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REVIEW

Modulation of olfactory signal detection in the olfactory epithelium: focus on the internal and external environment, and the emerging role of the immune system

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Abstract

Detection and discrimination of odorants by the olfactory system plays a pivotal role in animal survival. Olfactory-based behaviors must be adapted to an ever-changing environment. Part of these adaptations includes changes of odorant detection by olfactory sensory neurons localized in the olfactory epithelium. It is now well established that internal signals such as hormones, neurotransmitters, or paracrine signals directly affect the electric activity of olfactory neurons. Furthermore, recent data have shown that activity-dependent survival of olfactory neurons is important in the olfactory epithelium. Finally, as olfactory neurons are directly exposed to environmental toxicants and pathogens, the olfactory epithelium also interacts closely with the immune system leading to neuroimmune modulations. Here, we review how detection of odorants can be modulated in the vertebrate olfactory epithelium. We choose to focus on three cellular types of the olfactory epithelium (the olfactory sensory neuron, the sustentacular and microvillar cells) to present the diversity of modulation of the detection of odorant in the olfactory epithelium. We also present some of the growing literature on the importance of immune cells in the functioning of the olfactory epithelium, although their impact on odorant detection is only just beginning to be unravelled.

Abbreviations

EOG	Electro-olfactogram
OB	Olfactory bulb
OE	Olfactory epithelium
OR	Olfactory receptor
OSN	Olfactory sensory neuron
SC	Sustentacular cells
BC	Basal cell
MvC	Microvillar cell
OBP	Olfactory binding protein
NALT	Nasal associated lymphoid tissue

Introduction

In almost all sensory systems, sensory inputs are affected by external and internal stimuli allowing the adaptation of organisms to their environment. The most effective external stimuli are related to nociception which drives complex and major alterations in the animal behavior (Herz 1998). Internal signals such as hormones, neurotransmitters, or paracrine signals also influence sensory systems (McGann 2015). The vertebrate olfactory system is no exception to this rule. The olfactory peripheral system is mainly composed of the olfactory epithelium (OE) with the additional vomeronasal organ (VNO) in most mammals. Some mammals also have two, spatially segregated, clusters of chemosensory neurons: the septal organ of Masera and the Grueneberg ganglion (Hayden and Teeling 2014). The present review will be limited to modulation at the level of the main OE. In vertebrates, the OE is composed of three major cell types (Fig. 1): ciliated bipolar olfactory sensory neurons (OSNs), which are the main receptor cells detecting odorants; sustentacular cells (SCs), which support OSN activity; and basal cells (BCs), which are the stem cells of the OE (Hayden and Teeling 2014). BCs allow a continuous renewal of the OE cells which are exposed to toxins and pathogens leading to cellular death. In addition to these main cell types, microvillar cells (MvCs) form a

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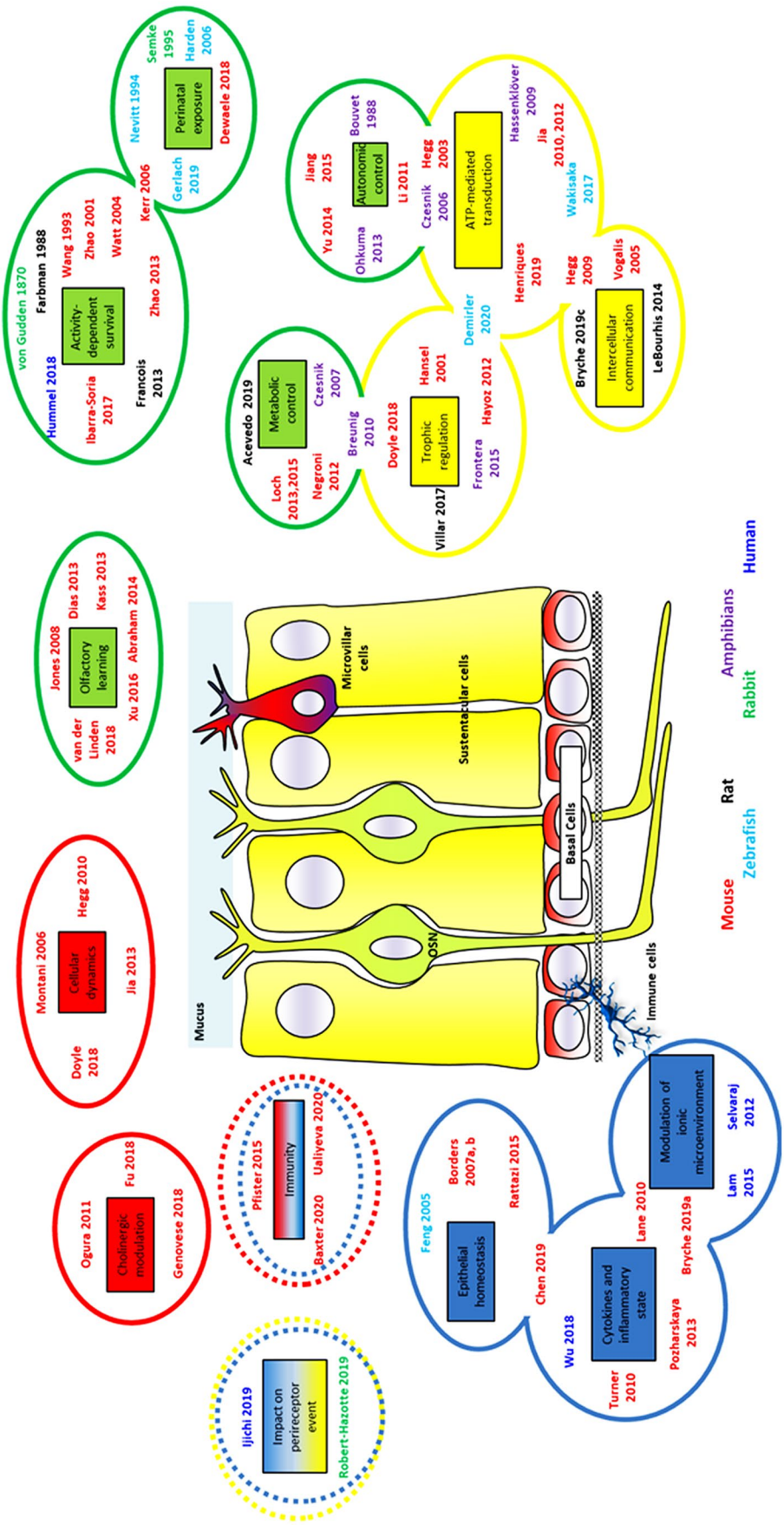

Fig. 1 Schematic representation of the regulatory roles of each of the main cells of the olfactory epithelium (OE) that are covered by this review. Each cell type is represented in a colored plain or dotted circle, green for OSN, yellow for sustentaculars cells (SCs), red for microvillar cells (MvCs), and blue for immune cells. Each circle contains information about its main role in OE modulation (box) with key references whose color indicates the species the study is based on. Some studies refer to complementary functions (fused circles), mixed functions (half-colored), or putative functions (dotted circles)

heterogeneous population of non-neuronal superficial cells mainly described in rodents but also in canines and primates (Miller et al. 1995; Elsaesser and Paysan 2007). Apart from the OSNs, which have been extensively studied, the precise roles of other cell types are less clear, but recent work shows that they participate to olfactory signal modulation. In this review, we will focus on the changes in the olfactory sensory input in response to variations in the internal and external environment which acts at the level of OSNs, SCs, and MvCs. We will discuss short-term changes of the response to odorants linked to a change in circulating hormones such as insulin as well as long-term changes linked to OSN population plasticity. In addition, immune cells are present in the OE (Mellert et al. 1992; Imamura and Hasegawa-Ishii 2016) and recent studies show that they can affect the response of OSN (Bryche et al. 2019a; Ualiyeva et al. 2020). Furthermore, recent reports of COVID-19-related olfactory disorders in humans highlight the importance of immune cells in the OE (Rodriguez et al. 2020; Bryche et al. 2020; Le Bon and Horoi 2020). We will describe the emerging role of these cells in the regulation of olfactory signal, in physiological situations (through the homeostatic presence of resident immune cells or immune components) and in pathological situations.

Modulation of the olfactory sensory neurons

OSNs are the receptor cells for the sense of smell, and their cell bodies are found in the OE, lining the nasal cavity. These neurons have a single dendrite, terminating in a knob covered in cilia and submerged in mucus that is in direct contact with the external environment. Olfactory receptors (ORs) are present in the cilia and are activated by odorants. One mature OSN expresses only one of the OR genes among hundreds found in vertebrate genomes. OSN axons project directly to the olfactory bulb (OB) in the central nervous system. In this section, we will first discuss how olfactory stimulation can shape OSN population and secondly the influence of internal messengers.

Activity-dependent survival of OSN

Plasticity was long thought to be solely occurring in the central nervous system, but it is now clearly established that it also takes place in the peripheral nervous system, including the OE (McGann 2015). Part of this plasticity depends on the direct stimulation of OSNs by odors, and recent data clearly show that the context of odorant exposure differentially impacts the neuronal population. We will thus distinguish between odors without association to a specific stimulus, which we will refer as "passive stimulation," and stimulation linked to a learning task, where odors are associated with a specific stimulus.

Impact of odorants

Since the pioneer works on motor neurons in chick embryos (Hollyday et al. 1977), the link between survival and activity of neurons is well established. The OE of vertebrates is a highly regenerative neuroepithelium that is maintained under normal conditions by a population of stem and progenitor cells. Due to this renewal capacity, it has been postulated that the population of OSNs has the potential to be shaped by environmental factors.

The first experiments to test effects of odorant stimulation on the OSN population were based on unilateral nostril occlusion (Gudden 1870). Unilateral nostril occlusion prevents stimulation of OSNs in the occluded nostril. According to the activity-driven survival hypothesis, OSN death rate should be higher compared to the non-occluded side. However, the occlusion also limits damages from inhaled pathogens and irritants, while amplifying them on the non-occluded side because the air flow is increased into the solely functional nostril. Thus, results obtained from unilateral nostril occlusions are difficult to interpret and often controversial (Farbman et al. 1988; Fitzwater and Coppola 2021). An interesting review by Coppola (2012) clearly describes biases and limitations of this experimental model. Nevertheless, some studies clearly show that the dynamic of OSN population is affected differentially in terms of the expressed OR populations, indicating that sensory experience could shape the olfactory response of the OE (He et al. 2012; Zhao et al. 2013; van der Linden et al. 2020).

Genetic tools offer another experimental approach to examine activity-dependent survival of OSNs. In mice, Zhao and Reed (2001) took advantage of the X chromosome location of the *OCNC1* gene, one of the key genes in olfactory transduction, encoding an essential subunit of the olfactory cyclic nucleotide gated channel, which is essential for the depolarization of OSNs (Reisert and Reingruber 2019). In their study, Zhao and Reed replaced *OCNC1* with the ß-galactosidase reporter gene, allowing a direct visualization of *OCNC1*-deficient olfactory neurons and their projections. In all female cells, one of the X chromosomes is inactivated randomly. Therefore, in heterozygous females, OSNs will randomly express either the ß-galactosidase or the olfactory cyclic nucleotide gated channel. Of the total OSN population, 50% are thus active, while the other inactive 50% are easily stained blue due to their reporter gene expression. If at birth, the OSN population in the OE reflected this proportion, the blue-stained OSN proportion dropped dramatically after one month. These results are consistent with the hypothesis that only active OSNs survive. Another study confirmed this result by overexpressing an OR activated by octanal in the OE (Watt et al. 2004). The authors found that the OSN population expressing this OR increased in

presence of octanal, consistent with an activity-dependent survival of OSNs in the OE.

A simpler experimental approach consists of exposure to different odors. The first clear demonstration was carried out on mice by measuring the evolution of the electrophysiological response in the OSN population, after repeated androstenone exposure (Wang et al. 1993). The authors observed a specific increase in the response to this odor, supporting the activity-dependent survival hypothesis. Alternatively, one can hypothesize that this change would be caused by an increase in the individual response of androstenone-sensitive OSNs through improvement in efficiency of the transduction pathway (Fig. 2). This second hypothesis was favored by another study, using genetically engineered mice expressing a reporter gene associated with a single OR (Kerr and Belluscio 2006). In this work, the authors manually counted the number of OSNs expressing an OR sensitive to octanal; this number did not change when the animals were exposed to this odorant. However, subsequent studies using a similar manual counting of the OSN population found opposite results with an increase in the number of OSNs expressing a stimulated OR by acetophenone or heptanal (François et al. 2013; Cadiou et al. 2014). Such discrepancies between studies indicate that activity-dependent survival might be influenced by the odorization protocol and is unlikely to be similar for all types of OSN, dependent on the OR they express

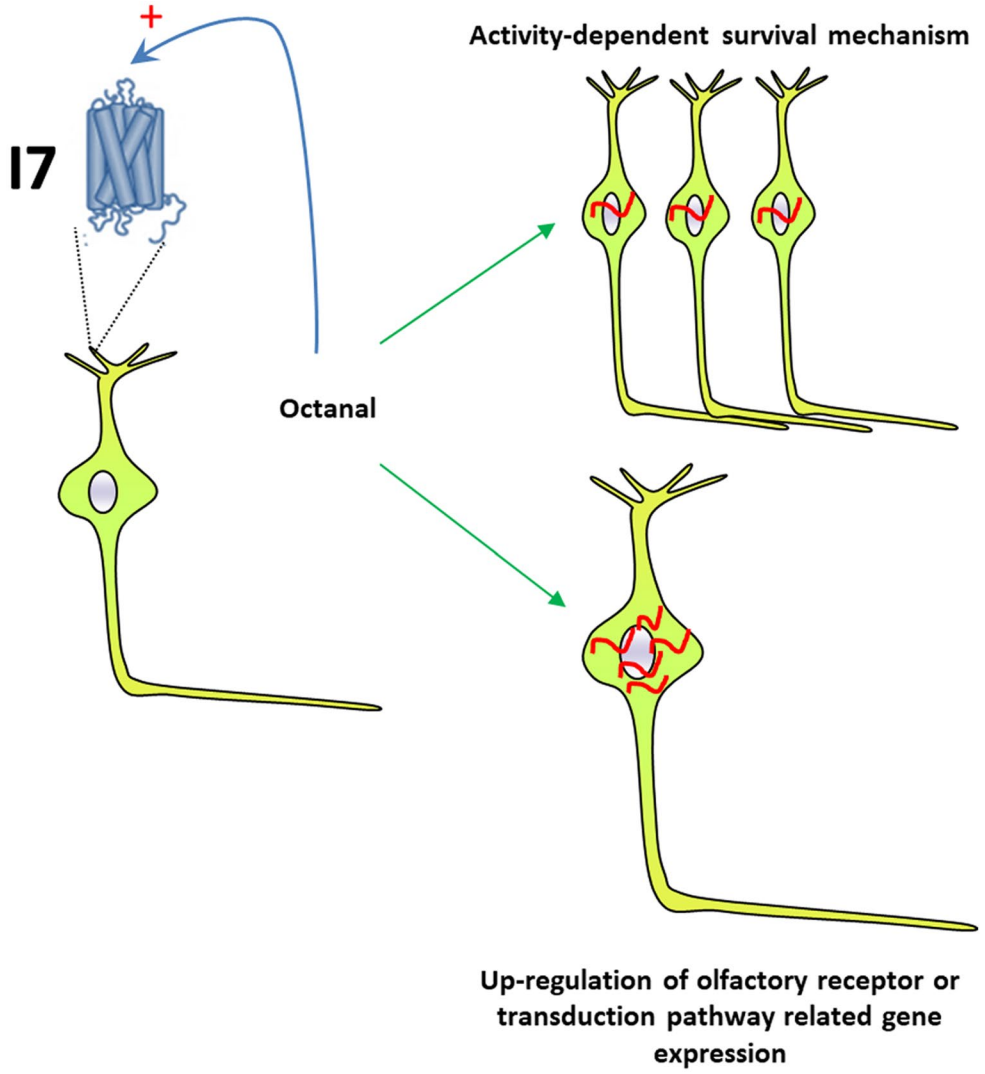

Fig. 2 Impact of the presence of an odorant on olfactory sensory neuron populations. Numerous studies have shown that the exposure to a broad range of odorant increases the response of the olfactory epithelium. Here, olfactory sensory neurons (OSNs) expressing the olfactory receptor I7 are stimulated most efficiently by octanal. Two different hypotheses can explain this change. Either the OSN population sensitive to this odorant increases through an activity-dependent survival mechanism (upper arrow), or the stimulated OSNs increase their response to the given odorant through an up-regulation of olfactory receptor gene expression or another mechanism improving the transduction pathway (lower arrow)

as well as the odorant used (Fitzwater and Coppola 2021). This is well illustrated by a review on the modulation of OR genes expression in the OE through activity-dependent mechanism (Wang et al. 2017).

A systematic study explored if activity-dependent survival of OSNs differs according to the OR they express. Using transcriptomics, the authors measured the evolution of mRNA levels coding for all ORs in the OE of mice living in various odorant environments (Ibarra-Soria et al. 2017). Based on the assumption that a given population of OSN expressing a specific OR is reflected by the mRNA level of this OR, they showed that only a small number of OSN subtypes are modulated by odorants. Furthermore, odorants must be present discontinuously, probably to limit the desensitization of the OSN. However, another study examining the impact of olfactory learning on OSN population plasticity (van der Linden et al. 2018) found that the correlation between a given population of OSNs and the mRNA level of ORs in the whole OE holds true only for part of the OSN population. Overall, these studies show that activity-dependent modulation of OSN activity may be controlled not only at the level of the OSN population but also by changing the transduction efficiency at the level of a single neuron (Fig. 2). The mechanism behind the tuning of the OSN population to the odorant environment remains mostly unexplored.

While all these studies have been performed in rodents, one group examined whether this plasticity also occurred in humans (Hummel et al. 2018). When participants were trained daily to smell a few odorants for 4–6 months, the amplitude of electro-olfactogram (EOG) recordings was increased. However, the effect was increased in response to all odorants tested by EOG, including the control odorants that were not used during the inhalation training. This result could be related to a global increase of olfactory performance after training due to central nervous system plasticity. More experiments are needed to show that activity driven survival of OSN is also a reality in humans.

Olfactory learning and OSN plasticity

In all the aforementioned experiments, odorant stimulations were used without associated cues. They can therefore be considered to involve "passive exposure" to odorants in contrast to the stimulus-associated odorants used in classical Pavlovian paradigms of associative learning (Herz 1998; McGann 2015). Here, we present studies specifically investigating the OE neuroplasticity during olfactory associated learning. The first study, performed by the Ressler group in 2008, explored the evolution of the OSN population sensitive to acetophenone during either aversive or appetitive conditioning in mice (Jones et al. 2008). For both conditionings, an increase was observed in the OSN population expressing *Olfr151*, an OR sensitive to acetophenone. Astonishingly, this associative learning in males was transmitted to the progeny which also displayed an increased representation of *Olfr151*-expressing OSNs in the OE (Dias and Ressler 2014). While this process could be reversed through extinction training (Morrison et al. 2015), the mechanism behind such intergenerational plasticity is still unknown, but probably involves epigenetic transmission of information. Indeed, the authors identified new epigenetic marks (i.e., methylation of cytosines followed by guanine residues in CpG sites) in the spermatozoid genome at the level of the *Olfr151* promoter, following an associative learning task with acetophenone. It remains to be determined how an integrated signal resulting in associative learning in the brain could impact DNA methylation in spermatozoa. Nevertheless, epigenetic marks induced by the neuronal activity may be essential for the activity-dependent plasticity of the OSN population. One key actor may be one of the DNA (cytosine-5)-methyltransferases (DNMTs), which are specific enzymes that cause methylation at CpG sites. Indeed, another group identified DNMT3A as necessary to ensure proper methylation of odorant-activated genes in OSNs (Colquitt et al. 2014).

Two research groups have also observed strong plasticity of the OSN population following associative learning. One study used odor-based fear conditioning (Kass et al. 2013b) and another go/no-go olfactory training (Abraham et al. 2014). Go/no-go olfactory training consists at obtaining a reward during a "Go" stimulus and at withholding the response for the "NoGo" stimulus (another odor usually similar to the first odor; Berditchevskaia et al. 2016). The modulation was observed in the OB at the level of the glomeruli by measuring OSN synapse activity. In both studies, this activity was increased following odor-based learning with a specificity of the OSN population responding to the odorant used. Interestingly, both studies investigated the impact of "passive exposure" without associated learning, which did not change the OSN output in the OB. This result confirms that the impact of "passive odorant exposure" on the OSN population is restricted to a few odorants (Ibarra-Soria et al. 2017) and probably less effective compared to learning tasks. However, while both studies observed that OSN are more effectively stimulated by an odorant previously used in a learning task, the authors did not evaluate if (1) the number of OSNs sensitive to the odorants used during learning was changed (although one group observed fast plasticity, after 3 days of associative learning (Kass et al. 2013b), which would not be consistent with significant OSN population changes); (2) the existing OSNs were more efficient in transmitting their information (Fig. 2); (3) a modification of the local circuitry through direct modulation by interneurons of OSN synapse effectiveness was involved.

While most studies focused on the main OE, one study explored the plasticity of OSNs in the VNO specialized in the detection of odorants with low volatility (Xu et al. 2016). In this study, Xu et al. evaluated an OSN population present only in males and activated specifically by a sulphated steroid present in female urine. Using calcium imaging, the authors observed that this OSN population became less responsive following co-housing with females. This effect could potentially be related to a diminution of the OSN number, which would be in contradiction to the results observed previously on the main OE. This difference was investigated further in another study focusing on the impact of co-housing of male and female mice on OSN populations in both the VNO and the main OE (van der Linden et al. 2018). In this work, the authors found that there is an optimal level of stimulation of OSNs in order to increase their lifespan through activity-dependent mechanisms. Interestingly, they observed that olfactory learning may impact both OSN population size and OR transcript levels in one OSN (Fig. 2) in contrast to other reports on passive odorant exposure, where only changes in the OSN population number were observed (Ibarra-Soria et al. 2017).

Perinatal exposure to odorants is a particular form of associative learning as the odorants will be associated to the maternal presence. This is nicely demonstrated by the work on odor cues inducing suckling in mice pups (Logan et al. 2012). In this study, the authors observed that pups initiate suckling thanks to the presence of amniotic fluid around the dam's nipples (present because the mother licks her own ventrum following birth). Mice pups probably learned these odors in utero as suckling can also be initiated in the presence of an artificial odorant around a washed nipple if the mother's diet was flavored with this odor during gestation. It suggests that the OSN population could be tuned to the odorant environment as early as during the perinatal period. The first study to explore the impact of prenatal odorant exposure on the OE was done in rabbits (Semke et al. 1995). In this study, pregnant rabbits were fed juniper berries and the authors recorded the electrophysiological response of the OE of the pups a few days after birth. They found a specific increase in the electrophysiological response to juniper oil in exposed pups in comparison to control pups which were not exposed to juniper berries. These results indicate that the OSN population can display an early plasticity similar to that observed in adults. These results contrast with other studies using other periods of exposure. Adding the odorant heptanal to the maternal food, during gestation then lactation specifically decreased the electrophysiological response of pup OSN to it (Dewaele et al. 2018). Other studies using an exposure limited to the postnatal period showed no effect on the OSN population (Kerr and Belluscio 2006; Monjaraz-Fuentes et al. 2017). Inducing plasticity at the level of the OE probably relies on the experimental conditions (odorant, concentration, type of exposure, period).

Olfactory-based memories are particularly important for imprinting, a mechanism well described in salmon which return to their natal river to reproduce. Such imprinting could be based on a tuning of the OE sensitivity to early exposure of odorants. A specific increase in the OE-sensitivity to imprinted odorants has been recorded in adult salmon (Nevitt et al. 1994). Furthermore, a study in zebrafish reported an OR expression modulation in a model of imprinting (Harden et al. 2006). Contrastingly, a recent review concludes that so far there is no clear evidence of such a mechanism, and extensive data indicate that olfactory imprinting in zebrafish is not based on modulation of OR expression, but rather on central processing modulation (Gerlach et al. 2019).

Concluding remark on OSN modulation by odorants

The effects of odorants exposure on OSN modulation are still controversial, mainly relying on different odorization protocols. The addition of odorants in the diet or environment at non-physiological concentrations may lead to a toxicity, which is rarely measured. In addition, the maternal gestational stress linked to an abrupt dietary transition from non-odorized to odorized food might also stress the pups and lead to a decrease in the OSN response to odorants as demonstrated for animals raised in unpredictable stress conditions (Raynaud et al. 2015). The effect of stress on the OE may be linked to the effect of glucocorticoids affecting this neuroepithelium (Meunier et al. 2020). Studies dealing with environmental modulations of OSN activity may thus also consider internal factors which are presented in the next section.

Direct modulation of OSN activity by internal signals

OSNs express a great diversity of receptors to hormones and local mediators; these can modulate their electric activity directly. In the following section, we have selected some neuromodulators where molecular evidence of direct interaction with OSNs has been illustrated.

Neurotransmitter: acetylcholine and OSN response potentiation

The vertebrate olfactory mucosa receives parasympathetic and sympathetic innervation participating in the peripheral modulation of olfactory signals in specific resting or stressing contexts, respectively (Lucero 2013). A direct modulation of the electrical response of OSNs by autonomic messengers was described first in frogs for acetylcholine (Bouvet et al. 1988). In isolated newt OSNs, acetylcholine enhances excitability by lowering the threshold of spike generation in

OSNs via the type 3 muscarinic acetylcholine receptor, M3 (Ohkuma et al. 2013). In mice, a M3 muscarinic acetylcholine receptor is expressed in the ciliary membrane of OSNs, which physically interacts with ORs to promote odorant-induced responses in vitro (Li and Matsunami 2011). The activation of M3 receptors amplifies OR activity by blocking the recruitment of β-arrestin 2, a scaffolding protein involved in the internalization-mediated desensitization of OR (Jiang and Matsunami 2015). It is likely that acetylcholine is not exclusively released from nerve ends, but could be locally supplied from cholinergic paracrine neighbouring cells, e.g., MvCs as discussed in the dedicated section (Ogura et al. 2011; Saunders et al. 2014).

Neurotransmitter: purinergic signaling and OSN inhibition

Presence of purinergic P2X (ligand-gated ion channels) and P2Y (metabotropic) receptors on OSNs is well described, and their activation is associated with olfactory response modulation in mice, whereas they are mainly present on sustentacular and basal cells in *Xenopus* tadpoles (Hegg et al. 2003; Czesnik et al. 2006). In mice, exogenous and endogenous ATP activates both receptors types to modulate the odor responsiveness, reducing odor-induced calcium transients in the majority of OSNs. Another study has shown that OSNs express distinct combinations of purinergic receptors leading to differential changes of OSN activity according to the OR expressed (Yu and Zhang 2014). Indeed, the response amplitude evoked by a mixture of ATP and benzaldehyde was half of that evoked by benzaldehyde alone, while a mixture of ATP and acetophenone evoked amplitudes similar to that evoked by acetophenone alone. Besides this direct impact on sensory signal transduction, detailed insights into other physiological properties and the functional significance of purinergic signalling in olfaction have been recently reviewed (Rotermund et al. 2019).

Hormones and peptides related to metabolic status

The OE is sensitive to the metabolic status of the animal, which could directly change odorant detection as OSNs express hormone receptors from the dendritic knob to the axon (Palouzier-Paulignan et al. 2012). In rodents, several metabolic factors exert short-term effects on electrophysiological responses to odorants as recorded by EOGs or patch-clamp after *ex-vivo* local application. Anorexigenic hormones such as insulin and leptin decrease odorant sensitivity, whereas orexigenic peptides such as orexin increase odorant sensitivity a few minutes after their application. In the years following two reviews focused on this subject (Palouzier-Paulignan et al. 2012; Lucero 2013), the number of known factors related to metabolic status that change OSN activity has increased in vertebrates. Their effects remain consistent with their main metabolic action. A single in vivo local nasal application of adiponectin, an adipocyte-derived starvation signal, and of ghrelin, another starvation-related hormone from the gastro-intestinal tract, rapidly increases the response to odorants (Loch et al. 2013, 2015). Similarly, application of neuropeptide Y (NPY), an orexigenic peptide, increases the electrophysiological response of OSNs, but only in fasted rats (Negroni et al. 2012). Endocannabinoids, which impact energy metabolism and feeding behaviour, have been also investigated for their functional importance in the olfactory system (reviewed Terral et al. 2020). Endocannabinoids exert contrasting effects depending on the species and differences between mammalian and other vertebrates are noticed: an endocannabinoid system was first described in the tadpole OE with a neuronal expression of CB1 receptors and endocannabinoid 2-arachidonoylglycerol synthesis in both neurons and SCs (Czesnik et al. 2007; Breunig et al. 2010). The authors concluded that modulation of odorant detection in the OE of larval *Xenopus laevis* depended on the metabolic state of the animal. In the mouse OE, functional CB1 receptors have been identified, but endocannabinoids probably do not modulate olfaction in this species, as CB1/2-deficient mice display intact olfactory-mediated behavioral performances, despite a significant loss in OSN population (Hutch et al. 2015). As in mammals, the presence of metabolic factors on olfactory organs in zebrafish suggests similar processes to control chemosensory stimuli (Montalbano et al. 2020).

Concluding remarks on modulation of OSN by internal environment

Several questions remain concerning the physiological relevance of these direct modulations of sensory signal transduction by internal factors:

1. What is the importance of peripheral versus central modulation in vivo?

   Many studies on modulation of olfactory sensitivity are based on behavioural integrated approaches. However, the importance of a peripheral direct modulation of the responses of OSNs in the OE relative to the one driven by central pathways remains to be explored. Indeed, the central processing of olfactory information may be impacted by in vivo intranasal treatment diffusing through the blood brain barrier and thus treating solely the OE in vivo is challenging. It could explain why in humans, the impact of hormones inhalation on odor sensitivity could be contradictory, depending on the experimental conditions (Brünner et al. 2013; Schöpf et al. 2015).

2. Is modulation of OSN activity a result of local action on cellular dynamics?

   OSNs synthetize ligands for several metabolic receptors as demonstrated for orexin, leptin, and insulin, some of them being locally modulated by the nutritional or metabolic status (Caillol et al. 2003; Baly et al. 2007; Lacroix et al. 2008). As these ligands have known pleiotropic roles, they could have additional roles independently of a short-term metabolic regulation. This has been clearly demonstrated for ATP and NPY which act synergistically to control OSN renewal in adult OE (Jia and Hegg 2010). Participation of these factors in the regulation of cell dynamics in the OE could change OSN sensitivity to odorants by affecting their population through long-term effects.

SCs

SCs form a tightly packed columnar monolayer in the OE. These glial cells lie on the *lamina propria* and possess numerous long microvilli that intermingle with the cilia of the OSNs on the apical side of the OE. SCs closely enwrap OSNs (Liang 2020) providing mechanical, trophic, and metabolic support. They are known to be involved in the secretion of mucus, biotransformation of noxious chemicals and in phagocytosis of dying cells. Numerous studies show that SCs impact the detection of odorants.

Indirect impact of SCs on OSN activity: focus on nucleotide signalling

SCs are known to act on OSNs by producing a myriad of neuromodulator molecules, e.g., endocannabinoids, insulin, NPY, peptide YY (an anorexigenic peptide), brain-derived neurotrophic factor (BDNF), and ATP (Hansel et al. 2001; Czesnik et al. 2007; Breunig et al. 2010; Hayoz et al. 2012; Frontera et al. 2015; Henriques et al. 2019). Some of these factors modulate olfactory sensitivity such as endocannabinoids in fasted tadpoles as described in the above OSN section (Breunig et al. 2010). In addition, SCs express receptors for insulin, leptin, orexin, and purinergic factors, making them targets for autocrine or paracrine regulations that are likely to participate in the crosstalk between SCs and OSNs. Numerous modulations of SCs are related to nucleotide signalling in the OE and we will focus on these modulators here (Housley et al. 2009; Rotermund et al. 2019). SCs express metabotropic P2Y purinergic receptors. ATP initiates intraepithelial Ca^{2+} influx in both OSNs and SCs in *Xenopus laevis* (Czesnik et al. 2006; Hassenklöver et al. 2009) and modulates the odor-evoked electrical activity of OSNs in rodents (Hegg et al. 2003, 2009). An ATP-activated chloride channel has been recently identified in mice SCs which may participate in this modulation (Henriques et al. 2019). In addition to the direct impact of SCs on odorant signal transduction, purinergic agonists such as ATP, ADP, and UTP could also be involved in trophic functions, particularly when OSNs are overstimulated. Purinergic signalling is also involved in the cellular dynamics of the OE as ATP initiates a cascade for neuroprotection and regeneration upon injuries (Hayoz et al. 2012). In this context, intranasal instillation of ATP in mice upregulates NPY expression in SCs which induces basal progenitor cell proliferation via activation of NPY1 receptors (Jia and Hegg 2012; Jia et al. 2013). Detailed insights into purinergic signalling have been published recently in the vertebrate olfactory system (Rotermund et al. 2019). Recent work in zebrafish indicates a similar role for ATP in activating among others a subset of OSNs (Wakisaka et al. 2017; Demirler et al. 2020). SCs also indirectly modulate rat OSN activity through the release of glucose in the mucus, where it could be transported into the OSN cilia by the major glucose transporter Glut3 and metabolized by glycolysis to generate ATP to ensure efficient olfactory transduction (Villar et al. 2017; Acevedo et al. 2019).

Direct impact of SCs on OSN activity: GAP junction communication

Gap junctions are composed of connexins and form a specialized intercellular connection between adjacent cells. They offer cytoplasmic continuity and electrical coupling between OSNs and SCs in the OE and therefore provide a pathway for intercellular communication (via Ca^{2+} and other signalling molecules—Vogalis et al. 2005; Hegg et al. 2009). Their importance in odorant sensitivity has been highlighted in a model of transgenic mice, for which an altered assembly of connexin-43 in OSNs reduces olfactory responses (Zhang 2010). In addition, acute treatment of OE with endothelin-1, one of the most potent vasoconstrictor peptides known to have pleiotropic roles (Masaki 2004) uncouples GAP junction in SCs (Le Bourhis et al. 2014). Concomitantly, endothelin-1 indirectly impacts OSNs response to odorants by delaying the repolarization kinetics of the olfactory responses (Bryche et al. 2019c). The mechanism behind such modulation remains to be clarified. It could be that endothelin-1 changes the SCs activity and impacts the maintenance of ionic concentration in the mucus which in turn would alter the OSN responses to odorants. It could also act simultaneously on OSNs as they are expressing connexins and are sensitive to endothelin-1 (Yu and Zhang 2015).

Microvillar cells: impact on odorant detection and link with the immune system

Microvillar cells (MvCs) are chemosensory cells scattered in the apical layer of the OE. They include various cell subtypes with similar characteristics, including an apical

tuft of short microvilli protruding into the nasal cavity and a basal cytoplasmic process resembling a short-axon-like process. At least three different types of MvCs have been described, based on their receptors and their signal transduction machinery, e.g., transient receptor potential cation channel subfamily M member 5 (TRPM5), 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-2 (PLC β2), transient receptor potential cation channel subfamily C member 6 (TRPC6), and receptor for inositol 1,4,5-trisphosphate (IP3R3) (Elsaesser et al. 2005; Montani et al. 2006; Lin et al. 2008; Hansen and Finger 2008; Genovese and Tizzano 2018). Their relative abundance and their location at regular intervals along the OE in the mouse suggest that MvCs play an important role in olfactory tissue homeostasis and modulation. MvCs are clearly involved in the control of neurogenesis of the OE (Montani et al. 2006; Hegg et al. 2010; Jia et al. 2013; Doyle et al. 2018). Furthermore, TRPM5-positive MvCs respond directly to chemical and thermal stimulations (Elsaesser et al. 2005). They probably impact OSN detection of odorants indirectly by releasing messengers like acetylcholine (Ogura et al. 2011; Fu et al. 2018). Indeed, acetylcholine changes the activity of neighbouring SCs and OSNs through muscarinic receptors as detailed in the OSN section of the manuscript. Some MvCs also express high levels of interleukin-25 (IL-25), and they generate cysteinyl leukotrienes in response to ATP or allergens indicating that they can elicit effector functions dedicated to local sentinel immune activities (Ualiyeva et al. 2020). They also selectively express a major regulator of mucus secretion and immune responsiveness, the cystic fibrosis transmembrane conductance regulator (CFTR) at their apical pole, whose knock-out impairs epithelial homeostasis, delays OE regeneration following methimazole-induced neurodegeneration and recruits inflammatory leukocytes (Pfister et al. 2015). A potential role for TRPM5-expressing cells in viral infection has been recently suggested, as a RNAseq library from MvCs displays an enrichment in molecules related to the inflammatory response elicited by viral infection of the OE (Baxter et al. 2020). Such a putative role of MvC as a sentinel against viral invasion remains to be confirmed by functional studies.

The importance of the immune system in the olfactory epithelium

Some studies have clearly demonstrated the importance of immune cells in the functioning of the OE including a change of odorant detection through ATP release from neighboring cells (Bryche et al. 2019a). The recent surge of anosmia linked to the COVID-19 pandemic has increased the number of studies of the importance of the immune system for the OE (Torabi et al. 2020).

At the interface of the environment and the nervous system, the OE constitutes a privileged pathway for harmful environmental agents including viruses, bacteria, amoebae, and environmental chemicals towards the central nervous system (Dando et al. 2014). This neuro-immune interface has been characterized in various vertebrates including salamanders (Getchell and Getchell 1991), humans (Mellert et al. 1992), chickens (Ohshima and Hiramatsu 2000), rodents (Imamura and Hasegawa-Ishii 2016), and teleost fishes (Yu et al. 2018). The OE is subject to immune cell infiltration and immune modulations, partly from a nasal associated lymphoid tissue (NALT) localized at the base of the nasal cavity (Tacchi et al. 2014) and described in most vertebrates (Tacchi et al. 2014). Cells of the OE synthetizes and secretes various immune and antimicrobial factors including mucosal immunoglobulins (Getchell and Getchell 1991) and chemokines (Ruitenberg et al. 2008). Moreover, the specific composition of the mucus covering the OE, which has not been fully characterized despite advances in proteomics approaches, appears to be central in the innate immune protection of the OE (Yoshikawa et al. 2018). Beyond the obvious role of the immune system in pathological situations, it appears also to be crucial in maintaining OE homeostasis and OSN activity, as indicated by a growing body of literature (Doty and Kamath 2014; Chen et al. 2019; Rustenhoven and Kipnis 2019).

We will first present studies showing changes of OSN activity linked to the immune system (in healthy or pathological conditions) before discussing possible mechanisms.

OSN activity and inflammation: roles of the immune system

There is a large body of literature linking nasal inflammation, damage to the OE, and olfactory disorders. In humans, chronic rhinosinusitis is one of the most common causes of olfactory loss (Gudis and Soler 2016). Several studies found correlations between olfactory cleft inflammatory cytokines/chemokines and olfactory performance in chronic rhinosinusitis patients (Yoo et al. 2019). In these patients, altered levels of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in olfactory cleft mucus are associated with reduced olfactory identification scores (Wu et al. 2018). Additionally, clinical studies indicate that immunodeficiencies (Magliulo et al. 2019) or uncontrolled activation of immune cells occurring in autoimmune diseases (Shin et al. 2019) can alter the capacity to smell, typically at the onset of disease. There are also olfactory disorders associated with immunomodulatory therapies, such as interferon-α treatment used to treat patients with hepatitis (Maruyama et al. 1998; Kraus and Vitezic 2000; Mayet 2007). The improvement of olfactory capacities through anti-inflammatory treatments like

glucocorticoid also testifies to the impact of inflammatory state on olfactory capacities (reviewed in Beecher et al. 2018).

To study more specifically the effect of cytokines on the olfactory system, and to explore inflammation-associated olfactory loss in vivo, a transgenic mouse with inducible olfactory inflammation was developed (Lane et al. 2010). This model, which mimics clinical aspects of human rhinosinusitis-associated olfactory loss, allows induction of OE cytokines expression, such as TNF-α.

Chronic inflammation induced by prolonged TNF-α expression causes an infiltration of inflammatory cells in the *lamina propria* (mainly macrophages), a thinning of the olfactory neuronal layer, and a progressive loss of olfactory function. These changes are accompanied by neuronal apoptosis and suppression of normal olfactory regeneration along with a decrease of ~ 60% in the response to odorant stimulation as recorded by EOGs (Lane et al. 2010; Turner et al. 2010). Further works with this model have highlighted the importance of TNF receptors of type II in such processes (Pozharskaya et al. 2013).

A functional immune system also appears necessary to maintain OE function. In 2015, Rattazi et al., identified impaired sense of smell and altered olfactory system in RAG-1−/− (recombination-activating gene 1) immunodeficient mice. RAG-1 is involved with RAG-2 in the rearrangement and recombination of the genes encoding immunoglobulin and T cell receptor molecules (Rattazzi et al. 2015). These two genes are therefore central to immune development. The OE of RAG-1−/− immunodeficient mice is atrophied and glomeruli in the OB are disorganized. These changes are correlated with diminished performance in olfactory tests (buried cookie test reviewed in Zou et al. 2015). Intriguingly, these defects only appear in adults and are not related to impaired development of the olfactory system. Among other hypotheses, the authors proposed that the NALT could be impaired in RAG-1−/− mice as it specifically develops after birth (Gänger and Schindowski 2018). NALT has been shown to be important for the release of factors regulating OE proliferation, differentiation, and maturation (Yu et al. 2018)—for review see Sepahi and Salinas 2016). Although these results contrast with a study performed in zebrafish where depletion of RAG-1 did not impact the development of the olfactory system (Feng et al. 2005), they do show the importance of the immune system for the maintenance of the integrity of olfactory function.

Proposed mechanisms for the modulation of vertebrate olfactory epithelium functionality by the immune system

Although there is an undeniable link between immune component inflammation and altered olfactory capacity, there is little evidence of a direct connection between these two phenomena and mechanistic data are lacking. Moreover, interactions between immune cells and the OE are mostly studied in pathological and multifactorial contexts and it is therefore difficult to uncover the specific mechanisms linking the two systems. Few hypotheses have been published; some of the main ones are presented below.

Linking olfactory sensory neuron transduction to immune system components: implication of perireceptor events

Over the last decade, a growing body of literature has shown the critical modulatory role of perireceptor events in the olfactory process (Heydel et al. 2019). These events rely on two main groups of proteins: odorant-binding proteins (OBPs) and enzymes surrounding the OR which are thought to be involved in odorant availability and/or olfactory signal termination (Robert-Hazotte et al. 2019; Heydel et al. 2019; Schwartz et al. 2020). Thus, any inflammatory process impacting mucus secretion, mucus composition, or the expression of compounds related to perireceptor events, including bioavailability of odorant-metabolizing enzymes (Morgan et al. 2008; Ijichi et al. 2019; Stanke-Labesque et al. 2020), may result in modulation of odorant detection (Fukuda et al. 2008; Robert-Hazotte et al. 2019).

OBPs are among the most expressed proteins in mucus (Kuntová et al. 2018). Their expression is affected by the inflammatory state in the nasal cavity (Yoshikawa et al. 2018). Our group found that OBP expression level is upregulated in axenic mice (François et al. 2016) and that viral infection of the OE also alters OBP expression in conventionally bred mice (Bryche et al. 2019b). Interestingly, a recent study highlights a relationship between the olfactory performance and the rs2590498 polymorphism of the *OBPIIa* gene (Sollai et al. 2019), which encodes the only OBP found in the OE of humans. This suggests a potential link between OBPIIa function and olfactory detection. Additionally, recent data suggest that OBPs may also act as antimicrobial components against pathogenic microorganisms (Bianchi et al. 2019). The dual role of OBPs in olfaction and immunity is also highlighted by a study indicating that OBPs may modulate neutrophil recruitment through binding to macrophage-derived inflammatory mediators in the upper airway (Mitchell et al. 2011).

Linking olfactory sensory neuron transduction to immune system components: ionic homeostasis in the mucus

Inflammation can also modify the ionic concentration in the mucus which is essential for an efficient olfactory transduction. As an example, chronic inflammation mediated by nasal instillation of a fungal protein extract of *A. fumigatus* in mice, led to a significant decrease in sodium concentration

and a marked increase in potassium concentration in the mucus (Selvaraj et al. 2012). These changes will impact OSN activity as olfactory transduction is based on cyclic nucleotide gated channels localized in their cilia (Li et al. 2016). Indeed, cyclic nucleotide gated channels mediate sensory transduction by conducting cationic currents carried primarily by sodium and calcium ions (Pifferi et al. 2006). Additionally, alteration of the ionic olfactory micro-environment by nasal irrigation (i.e., a sinus instillation with solutions of various ionic concentrations) in healthy patients lead to a significant olfactory threshold shift assessed by Sniffin' Sticks test (a psychophysical test that allows assessment of the patient's olfactory performance by means of 3 subtests: threshold test, identification test, and discrimination test) (see technical note—Rumeau et al. 2016).

These results were confirmed later by another group, which clearly demonstrates that deviations of both sodium and potassium levels from their homeostatic values can result in olfactory threshold elevations and therefore explain, at least in part, the olfactory dysfunction associated with chronic inflammation (Lam et al. 2015).

Using an induced olfactory inflammation model, Lane et al. (2010) found that OSNs respond to TNF-α with a Ca^{2+} influx, which may explain the reduced EOG responses. Lane and collaborators propose that the chronic presence of proinflammatory cytokines could reduce EOG responses by establishing a desensitized state that leads to reduced neuronal firing (Lane et al. 2010). Such an importance for a finely regulated spatial and temporal dynamics of calcium influx in the modulation of olfactory transduction has been confirmed later (Reisert and Reingruber 2019). Our group recently focused on IL-17C, an interleukin playing a crucial role in mucosal areas and whose neuromodulatory properties are well-described in the peripheral nervous system (Peng et al. 2017). By performing calcium imaging on olfactory mucosa slices, we found that IL-17C modulates the calcium levels in the OE within seconds of application (Bryche et al. 2019a). This modulation appears to be indirect via the release of ATP from neighbouring cells, which inhibit calcium responses upon stimulation by odors (Rotermund et al. 2019). Indeed, IL-17C induced calcium responses were effectively blocked by purinergic receptor antagonists supporting an involvement of purinergic signalling. Additionally, our EOG results showed that IL-17C decreases the amplitude of odor-induced responses in the OE, accordingly to the purinergic implication hypothesis. Overall, these results are consistent with an IL-17C-induced ATP release in mice, leading to calcium variation and a subsequent decrease in EOG responses.

Olfactory epithelium cell dynamics: functional switch of cells from neuro-regeneration to immune defence

During the past decade, immune cells and cytokines have been shown to play pivotal roles in regulation of apoptosis and neurogenesis in the OE, which is a unique self-renewing tissue. In addition to the review of Imamura and Hasegawa-Ishii (2016) exploring this topic in murine species, Borders et al. showed in mice that activated macrophages regulate neural progenitor cell proliferation, differentiation, maturation, and survival of OSN through the modulation of the expression of several genes (Borders et al. 2007a, b). Data obtained with the induced olfactory inflammation model suggest that there are two distinct phases of the olfactory deficit related to inflammation: an initial phase of physiological desensitization, followed by a cellular loss that results in a profound elimination of sensory activity (Lane et al. 2010). This model has been refined recently with the work of Chen et al. (2019). In their study, they describe the inflammation-induced switching of olfactory stem cells from a regenerative phenotype to one participating in immune defense. Indeed, acute olfactory inflammation causes an initial loss of OSNs which greatly impacts olfactory function. It results in the proliferation of previously quiescent basal cells which can differentiate to restore mature OSNs. Contrastingly, during chronic inflammation, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling in basal cells is activated. This large family of inducible transcription factors, which regulates a large array of genes involved in different processes of the inflammatory and immune responses (Liu et al. 2017) triggers a functional switch from a regenerative phenotype to a quiescent one. This switch allows the recruitment and the regulation of peripheral immune populations through chemokine secretion and therefore prioritizes pathogen removal (Fig. 3 and Chen et al. 2019; Rustenhoven and Kipnis 2019). Such chronic or severe inflammation could result in impaired regeneration of the OE as well as long lasting if not permanent anosmia.

Concluding remarks on neuroimmune interactions

Several areas of research remain to be explored to improve our understanding of the role of the immune system within the OE. These include:

1. to identify precisely resident immune cells within the OE and their relative involvement in the OE homeostasis,
2. to determine accurately how the immune response in the nasal cavity affects OSNs.

Finally, the position of the OE at the interface between the environment and the central nervous system also raises questions about the relative contribution of nasal inflammation to the pathogenesis of neurodegenerative disorders (Imamura and Hasegawa-Ishii 2016). This is particularly well illustrated by the hypothesis of Parkinson disease originating from viral infection of the OM (Doty 2008). New

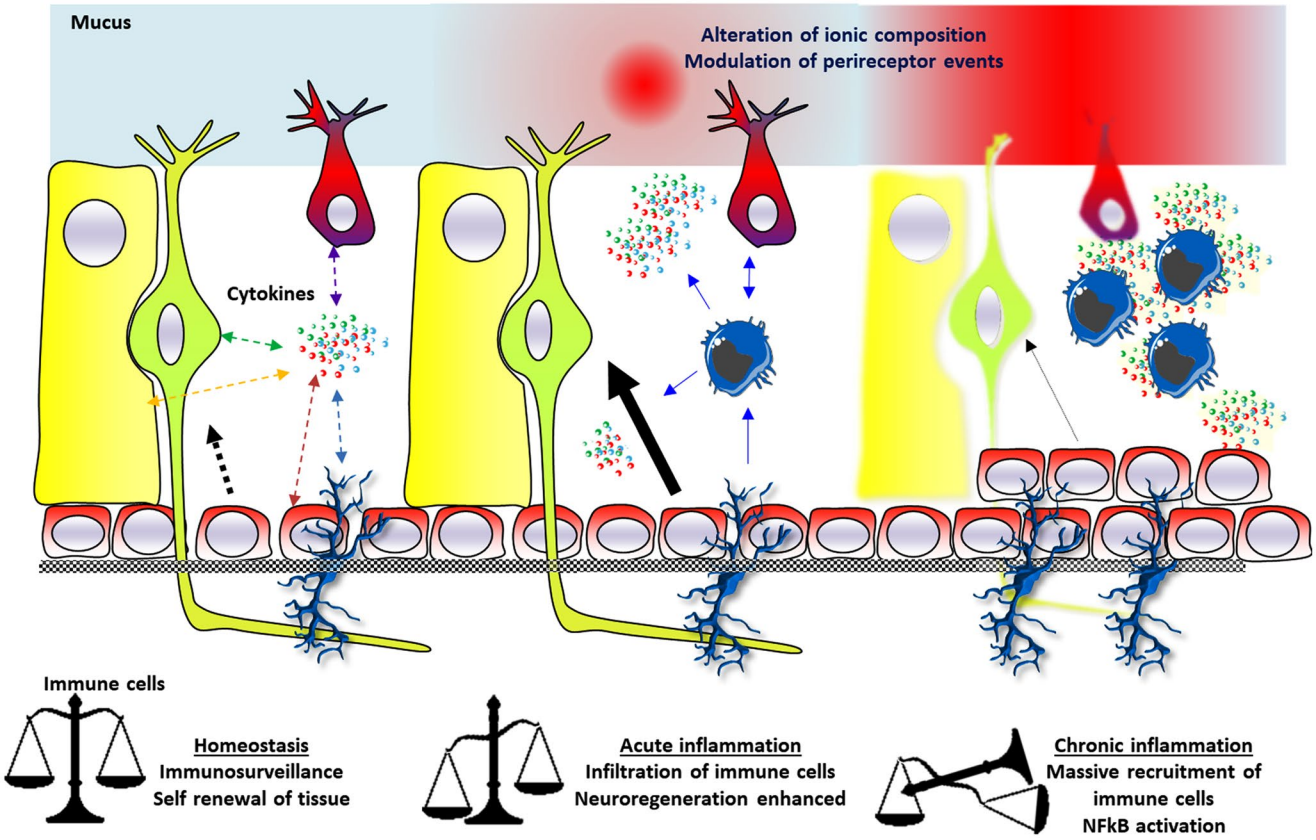

Fig. 3 Overview of the importance of the immune system in the olfactory epithelium. Cells of the olfactory epithelium (OE) are capable of synthesizing and releasing cytokines for autocrine or paracrine actions. In a homeostasis situation, proliferative basal cells allow for self-renewal of the whole tissue, including generation of olfactory sensory neurons which maintain appropriate odor-sensing capabilities despite the presence of pathogens and xenobiotics in the mucus. Immune cells exert immunosurveillance. During an acute infection, neuronal death is observed, which is limited by the rapid OE renewal, linked to immune cell infiltration (regenerative state). Immune components may alter mucus secretion and composition, modulate ionic balance and perireceptor events and therefore change the olfactory signal. Conversely, with chronic inflammation, there is a switch from a regenerative phenotype of basal cells to proliferation without differentiation in OE cells. This switch prioritizes pathogen removal involving massive immune cell recruitment and activation of nuclear factor-κB (NFkB) in basal cells

insights into the role of cytokines and immune cells in causing human olfactory dysfunction will potentially lead to new and more efficient therapies.

Conclusion

In this review, we tried to provide an overall albeit non-exhaustive view of the changes in olfactory signals in the OE. Previous studies on the expression of modulator receptors in the OE clearly showed that most are also expressed in the OB raising the question of a potential redundancy of modulation at these two levels of olfactory processing. There are several future research directions:

1. Similarly to many other research fields, we need to consider the use of diverse species in research before generalizing the importance of a modulation that is often studied solely in mice. Indeed, Fig. 1 clearly demonstrates the over-representation of mice studies, even if we tried to include as many relevant studies as possible from other vertebrates.
2. The development of genetically engineered mice expressing reporter genes in a subpopulation of OSNs has drawn much attention to a limited number of OR genes (mainly I7 and m71) and recent transcriptomic studies have demonstrated that the OSN modulation is variable according to the expressed receptor and mouse strain (Ibarra-Soria et al. 2017). Thus, caution must be applied before generalizing the observed modulation of OSN activity.
3. Due to the complexity of understanding the role of a single modulator, most are studied alone at non-physiological concentrations and in ex vivo conditions.

Antagonism or synergy between different messengers certainly exists. For example, the perception of odors can be influenced by stress and the inner emotional state of the animal (Raynaud et al. 2015; Bombail 2019; Meunier et al. 2020). Many experiments using anesthesia, animal manipulation, and intranasal instillation may induce stress and thus interact with the studied modulator. Exploring such interactions between modulators will be a future challenge to understand olfactory modulation at its higher level of integration, as demonstrated for ATP interactions with many other messengers such as NPY (Jia and Hegg 2010) or IL-17C (Bryche et al. 2019a). As ATP production is related to other modulators, it also raises the more general question of the nature of the signal triggering this production. Understanding the release mechanism behind these modulators and identifying cells releasing such compounds constitute a further step in the understanding of these messenger actions.

Finally, the main action of modulators may have been overlooked. For instance, the olfactory marker protein (OMP) has been identified more than 40 years ago (Hartman and Margolis 1975). OMP has been suspected for a long time to play a very important role in OSN maturation and OSN plasticity notably induced by external stimuli (Lee et al. 2011; Kass et al. 2013a). Astonishingly, a very recent study demonstrated that OMP was a cAMP buffer which was completely unexpected (Nakashima et al. 2020). Similarly, future studies may reveal previously unknown roles for OSN response modulators.

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Declarations

Ethical approval On behalf of all authors, the corresponding author states that there is no conflict of interest. This review was written without specific funding, and was performed using previously published results, without additional experimentation involving human participants or animals.

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