Review of: "The structural basis of odorant recognition in insect olfactory receptors"

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An elegant study by Josefina del Mármol, Mackenzie Yedlin and Vanessa Ruta came into the spotlight immediately after its preprint had been published on Biorxiv at the beginning of the year (https://www.biorxiv.org/content/10.1101/2021.01.24.427933v1). Undoubtedly, enthusiasts in the field of insect chemoreception recognized this publication as a long-waited sequel of the scientific saga released in 2018 by Butterwick *et al.* (https://www.nature.com/articles/s41586-018-0420-8). Indeed, the structure of Orco co-receptor determined 3 years ago was necessary but insufficient component for understanding the molecular principles of insect olfaction. It might be expected that the next step in deciphering ORs architecture is solving the structure of OrX/Orco heteromer, but in fact Ruta's lab offered much more intriguing scenario. The authors used molecular phylogeny to find the evolutionarily ancient species (jumping bristletail), in which Orco had not yet appeared and ORs function as homomers. Studying this unusual object thus can be essential for understanding the evolutionary logic in the olfaction development.

Although the authors found the structural determinants of ion pore functioning and suggested a mechanistic model for the odorant-dependent gating, their study, perhaps, is more focused on the issue of ligand specificity. Analyzing the structural data of MhOR5 – a homotetrameric receptor with broad odorant specificity – they revealed a ligand binding site constituted of ten amino acid residues. Mutations at these positions allowed tuning of both specificity and sensitivity of the receptor. It sounds counterintuitive and therefore especially intriguing that the ligand-binding site of MhOR5 is built of conserved residues, and its spatial organization appears to be rather archetypic than uniquely adapted one.
Researchers dealing with heterologous expression of ORs in mammalian cells could also mention important findings regarding the structural evidence of spontaneous opening of MhOR5 channel reported in the paper. Thanks to these data, it becomes clearer why the expression of ORs in HEK293/HeLa and especially in neurons is associated with severe cytotoxicity.

The insect olfaction still holds many secrets. Thus, the controversial issue of signal transduction mechanisms characteristic of these receptors, in particular, the role of G-protein signaling in smell perception, remains generally unresolved. The structural and functional homogeneity of ORs within an insect species and larger taxonomic groups also raises questions. However, research standards implemented in the field by Josefina del Mármol, Mackenzie Yedlin and Vanessa Ruta inspire with hope that

the answers await us in the near future.