the formation of the first glomerulus in a time-space dependent manner [52,63]. Moreover, changes in the mRNA levels of a complex array of factors, seem to govern the ability of olfactory axons to undergo guidance, targeting and synaptogenesis.

Concluding remarks

Regardless of the striking features showed by the olfactory system and the large amount of cell populations and molecular signals involved in these processes, it is still unknown how all these processes cooperate together. Axonal growth and targeting between OE/

Table 2. Significant differences in the mRNA levels of different genes implicated in migration, ECM interaction, proliferation, apoptosis and differentiation in the ventro-medial part of the OB during the sensitive phase. Table shows the expression values of each gene, the comparison between the three stages of the sensitive phase (E14, E15 and E16), as well as the fold differences between each stage.

Gene	2-ΔCt		Fold Difference	p-value	Fold Up(+) or Down(-) Regulation
	E14	**E15**	**E14 /E15**		**E14 /E15**
Acan (Aggrecan)	5.33 E-08	4.82 E-07	0.11	0.008	– 9.04
Bcan (Brevican)	2.68 E-07	1.28 E-06	0.21	0.013	– 4.79
Col4a3 (Collagen, type IV, alpha 3)	1.41 E-08	3.24 E-08	0.44	0.001	– 2.29
Nlgn1 (Neuroligin-1)	1.19 E-08	1.64 E-07	0.07	0.012	– 13.74
Nrcam (Neuronal cell adhesion molecule)	6.63 E-06	3.07 E-05	0.22	0.028	– 4.63
Psen1 (Presenilin-1)	7.15 E-06	2.44 E-05	0.29	0.001	– 3.41
Sema3c (Semaphorin 3C)	1.57 E-06	4.25 E-06	0.37	0.032	– 2.72
		E15 vs E16			
	E15	**E16**		**E15/E16**	
Nrp2 (Neuropilin 2)	5.07 E-06	5.47E-10	9270.94	N/A	+ 9 270.94
		E14 vs E16			
	E14	**E16**		**E14/E16**	
Acan (Agrecan)	5.33 E-08	3.64 E-07	0.15	0.003	– 6.83
Bcan (Brevican)	2.68 E-07	1.04 E-06	0.26	0.003	– 3.88
Ccr5 (C-C chemokine receptor type 5)	2.14 E-08	5.93 E-08	0.36	0.014	– 2.77
Col4a3 (Collagen, type IV, alpha 3)	1.41 E-08	4.59 E-08	0.31	0.009	– 3.25
Cxcl1 (Chemokine (C-X-C motif) ligand 1)	1.60 E-08	2.20 E-07	0.07	0.039	– 13.76
Dcc (Deleted in Colorectal Carcinoma)	6.87 E-05	2.82 E-05	2.44	0.001	+ 2.44
Gpc2 (Glypican 2, also known cerebroglycan)	6.26 E-05	2.69 E-05	2.33	0.001	+ 2.33
Nisch (Nischarin)	6.04 E-05	2.07 E-03	0.03	0.007	– 34.19
Nrcam (Neuronal cell adhesion molecule)	6.63 E-06	2.59 E-05	0.26	0.016	– 3.92
Ntrk3 (neurotrophic tyrosine kinase, receptor, type 3)	3.92 E-06	2.00 E-06	1.96	0.005	+ 1.96
Sema3e (Semaphorin 3A)	4.71 E-06	5.12 E-05	0.09	0.018	– 10.89
Slit1	3.77 E-06	2.20 E-06	1.72	0.009	+ 1.72
Tlx3 (T-cell leukemiahomeobox 3)	2.14 E-08	3.38 E-07	0.06	0.023	– 15.83

OB during the sensitive phase is a dynamic and comparative process in which cells and axons respond to qualitative and quantitative molecular differences, expressed by neighbouring targets, and make their decisions based on the relative balance of attractive and repulsive forces. Besides, because the well structured spatial organization and specificity in the OB innervations, this system could serve as a good model to address the important issue involving how the wiring between the PNS and CNS is performed.

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References

[1] Polak E. T., Trotier D., Baliguand E., Odor similarities in structurally related odorants, Chem. Sens. Flav., 1978, 3, 369–380

[2] Døving K. B., Trotier D., Structure and function of the vomeronasal organ, J. Exp. Biol., 1998, 201, 2913-2925

[3] Dulac C., Torello A. T., Molecular dandection of pheromone signals in mammals, from genes to behaviour, Nat. Rev. Neurosci., 2003, 4, 551-562

[4] Meredith M., Graziadei P. P., Graziadei G. A., Rashotti M. E., Smith J. C., Olfactory function after bulbectomy, Science, 1983, 222, 1254-1255

[5] Spehr M., Spehr J., Ukhanov K., Kelliher K. R., Leinders-Zufall T., Zufall F., Parallel processing of social signals by the mammalian main and accessory olfactory systems, Cell. Mol. Life Sci., 2006, 63, 1476-1484

[6] Trinh K., Storm D. R., Vomeronasal organ dandects odorants in absence of signaling through main olfactory epithelium, Nat. Neurosci., 2003, 6, 519-525

[7] Lin D. M., Wang F., Lowe G., Gold G. H., Axel R., Ngai J. et al., Formation of precise connections in the olfactory bulb occurs in the absence of odorant-evoked neuronal activity, Neuron, 2000, 26, 69-80

[8] Golgi C., Sulla fine struttura dei bulbi olfattori, Rivista Sperimentale di Freniatria e di Medicina Legale, Regio-Emilia, 1875

[9] Cajal S. R., Origen y terminación de las fibras nerviosas olfatorias, Gac. San. Barcelona, 1890

[10] Cajal S. R., La textura del sistema nervioso del hombre y los vertebrados, Moya, Madrid, 1904

[11] Chess A., Simon I., Cedar H., Axel R., Allelic inactivation regulates olfactory receptor gene expression, Cell, 1994, 78, 823-834

[12] Malnic B., Hirono J., Sato T., Buck L. B., Combinatorial receptor codes for odors, Cell, 1999, 96, 713-723

[13] Buck L., Axel R., A novel multigene family may encode odorant receptors: a molecular basis for odor recognition, Cell, 1991, 65, 175-187

[14] Zhang X., Firestein S., The olfactory receptor gene superfamily of the mouse, Nat. Neurosci., 2002, 5, 124-133

[15] Godfrey P. A., Malnic B., Buck L. B., The mouse olfactory receptor gene family, Proc. Natl. Acad. Sci. U S A, 2004, 101, 2156-2161

[16] Malnic B., Godfrey P. A., Buck L. B., The human olfactory receptor gene family, Proc. Natl. Acad. Sci. U S A, 2004, 101, 2584-2589

[17] Ressler K. J., Sullivan S. L., Buck L. B., A zonal organization of odorant receptor gene expression in the olfactory epithelium, Cell, 1993, 73, 597-609

[18] Vassar R., Ngai J., Axel R., Spatial segregation of odorant receptor expression in the mammalian olfactory epithelium, Cell, 1993, 74, 309-318

[19] Ressler K. J., Sullivan S. L., Buck L. B., Information coding in the olfactory system: evidence for a stereotyped and highly organized epitope map in the olfactory bulb, Cell, 1994, 79, 1245-1255

[20] Vassar R., Chao S. K., Sitcheran R., Nuñez J. M., Vosshall L. B., Axel R., Topographic organization of sensory projections to the olfactory bulb, Cell, 1994, 79, 981-991

[21] Mombaerts P., Wang F., Dulac C., Chao S. K., Nemes A., Mendelsohn M. et al., Visualizing an olfactory sensory map, Cell, 1996, 87, 675-686

[22] Wang F., Nemes A., Mendelsohn M., Axel R., Odorant receptors govern the formation of a precise topographic map, Cell, 1998, 93, 47-60

[23] Miller A. M., Maurer L. R., Zou D. J., Firestein S., Greer C. A., Axon fasciculation in the developing olfactory nerve, Neural Dev., 2010, 5, 20

[24] Valverde F., Studies on the Piriform Lobe, Harvard University Press, 1965

[25] Price J. L., A study of complementary laminar patterns of termination of afferent fibers to the olfactory cortex, J. Comp. Neurol., 1973, 150, 87-108

[26] Devor M., Fiber trajectories of olfactory bulb efferents in the hamster, J. Comp. Neurol., 1976, 166, 31-48

[27] Schwob J. E., Price J. L., The development of lamination of afferent fibers to the olfactory cortex in rats, with additional observations in the adult, J. Comp. Neurol., 1984, 223, 203-222

[28] López-Mascaraque L., De Carlos J. A., Valverde F., Early onset of the rat olfactory bulb projections, Neuroscience, 1996, 70, 255-266

[29] Walz A., Omura M., Mombaerts P., Development and topography of the lateral olfactory tract in the mouse, imaging by genetically encoded and injected fluorescent markers, J. Neurobiol., 2006, 66, 835-846

[30] Inaki K., Nishimura S., Nakashiba T., Itohara S., Yoshihara Y., Laminar organization of the developing lateral olfactory tract revealed by differential expression of cell recognition molecules, J. Comp. Neurol., 2004, 479, 243-256

[31] Yamatani H., Sato Y., Fujisawa H., Hirata T., Chronotopic organization of the olfactory bulb axons in the lateral olfactory tract, J. Comp. Neurol., 2004, 475, 247-260

[32] Altman J., Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb, J. Comp. Neurol., 1969, 137, 433-457

[33] Graziadei G. A., Graziadei P. P., Neurogenesis and neuron regeneration in the olfactory system of mammals. II. Degeneration and reconstitution of the olfactory sensory neurons after axotomy, J. Neurocytol., 1979, 8, 197-213

[34] Mombaerts P., Axonal wiring in the mouse olfactory system, Annu. Rev. Cell. Dev. Biol., 2006, 22, 713-737

[35] Luskin M. B., Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone, Neuron, 1993, 11, 173-189

[36] Lois C., Alvarez-Buylla A., Long-distance neuronal migration in the adult mammalian brain, Science, 1994, 264, 1145-1148

[37] Doetsch F., Caillé I., Lim D. A., García-Verdugo J. M., Alvarez-Buylla A., Subventricular zone astrocytes are neural stem cells in the adult mammalian brain, Cell, 1999, 97, 703-716

[38] Suzuki S. O., Goldman J. E., Multiple cell populations in the early postnatal subventricular zone take distinct migratory pathways,

a dynamic study of glial and neuronal progenitor migration, J. Neurosci., 2003, 23, 4240-4250

[39] Alvarez-Buylla A., Kohwi M., Nguyen T. M., Merkle F. T., The heterogeneity of adult stem cells and the emerging complexity of their niche, Cold Spring Harb. Symp. Quant. Biol., 2008, 73, 357-365

[40] García-Moreno F., López-Mascaraque L., De Carlos J. A., Early telencephalic migration topographically converging in the olfactory cortex, Cereb. Cortex, 2008, 18, 1239-1252

[41] Ninkovic J., Mori T., Götz M., Distinct modes of neuron addition in adult mouse neurogenesis, J. Neurosci., 2007, 27, 10906-10911

[42] Brill M. S., Ninkovic J., Winpenny E., Hodge R. D., Ozen I., Yang R. et al., Adult generation of glutamatergic olfactory bulb interneurons, Nat. Neurosci., 2009, 12, 1524-1533

[43] Doucette J. R. The glial cells in the nerve fiber layer of the rat olfactory bulb, Anat. Rec., 1984, 210, 385-391

[44] Valverde F., Santacana M., Heredia M., Formation of an olfactory glomerulus, morphological aspects of development and organization, Neuroscience, 1992, 49, 255-275

[45] Farbman A. I., Squinto L. M., Early development of olfactory receptor cell axons, Brain Res., 1985, 351, 205-213

[46] Marin-Padilla M., Amieva M. R., Early neurogenesis of the mouse olfactory nerve, Golgi and electron microscopic studies, J. Comp. Neurol., 1989, 288, 339-352

[47] De Carlos J. A., López-Mascaraque L., Valverde F., The telencephalic vesicles are innervated by olfactory placode-derived cells, a possible mechanism to induce neocortical development, Neuroscience, 1995, 68, 1167-1178

[48] Fornaro M., Geuna S., Fasolo A., Giacobini-Robecchi M. G., Evidence of very early neuronal migration from the olfactory placode of the chick embryo, Neuroscience, 2001, 107, 191-197

[49] Hinds J. W., Autoradiographic study of histogenesis in the mouse olfactory bulb. I. Time of ori-gin of neurons and neuroglia, J. Comp. Neurol., 1968, 134, 287-304

[50] Bayer S. A., 3H-thymidine-radiographic studies of neurogenesis in the rat olfactory bulb, Exp. Brain Res., 1983, 50, 329-340

[51] Jiménez D., García C., de Castro F., Chédotal A., Sotelo C., De Carlos J. A. et al., Evidence for intrinsic development of olfactory structures in Pax-6 mutant mice, J. Comp. Neurol., 2000, 428, 511-526

[52] Blanchart A., De Carlos J. A., López-Mascaraque L., Time frame of mitral cell development in the mice olfactory bulb, J. Comp. Neurol., 2006, 496, 529-543

[53] Santacana M., Heredia M., Valverde F., Development of the main efferent cells of the olfactory bulb and of the bulbar component of the anterior commissure, Brain Res. Dev. Brain Res., 1992, 65, 75-83

[54] Gong Q., Shipley M. T., Evidence that pioneer olfactory axons regulate telencephalon cell cycle kinetics to induce the formation of the olfactory bulb, Neuron, 1995, 14, 91-101

[55] López-Mascaraque L., García C., Valverde F., de Carlos J.A., Central olfactory structures in Pax-6 mutant mice, Ann. N Y Acad. Sci., 1998, 855, 83-94

[56] López-Mascaraque L., de Castro F., The olfactory bulb as an independent developmental domain, Cell Death Differ., 2002, 9, 1279-1286

[57] Doucette R., Development of the nerve fiber layer in the olfactory bulb of mouse embryos, J. Comp. Neurol., 1989, 285, 514-527

[58] Pellier V., Astic L., Oestreicher A. B., Saucier D., B-50/GAP-43 expression by the olfactory receptor cells and the neurons migrating from the olfactory placode in embryonic rats, Brain Res. Dev. Brain Res., 1994, 80, 63-72

[59] Honma S., Kawano M., Hayashi S., Kawano H., Hisano S., Expression and immunohistochemical localization of vesicular glutamate transporter 2 in the migratory pathway from the rat olfactory placode, Eur. J. Neurosci., 2004, 20, 923-936

[60] Miller A. M., Treloar H. B., Greer C. A., Composition of the migratory mass during development of the olfactory nerve, J. Comp. Neurol., 2010, 518, 4825-4841

[61] Blanchart A., Martín-López E., De Carlos J. A., López-Mascaraque L., Peripheral contributions to olfactory bulb cell populations (migrations towards the olfactory bulb), Glia, 2011, 59, 278-292

[62] Murdoch B., Roskams A. J., A novel embryonic nestin-expressing radial glia-like progenitor gives rise to zonally restricted olfactory and vomeronasal neurons, J. Neurosci., 2008, 28, 4271-4282

[63] Blanchart A., Romaguera M., García-Verdugo J. M., De Carlos J. A., López-Mascaraque L., Synaptogenesis in the mouse olfactory bulb during glomerulus development, Eur. J. Neurosci., 2008, 27, 2838-2846

[64] Blanes T., Sobre algunos puntos dudoses de la estructura del bulbo olfatorio, Rev. Trimest. Microgr., 1898, 3, 99-127

[65] Valverde F., López-Mascaraque L., Neuroglial arrangements in the olfactory glomeruli of the hedgehog, J. Comp. Neurol., 1991, 307, 658-674

[66] Goodman M. N., Silver J., Jacobberger J. W., Establishment and neurite outgrowth properties of neonatal and adult rat olfactory bulb glial cell lines, Brain Res., 1993, 619, 199-213

[67] Tisay K. T., Key B., The extracellular matrix modulates olfactory neurite outgrowth on ensheathing cells, J. Neurosci., 1999, 19, 9890-9899

[68] Kafitz K. W., Greer C. A., Olfactory ensheathing cells promote neurite extension from embryonic olfactory receptor cells in vitro, Glia, 1999, 25, 99-110

[69] Lipson A. C., Widenfalk J., Lindqvist E., Ebendal T., Olson L., Neurotrophic properties of olfactory ensheathing glia, Exp., Neurol., 2003, 180, 167-171

[70] Chung R. S., Woodhouse A., Fung S., Dickson T. C., West A. K., Vickers J. C. et al., Olfactory ensheathing cells promote neurite sprouting of injured axons in vitro by direct cellular contact and secretion of soluble factors, Cell. Mol. Life Sci., 2004, 61, 1238-1245

[71] Leaver S. G., Harvey A. R., Plant G. W., Adult olfactory ensheathing glia promote the long-distance growth of adult retinal ganglion cell neurites in vitro, Glia, 2006, 53, 467-476

[72] Deumens R., Koopmans G. C., Honig W. M., Hamers F. P., Maquet V., Jérôme R., et al., Olfactory ensheathing cells, olfactory nerve fibroblasts and biomatrices to promote long-distance axon regrowth and functional recovery in the dorsally hemisected adult rat spinal cord, Exp. Neurol., 2006, 200, 89-103

[73] Au E., Richter M. W., Vincent A. J., Tetzlaff W., Aebersold R., Sage E.H. et al., SPARC from olfactory ensheathing cells stimulates Schwann cells

to promote neurite outgrowth and enhances spinal cord repair, J. Neurosci., 2007, 27, 7208-7221

[74] Runyan S. A., Phelps P. E., Mouse olfactory ensheathing glia enhance axon outgrowth on a myelin substrate in vitro, Exp. Neurol., 2009, 216, 95-104

[75] Pellitteri R., Spatuzza M., Russo A., Zaccheo D., Stanzani S., Olfactory ensheathing cells represent an optimal substrate for hippocampal neurons, an in vitro study, Int. J. Dev., Neurosci., 2009, 27, 453-458

[76] Wang Y. Z., Molotkov A., Song L., Li Y., Pleasure D. E., Zhou C. J., Activation of the Wnt/beta-catenin signaling reporter in developing mouse olfactory nerve layer marks a specialized subgroup of olfactory ensheathing cells, Dev. Dynam., 2008, 237, 3157-3168

[77] Zaghetto A. A., Paina S., Mantero S., Platonov N., Peretto P., Bovetti S. et al., Activation of the Wnt-beta catenin pathway in a cell population on the surface of the forebrain is essential for the establishment of olfactory axon connections, J. Neurosci., 2007, 27, 9757-9768

[78] Liu K. L., Chuah M. I., Lee K. K., Soluble factors from the olfactory bulb attract olfactory Schwann cells, J. Neurosci., 1995, 15, 990-1000

[79] López-Mascaraque L., García C., Blanchart A., De Carlos J. A., Olfactory epithelium influences the orientation of mitral cell dendrites during development, Dev. Dynam., 2005, 232, 325-335

[80] Jefferis G. S., Vyas R. M., Berdnik D., Ramaekers A., Stocker R. F., Tanaka N. K. et al. Developmental origin of wiring specificity in the olfactory system of Drosophila, Development, 2004, 131, 117-130

[81] Graziadei P. P., Monti-Graziadei A. G., The influence of the olfactory placode on the development of the telencephalon in Xenopus laevis, Neuroscience, 1992, 46, 617-629

[82] LaMantia A. S., Bhasin N., Rhodes K., Heemskerk J., Mesenchymal/epithelial induction mediates olfactory pathway formation, Neuron, 2000, 28, 411-425

[83] Anchan R. M., Drake D. P., Haines C. F., Gerwe E. A., LaMantia A. S., Disruption of local retinoid-mediated gene expression accompanies abnormal development in the mammalian olfactory pathway, J. Comp. Neurol., 1997, 379, 171-184

[84] Mizrahi A., Katz L. C., Dendritic stability in the adult olfactory bulb, Nat. Neurosci., 2003, 6, 1201-1207

[85] Kossel A. H., Williams C. V., Schweizer M., Kater S. B., Afferent innervation influences the development of dendritic branches and spines via both activity-dependent and non-activity-dependent mechanisms, J. Neurosci., 1997, 17, 6314-6324

[86] Acebes A., Ferrús A., Cellular and molecular features of axon collaterals and dendrites, Trends Neurosci., 2000, 23, 557-565

[87] Cline, H. T., Dendritic arbor development and synaptogenesis, Curr. Opin. Neurobiol., 2001, 11, 118-126

[88] Wong R. O., Ghosh A., Activity-dependent regulation of dendritic growth and patterning, Nat. Rev. Neurosci., 2002, 3, 803-812

[89] Yuan Q., Knöpfel T., Olfactory nerve stimulation-induced calcium signaling in the mitral cell distal dendritic tuft, J. Neurophysiol., 2006, 95, 2417-2426

[90] Zhou Z., Xiong W., Masurkar A. V., Chen W. R., Shepherd G. M., Dendritic calcium plateau potentials modulate input-output properties of juxtaglomerular cells in the rat olfactory bulb, J. Neurophysiol., 2006, 96, 2354-2363

[91] Hinds J. W., Ruffett T. L., Mitral cell development in the mouse olfactory bulb, reorientation of the perikaryon and maturation of the axon initial segment, J. Comp. Neurol., 1973, 151, 281-306

[92] Chen H., He Z., Bagri A., Tessier-Lavigne M., Semaphorin-neuropilin interactions underlying sympathetic axon responses to class III semaphorins, Neuron, 1998, 21, 1283-1290

[93] Zou Y., Stoeckli E., Chen H., Tessier-Lavigne M., Squeezing axons out of the gray matter, a role for slit and semaphorin proteins from midline and ventral spinal cord, Cell, 2000, 102, 363-375

[94] Giger R. J., Cloutier J. F., Sahay A., Prinjha R. K., Levengood D. V., Moore S. E. et al., Neuropilin-2 is required in vivo for selective axon guidance responses to secreted semaphorins, Neuron, 2000, 25, 29–41

[95] Kobayashi H., Koppel A. M., Luo Y., Raper J. A., A role for collapsin-1 in olfactory and cranial sensory axon guidance, J. Neurosci., 1997, 17, 8339-8352

[96] Schwarting G. A., Kostek C., Ahmad N., Dibble C., Pays L., Puschel A. W., Semaphorin 3A is required for guidance of olfactory axons in mice, J. Neurosci., 2000, 20, 7691-7697

[97] Takeuchi H., Inokuchi K., Aoki M., Suto F., Tsuboi A., Matsuda I. et al., Sequential arrival and graded secretion of Sema3F by olfactory neuron axons specify map topography at the bulb, Cell, 2010, 141, 1056-1067

[98] Walz A., Rodriguez I., Mombaerts P., Aberrant sensory innervation of the olfactory bulb in neuropilin-2 mutant mice, J. Neurosci., 2002, 22, 4025-4035

[99] Renzi M. J., Wexler T. L., Raper J. A., Olfactory sensory axons expressing a dominant-negative semaphorin receptor enter the CNS early and overshoot their target, Neuron, 2000, 28, 437-447

[100] Giger R. J., Urquhart E. R., Gillespie S. K., Levengood D. V., Ginty D. D., Kolodkin A. L., Neuropilin-2 is a receptor for semaphorin IV, insight into the structural basis of receptor function and specificity, Neuron, 1998, 21, 1079-1092

[101] De Castro F., Wiring olfaction: the cellular and molecular mechanisms that guide the development of synaptic connections from the nose to the cortex, Front. Neurosci., 2009, doi: 10.3389/neuro.22.004.2009.

[102] Chen H., Chédotal A., He Z., Goodman C. S., Tessier-Lavigne M., Neuropilin-2, a novel member of the neuropilin family, is a high affinity receptor for the semaphorinsSema E and Sema IV but not Sema III, Neuron, 1997, 19, 547–559

[103] Chen H., Bagri A., Zupicich J. A., Zou Y., Stoeckli E., Pleasure S. J., et al., Neuropilin-2 regulates the development of selective cranial and sensory nerves and hippocampal mossy fiber projections, 2000, Neuron, 25, 43–56

[104] Kiani C., Chen L., Wu Y. J., Yee A. J., Yang B. B., Structure and function of aggrecan, Cell Res., 2002, 12, 19-32

[105] Seidenbecher C. I., Richter K., Rauch U., Fässler R., Garner C. C., Gundelfinger E. D., Brevican, a chondroitin sulfate proteoglycan of rat brain, occurs as secreted and cell surface glycosylphosphatidylinositol-anchored isoforms, J. Biol. Chem., 1995, 270, 27, 206-212

[106] Pyka M., Wetzel C., Aguado A., Geissler M., Hatt H., Faissner A., Chondroitin sulfate proteoglycans regulate astrocyte-dependent synaptogenesis and modulate synaptic activity in primary embryonic hippocampal neurons, Eur. J. Neurosci., 2011, 33, 2187-2202

[107] Yamada H., Fredette B., Shitara K., Hagihara K., Miura R., Ranscht B. et al., The brain chondroitin sulfate proteoglycan brevican associates with astrocytes ensheathing cerebellar glomeruli and inhibits neurite outgrowth from granule neurons, J. Neurosci., 1997, 17, 7784-7795

[108] Turner N., Mason P. J., Brown R., Fox M., Povey S., Rees A. et al., Molecular cloning of the human Goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen, J. Clin. Invest., 1992, 89, 592–601

[109] Abrahamson D. R., Isom K., Roach E., Stroganova L., Zelenchuk A., Miner J.H. et al., Laminin compensation in collagen alpha3(IV) knockout (Alport) glomeruli contributes to permeability defects, J. Am. Soc. Nephrol., 2007, 18, 2465-2472

[110] Tanaka M., Asada M., Higashi A. Y., Nakamura J., Oguchi A., Tomita M. et al., Loss of the BMP antagonist USAG-1 ameliorates disease in a mouse model of the progressive hereditary kidney disease Alport syndrome, J. Clin. Invest., 2010, 120, 768-777

[111] Demyanenko G. P., Riday T. T., Tran T. S., Dalal J., Darnell E. P., Brennaman L. H., et al., NrCAM deletion causes topographic mistargeting of thalamocortical axons to the visual cortex and disrupts visual acuity, J. Neurosci., 2011, 31, 1545-1558

[112] De Carlos J. A., López-Mascaraque L., Valverde F., Early olfactory fiber projections and cell migration into the rat telencephalon, Int. J. Dev. Neurosci., 1996, 14, 853–866

[113] Bailey M., Puche A. C., Shipley M. T., Development of the olfactory bulb, evidence for glia-neuron interactions in glomerular formation, J. Comp. Neurol., 1999, 415, 423–448

[114] Treloar H. B., Purcell A. L., Greer C. A., Glomerular formation in the developing rat olfactory bulb, J. Comp. Neurol., 1999, 413, 289-304

[115] Treloar H. B, Uboha U., Jeromin A., Greer C. A., Expression of the neuronal calcium sensor protein NCS-1 in the developing mouse olfactory pathways, J. Comp. Neurol., 2005, 482, 201–216

[116] Aiga M., Levinson J. N., Bamji S. X., N-cadherin and neuroligins cooperate to regulate synapse formation in hippocampal cultures, J. Biol. Chem., 2011, 286, 851-858

[117] Lee H., Dean C., Isacoff E., Alternative splicing of neuroligin regulates the rate of presynaptic differentiation, J. Neurosci., 2010, 30, 11435-11446

[118] Ahn K., Shelton C. C., Tian Y., Zhang X., Gilchrist M. L., Sisodia S. S., et al., Activation and intrinsic gamma-secretase activity of presenilin 1, Proc. Natl. Acad. Sci. U S A, 2010, 107, 21435-21440

[119] Gadadhar A., Marr R., Lazarov O., Presenilin-1 regulates neural progenitor cell differentiation in the adult brain, J. Neurosci., 2011, 31, 2615-2623

[120] Tran P. B., Banisadr G., Ren D., Chenn A., Miller R. J., Chemokine receptor expression by neural progenitor cells in neurogenic regions of mouse brain, J. Comp. Neurol., 2007, 500, 1007-1033

[121] Skuljec J., Sun H., Pul R., Bénardais K., Ragancokova D., Moharregh-Khiabani D. et al., CCL5 induces a pro-inflammatory profile in microglia in vitro, Cell Immunol., 2011, 270, 164-171

[122] Bolitho C., Hahn M. A., Baxter R. C., Marsh D. J., The chemokine CXCL1 induces proliferation in epithelial ovarian cancer cells by transactivation of the epidermal growth factor receptor, Endocr. Relat. Cancer, 2010, 17, 929-940

[123] Pineau I., Sun L., Bastien D., Lacroix S., Astrocytes initiate inflammation in the injured mouse spinal cord by promoting the entry of neutrophils and inflammatory monocytes in an IL-1 receptor/MyD88-dependent fashion, Brain Behav. Immun., 2010, 24, 540-553

[124] Krathwohl M. D., Kaiser J. L., Chemokines promote quiescence and survival of human neural progenitor cells, Stem Cells, 2004, 22, 109-118

[125] Ni H. T., Hu S., Sheng W. S., Olson J. M., Cheeran M. C., Chan A. S. et al., High-level expression of functional chemokine receptor CXCR4 on human neural precursor cells, Brain Res. Dev. Brain Res., 2004, 152, 159-169

[126] Tran P. B., Ren D., Miller R. J., The HIV-1 coat protein gp120 regulates CXCR4-mediated signaling in neural progenitor cells, J. Neuroimmunol., 2005, 160, 68-76

[127] Ceci M. L., López-Mascaraque L., De Carlos J. A., The influence of the environment on Cajal-Retzius cell migration, Cereb. Cortex, 2010, 20, 2348-2360

[128] Fearon E. R., Cho K. R., Nigro J. M., Kern S. E., Simons J. W., Ruppert J. M. et al., Identification of a chromosome 18q gene that is altered in colorectal cancers. Science, 1990, 247, 49-56

[129] Keino-Masu K., Masu M., Hinck L., Leonardo E. D., Chan S. S., Culotti J. G. et al. Deleted in Colorectal Cancer (DCC) encodes a netrin receptor, Cell, 1996, 87, 175–185

[130] Chan S. S., Zheng H., Su M. W., Wilk R., Killeen M. T., Hedgecock E. M. et al., UNC-40, a C. elegans homolog of DCC (Deleted in Colorectal Cancer), is required in motile cells responding to UNC-6 netrin cues, Cell, 1996, 87, 187-195

[131] Fazeli A., Dickinson S. L., Hermiston M. L., Tighe R. V., Steen R. G., Small C. G. et al., Phenotype of mice lacking functional Deleted in colorectal cancer (Dcc) gene, Nature, 1997, 386, 796-804

[132] Stein E., Tessier-Lavigne M., Hierarchical organization of guidance receptors, silencing of netrin attraction by slit through a Robo/DCC receptor complex, Science, 2001, 291, 1928-1938

[133] Mehlen P., Rabizadeh S., Snipas S. J., Assa-Munt N., Salvesen G. S., Bredesen D.E., The DCC gene product induces apoptosis by a mechanism requiring receptor proteolysis, Nature, 1998, 395, 801–804

[134] Shi M., Zheng M. H., Liu Z. R., Hu Z. L., Huang Y., Chen J. Y. et al., DCC is specifically required for the survival of retinal ganglion and displaced amacrine cells in the developing mouse retina, Dev. Biol., 2010, 348, 87-96

[135] Pellier V., Saucier D., Oestreicher A. B., Astic L., Ultrastructural and cytochemical identification of apoptotic cell death accompanying development of the fetal rat olfactory nerve layer, Anat. Embryol., 1996, 194, 99-109

[136] Beltaifa S., Webster M. J., Ligons D. L., Fatula R. J., Herman M. M., Kleinman J. E. et al., Discordant changes in cortical TrkC mRNA and protein during the human lifespan, Eur. J. Neurosci., 2005, 21, 2433-2444

[137] Nikoletopoulou V., Lickert H., Frade J. M., Rencurel C., Giallonardo P., Zhang L. et al., Neurotrophin receptors TrkA and TrkC cause neuronal death whereas TrkB does not, Nature, 2010, 467, 59-63

[138] Irie A., Yates E. A., Turnbull J. E., Holt C. E., Specific heparan sulfate structures involved in retinal axon targeting, Development, 2002, 129, 61-70

[139] Inatani M., Irie F., Plump A. S., Tessier-Lavigne M., Yamaguchi Y., Mammalian brain morphogenesis and midline axon guidance require heparan sulphate, Science, 2003, 302, 1044-1046

[140] Johnson K. G., Ghose A., Epstein E., Lincecum J., O'Connor M. B., Van Vactor D., Axonal heparan sulfate proteoglycans regulate the distribution and efficiency of the repellent slit during midline axon guidance, Curr. Biol., 2004, 14, 499-504

[141] Steigemann P., Molitor A., Fellert S., Jäckle H., Vorbrüggen G., Heparan sulfate proteoglycan syndecan promotes axonal and myotube guidance by slit/robo signalling, Curr. Biol., 2004, 14, 225-230

[142] Ivins J. K., Litwack E. D., Kumbasar A., Stipp C. S., Lander A. D., Cerebroglycan, a developmentally regulated cell-surface heparansulfate proteoglycan, is expressed on developing axons and growth cones, Dev. Biol.,1997, 184, 320–332

[143] Alahari S. K., Lee J. W., Juliano R. L., Nischarin, a novel protein that interacts with the integrin alpha5 subunit and inhibits cell migration, J. Cell. Biol., 2000, 151, 1141-1154

[144] Alahari S. K., Nasrallah H., A membrane proximal region of the integrin alpha5 subunit is important for its interaction with nischarin, Biochem. J., 2004, 377, 449-457

[145] Cho J. H., Lépine M., Andrews W., Parnavelas J., Cloutier J. F., Requirement for Slit-1 and Robo-2 in zonal segregation of olfactory sensory neuron axons in the main olfactory bulb, J. Neurosci., 2007, 27, 9094-9104

[146] Nguyen-Ba-Charvet K. T., Di Meglio T., Fouquet C., Chédotal A., Robos and slits control the pathfinding and targeting of mouse olfactory sensory axons, J. Neurosci., 2008, 28, 4244-4249

[147] Prince J. E., Cho J. H., Dumontier E., Andrews W., Cutforth T., Tessier-Lavigne M. et al., Robo-2 controls the segregation of a portion of basal vomeronasal sensory neuron axons to the posterior region of the accessory olfactory bulb, J. Neurosci, 2009, 29, 14211-14222

[148] Patel K., Nash J. A., Itoh A., Liu Z., Sundaresan V., Pini A., Slit proteins are not dominant chemorepellents for olfactory tract and spinal motor axons, Development, 2001, 128, 5031-5037

[149] Dugan J. P., Stratton A., Riley H. P., Farmer W. T., Mastick G. S., Midbrain dopaminergic axons are guided longitudinally through the diencephalon by Slit/Robo signals, Mol. Cell. Neurosci., 2011, 46, 347-356

[150] Indulekha C. L., Divya T. S., Divya M. S., Sanalkumar R., Rasheed V. A., Dhanesh S. B. et al., Hes-1 regulates the excitatory fate of neural progenitors through modulation of Tlx3 (HOX11L2) expression, Cell. Mol. Life Sci., 2011, in press, DOI 10.1007/s00018-011-0765-8

[151] Kondo T., Matsuoka A. J., Shimomura A., Koehler K. R., Chan R. J., Miller J. M., et al., Wnt signaling promotes neuronal differentiation from mesenchymal stem cells through activation of Tlx3, Stem Cells, 2011, 29, 836-846

[152] Wang Y. Z., Molotkov A., Song L., Li Y., Pleasure D. E., Zhou C. J., Activation of the Wnt/beta-catenin signalling reporter in developing mouse olfactory nerve layer marks a specialized subgroup of olfactory ensheating cells, Dev. Dynam., 2008, 237, 157-168

[153] Corotto F. S., Henegar J. A., Maruniak J. A., Neurogenesis persists in the subependymal layer of the adult mouse brain, Neurosci. Lett., 1993, 149, 111-114

[154] Yoon S. O., Lois C., Alvirez M., Alvarez-Buylla A., Falck-Pedersen E., Chao M. V., Adenovirus-mediated gene delivery into neuronal precursors of the adult mouse brain, Proc. Natl. Acad. Sci. U S A, 1996, 93, 11974-11979

[155] Batista-Brito R., Close J., Machold R., Fishell G., The distinct temporal origins of olfactory bulb interneuron subtypes, J. Neurosci., 2008, 28, 3966-3975

[156] Popp S., Andersen J. S., Maurel P., Margolis R. U., Localization of aggrecan and versican in the developing rat central nervous system, Dev. Dynam., 2003, 227, 143-149

[157] Adams N. C., Tomoda T., Cooper M., Dietz G., Hatten M. E., Mice that lack astrotactin have slowed neuronal migration, Development, 2002, 129, 965-972

[158] Samson M., Labbe O., Mollereau C., Vassart G., Parmentier M., Molecular cloning and functional expression of a new human CC-chemokine receptor gene", Biochemistry, 1996, 35, 3362–3367

[159] Wu Q, Maniatis T., A striking organization of a large family of human neural cadherin-like cell adhesion genes, Cell, 1999, 97, 779–790

[160] Anisowicz A., Bardwell L., Sager R., Constitutive overexpression of a growth-regulated gene in transformed Chinese hamster and human cells, Proc. Natl. Acad. Sci. U S A,1987, 84, 7188–7192

[161] Bagri A., Gurney T., He X., Zou Y. R., Littman D. R., Tessier-Lavigne M. et al., The chemokine SDF1 regulates migration of dentate granule cells, Development, 2002, 129, 4249-4260

[162] Tissir F., Wang C. E., Goffinet A. M., Expression of the chemokine receptor Cxcr4 mRNA during mouse brain development, Brain Res. Dev. Brain Res., 2004,149, 63-71

[163] Lieberam I., Agalliu D., Nagasawa T., Ericson J., Jessell T. M., A Cxcl12-CXCR4 chemokine signaling pathway defines the initial trajectory of mammalian motor axons, Neuron, 2005, 47, 667-679

[164] Belmadani A., Tran P. B., Ren D., Assimacopoulos S., Grove E. A., Miller R. J., The chemokine stromal cell-derived factor-1 regulates the migration of sensory neuron progenitors, J. Neurosci., 2005, 25, 3995-4003

[165] Martín-López E., Blanchart A., De Carlos J. A., López-Mascaraque L., Dab1 (disable homolog-1) reelin adaptor protein is overexpressed in the olfactory bulb at early postnatal stages. PLoS One, 2011, 6, e26673

[166] Mehlen P., Bredesen D. E., The dependence receptor hypothesis, Apoptosis, 2004, 9, 37-49

[167] Fischman K., Edman J. C., Shackleford G. M., Turner J. A., Rutter W. J., Nir U., A murine fer testis-specific transcript (ferT) encodes a truncated Fer protein, Mol. Cell Biol., 1990, 10, 146-153

[168] Craig A. W., Greer P. A., Fer kinase is required for sustained p38 kinase activation and maximal chemotaxis of activated mast cells, Mol. Cell. Biol., 2002, 22, 6363-6367

[169] Herndon M. E., Stipp C. S., Lander A. D., Interactions of neural glycosaminoglycans and proteoglycans with protein ligands, assessment of selectivity, heterogeneity and the participation of core proteins in binding, Glycobiology, 1999, 9, 143–155

[170] Chuang P. T., McMahon A. P., Vertebrate Hedgehog signalling modulated by induction of a Hedgehog-binding protein, Nature, 1999, 397, 617–621

[171] Semple B. D., Kossmann T., Morganti-Kossmann M. C., Role of chemokines in CNS health and pathology, a focus on the CCL2/CCR2 and CXCL8/CXCR2 networks, J. Cereb. Blood Flow Metab., 2010, 30, 459-473

[172] Deng Q., Andersson E., Hedlund E., Alekseenko Z., Coppola E., Panman L., et al., Specific and integrated roles of Lmx1a, Lmx1b and Phox2a in ventral midbrain development, Development, 2011, 138, 3399-3408

[173] Li H. P., Oohira A., Ogawa M., Kawamura K., Kawano H., Aberrant trajectory of thalamocortical axons associated with abnormal localization of neurocan immunoreactivity in the cerebral neocortex of reeler mutant mice, Eur. J. Neurosci., 2005, 22, 2689-2696

[174] Pollard J. D., Armati P. J., CIDP - the relevance of recent advances in Schwann cell/axonal neurobiology, J. Peripher. Nerv. Syst., 2011, 16, 15-23

[175] Cariboni A., Davidson K., Rakic S., Maggi R., Parnavelas J. G., Ruhrberg C., Defective gonadotropin-releasing hormone neuron migration in mice lacking SEMA3A signalling through NRP1 and NRP2: implications for the aetiology of hypogonadotropic hypogonadism, Hum. Mol. Genet., 2011, 20, 336-344

[176] McIntyre J. C., Titlow W. B., McClintock T. S., Axon growth and guidance genes identify nascent, immature, and mature olfactory sensory neurons, J. Neurosci. Res., 2010, 88, 3243-3256

[177] Barallobre M. J., Pascual M., Del Río J. A., Soriano E., The netrin family of guidance factors: emphasis on netrin-1 signalling, Brain Res. Brain Res. Rev., 2005, 49, 22-47

[178] Hakanen J., Duprat S., Salminen M., Netrin1 is required for neural and glial precursor migrations into the olfactory bulb, Dev. Biol., 2011, 355, 101-114

[179] Imamura F., Greer C. A., Dendritic branching of olfactory bulb mitral and tufted cells, regulation by TrkB, PLoS One, 2009, 4, e6729

[180] Hasegawa R., Takami S., Nishiyama F., Immunoelectron microscopic analysis of the distribution of tyrosine kinase receptor B in olfactory axons, Anat. Sci. Int., 2008, 83, 186-194

[181] Levy J. B., Canoll P. D., Silvennoinen O., Barnea G., Morse B., Honegger A. M. et al., The cloning of a receptor-type protein tyrosine phosphatase expressed in the central nervous system, J. Biol. Chem., 1993, 268, 10573-10581

[182] Ulbricht U., Eckerich C., Fillbrandt R., Westphal M., Lamszus K., RNA interference targeting protein tyrosine phosphatase zeta/receptor-type protein tyrosine phosphatase beta suppresses glioblastoma growth in vitro and in vivo, J. Neurochem., 2006, 98, 1497-1506

[183] Hivert B., Liu Z., Chuang C. Y., Doherty P., Sundaresan V., Robo1 and Robo2 are homophilic binding molecules that promote axonal growth, Mol. Cell. Neurosci., 2002, 21, 534-545

[184] Walz A., Feinstein P., Khan M., Mombaerts P., Axonal wiring of guanylate cyclase-D-expressing olfactory neurons is dependent on neuropilin 2 and semaphorin 3F, Development, 2007, 134, 4063-4072

[185] Cloutier J. F., Sahay A., Chang E. C., Tessier-Lavigne M., Dulac C., Kolodkin A. L. et al., Differential requirements for semaphorin 3F and Slit-1 in axonal targeting, fasciculation, and segregation of olfactory sensory neuron projections, J. Neurosci., 2004, 24, 9087-9096

[186] Tsim T. Y., Wong E. Y., Leung M. S., Wong C. C., Expression of axon guidance molecules and their related genes during development and sexual differentiation of the olfactory bulb in rats, Neuroscience, 2004, 123, 951-965

[187] Nguyen-Ba-Charvet K. T., Brose K., Marillat V., Kidd T., Goodman C. S., Tessier-Lavigne M. et al., Slit2-mediated chemorepulsion and collapse of developing forebrain axons, Neuron, 1999, 22, 1-20

[188] Scherberich A., Tucker R. P., Samandari E., Brown-Luedi M., Martin D., Chiquet-Ehrismann R., Murine tenascin-W, a novel mammalian tenascin expressed in kidney and at sites of bone and smooth muscle development, J. Cell. Sci., 2004, 117, 571-581

[189] Kim D., Ackerman S. L., The UNC5C netrin receptor regulates dorsal guidance of mouse hindbrain axons, J. Neurosci., 2011, 31, 2167-2179

[190] Cariboni A., Rakic S., Liapi A., Maggi R., Goffinet A., Parnavelas J. G., Reelin provides an inhibitory signal in the migration of gonadotropin-releasing hormone neurons, Development, 2005, 132, 4709-4718