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NEUROGENESIS

Neurogenesis right under your nose

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Post-mortem studies have previously suggested that adult olfactory neurogenesis occurs in humans. Here, Durante and colleagues obtained fresh tissue from healthy adult humans via endoscopic nasal surgery and used single-cell RNA sequencing (RNAseq) to identify the entire neurogenic trajectory in the olfactory epithelium, confirming the existence of human olfactory neurogenesis.

'To be or not to be' was clearly 'the question' in the field of human adult neurogenesis during the past couple of years. The hippocampus, one of the regions where mammalian adult neurogenesis occurs, was placed directly under the spotlight when several contradicting studies were published one after another. They collectively put a question mark on the dogma established over half a decade of research and spurred a debate on whether neurogenesis persists in the human adult hippocampus ^{1,2}. Those in the field of hippocampal neurogenesis agree that the discussions are likely to continue until direct evidence of adult neurogenesis is provided from live human subjects ³. While it seems impossible to non-invasively obtain tissue from living humans to investigate hippocampal neurogenesis up to this day, Durante and colleagues recently took advantage of combining the use of extracranial tissue and single-cell RNAseq technology to study whether adult neurogenesis persists in another controversially discussed neurogenic niche, the human olfactory epithelium (OE) and elegantly demonstrates that it appears to ⁴.

The classical view on adult olfactory neurogenesis was established from rodent studies where neural stem cells residing in the subventricular zone (SVZ), a stem cell niche, begin to differentiate into neuroblasts which then migrate along the rostral migratory stream towards the olfactory bulb ⁵. In rodents, a large fraction of new-born neurons in the olfactory bulb are known to arise from neuroblasts that migrate from the SVZ to the OE ⁶. However, the OE is also a germinal zone in its own right where locally residing neural stem/progenitor cells (such as horizontal and globose basal cells) provide the source for continuous olfactory neurogenesis throughout adulthood ⁷. In addition, the OE is where olfaction begins, and the tissue can be easily obtained compared to the SVZ as it is located outside of the brain ⁸.

Durante and colleagues ⁴ derived fresh extracranial tissue containing the OE from 7 adult patients aged 23 - 52 who underwent endoscopic nasal surgery and conducted single-cell RNAseq as well as immunohistochemistry experiments to investigate evidence of adult neurogenesis. They hypothesised that neural stem/progenitor cells, immature olfactory neurons, and mature olfactory neurons should all be found in the adult human OE if there is ongoing neurogenesis in this region. Single-cell RNAseq on the dissected tissues revealed distinct groups of cells that can be distinguished via their respective transcriptomic profiles representing various stages of olfactory neuronal differentiation. Their findings highlighted noteworthy differences between humans and rodents. One of the most interesting differences pertains to the proportions of immature and mature olfactory neurons in the OE. Rodents generally show a moderate fraction of immature neurons in their OE ⁶. In contrast, more than half of the neuronal cells analysed in the human OE (~55%) showed characteristics of immature cells. Nevertheless, Durante and colleagues' ⁴ findings could verify certain predictions that had come from rodent studies. For instance, they analysed the expression pattern of 140 different olfactory receptors and found that the majority of mature olfactory neurons expressed only one olfactory receptor which was in agreement with the "one-neuron/one-receptor" rule in the olfactory system⁹.

Numerous studies have aimed to investigate whether there is evidence of adult olfactory neurogenesis in the human SVZ. However, structural characterization of human SVZ revealed striking differences between humans and rodents, and to date there is no robust data to support the idea of adult neurogenesis in the human SVZ ⁵. The human OE, on the other hand, has been shown to be similar to that of rodents. Although the morphology and cellular marker expression patterns of each cell type may differ to some extent, both human and rodent OE harbor neural stem cells, immature neurons, and newly born olfactory receptor neurons, all of which are cell types that arise during olfactory neurogenesis ^{10,11}. Furthermore, neural stem cells in explanted human OE are capable of differentiating into olfactory neurons ex vivo ¹⁰.

Although the human OE was shown by numerous studies to qualify as a stem cell niche for adult olfactory neurogenesis, a nuclear bomb-derived ^{14}C birth-dating study of mature neurons in the human olfactory bulb suggested that postnatal neurogenesis does not seem to persist in this region. This was based on the observation that virtually all neuronal nuclei (NeuN)-expressing cells (mature neurons) in the adult human olfactory bulb were the same age as the subjects' age¹². However, it is not clear whether the olfactory bulb samples analyzed included OE tissue. Unlike Bergmann and colleagues, Durante's team specifically focused on the OE as a neurogenic niche.

Using freshly obtained tissues from live subjects with no obvious olfactory dysfunction and clustering tens-of-thousands of cells in these tissues based on their transcriptomic profiles, Durante and colleagues shed new light on this debate and elegantly provide evidence that adult neurogenesis may persist in the human olfactory system ⁴.

Biopsy of human OE from live subjects is not a novel form of surgery and has been used extensively by multiple research groups in OE characterization studies ^{8,11}. However, Durante and colleagues were the first group to combine this biopsy technique with single-cell RNAseq to study adult neurogenesis. To our knowledge, no one has done a similar kind of analysis before. Such a combination opens up new opportunities for investigating the role of olfaction directly in healthy subjects and patients with various diseases, as previous studies have shown that the OE is highly sensitive to environmental changes such as sensory deprivation and inflammation. Using Durante and colleagues' approach, future investigators might elucidate how adult olfactory neurogenesis is regulated in the context of health and disease and help to pinpoint the relevant mechanisms at the molecular level.

Even though it was just a side observation, a particularly interesting finding reported by Durante and colleagues is the presence of immune cells in the adult human OE. Notably, a population of activated leukocytes was detected in the human OE tissues, that showed the OE harbors a large fraction of immune cells that constitute both the innate immune system (i.e. natural killer cells, macrophages, antigen presenting cells) and the adaptive immune system (i.e. B cells, plasma cells, helper and cytotoxic T cells). Although the impact of activated leukocytes in the adult human OE was not within their scope of investigation, Durante and colleagues' observation of the abundance of those cells in the adult human OE directly supports the idea that the immune system and inflammatory response play an important role in this niche. Indeed, this falls nicely in line with Chen and colleagues' recent study where the authors demonstrated the regulation of local immune cells by neural stem cells in the mouse OE ¹². Chen and colleagues found that acute inflammation in the nasal cavity of mice led to a compensatory increase in the number of newly born neurons in the

OE. However, when the inflammation persists and becomes chronic, murine OE neural stem cells became 'locked' in a non-proliferative state. Instead of making new neurons, they took over an immune-mediating role which involved secreting cytokines and chemokines which had a direct impact on the local immune cells¹³.

Durante and colleagues' data confirm that such immune cells can also be found in the human OE and prompt further investigations to be carried out in the future to address the following questions. For example, do humans and rodents have a similar immune cell composition in the OE? Would acute and chronic inflammation in the nasal cavity change the behavior of human OE neural stem cells like Chen and colleagues described in their mouse model? Employing the techniques used by Durante and colleagues to address these questions in live human subjects would help to connect these dots.

Olfactory dysfunction is associated with different forms of dementia including Alzheimer's disease, vascular dementia, Parkinson's disease and frontotemporal dementia. However, the underlying mechanisms are not entirely clear ¹⁴. In the context of adult neurogenesis, it would be interesting to analyze the OE niche in patients with various forms of dementia and profile their cellular and molecular composition. Recently, it was shown in a mouse model that impaired adult olfactory neurogenesis was an early event in an Alzheimer's disease model ¹⁵. Investigating whether this is also true in humans using the techniques used by Durante and colleagues will not only give us a better understanding of disease-relevant mechanisms but also facilitate disease prediction and earlier diagnosis, as well as the development of effective intervention strategies. For example, one could conduct a longitudinal cohort study in mild cognitive impairment and Alzheimer's disease subjects and examine the changes in the cellular and molecular composition of the OE niche. If used in conjunction with the subjects' cognitive performance data, such an experiment would have great implications in both disease prediction and early intervention.

Durante and colleagues showcase their highly versatile approach to investigate adult neurogenesis in live humans. Their single-cell analysis confirms the findings of previous studies of adult olfactory neurogenesis in the human OE and suggests a role of the immune system in the homeostasis of the neurogenic niche. These findings open up possibilities to investigate the involvement of the immune system in the olfactory niche and the investigation of adult neurogenesis in the context of disease using fresh human primary tissue with no post-mortem delay.

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