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Ionotropic Receptors (IRs): Chemosensory ionotropic glutamate receptors in *Drosophila* and beyond

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ABSTRACT

Ionotropic Receptors (IRs) are a recently characterized family of olfactory receptors in the fruit fly, *Drosophila melanogaster*. IRs are not related to insect Odorant Receptors (ORs), but rather have evolved from ionotropic glutamate receptors (iGluRs), a conserved family of synaptic ligand-gated ion channels. Here, we review the expression and function of IRs in *Drosophila*, highlighting similarities and differences with iGluRs. We also briefly describe the organization of the neuronal circuits in which IRs function, comparing and contrasting them with the sensory pathways expressing ORs. Finally, we summarize the bioinformatic identification and initial characterization of IRs in other species, which imply an evolutionarily conserved role for these receptors in chemosensation in insects and other protostomes.

1. Introduction

In 1999, the discovery of Odorant Receptor (OR) genes in the fruit fly, *Drosophila melanogaster*, allowed definition of the molecular logic of insect olfactory system organization, permitted the development of genetic tools to visualize and manipulate specific olfactory pathways to determine how odors are encoded to evoke behavior, and founded comparative molecular evolutionary studies of the olfactory system across insects (Benton, 2007; Hansson and Stensmyr, 2011; Masse et al., 2009; Su et al., 2009; Vosshall and Stocker, 2007).

During the following decade, comprehensive anatomical and functional maps of Olfactory Sensory Neurons (OSNs) in both the peripheral sensory organs (the third antennal segment [hereafter, antenna] and maxillary palp) and the primary olfactory center in the brain (the antennal lobe) of *Drosophila* (Su et al., 2009; Vosshall and Stocker, 2007), revealed a large number of antennal neurons that do not express OR genes, or the related Gustatory Receptor (GR) genes (Montell, 2009; Vosshall and Stocker, 2007), implying the existence of another family of insect olfactory receptors. In 2009, through a bioinformatic and expression screen for novel olfactory genes (Benton et al., 2007), a large and highly divergent family of ionotropic glutamate receptor (iGluR)-related genes, named Ionotropic Receptors (IRs), was proposed as the "missing" receptor repertoire (Benton et al., 2009).

In the past four years, characterization of *Drosophila* IRs, the neuronal circuits in which they function, and their homologs in other species, have revealed them to be an important and ancient repertoire of chemosensory receptors. Here, we synthesize these studies to provide a view of the current knowledge and open questions on the IRs.

2. IR expression in the *Drosophila* olfactory system

The *Drosophila* antenna is covered with porous sensory hairs, or sensilla, of three morphological classes – basiconic, trichoid and coeloconic – which house the ciliated dendritic endings of 1–4 OSNs (Fig. 1A). All basiconic and trichoid OSNs (as well as all maxillary palp OSNs) express OR genes, with the exception of the GR21a/GR63a CO_2-sensing neurons (Couto et al., 2005; Fishilevich and Vosshall, 2005; Jones et al., 2007; Kwon et al., 2007; Su et al., 2009; Vosshall and Stocker, 2007). By contrast, antennal coeloconic ("ac") sensilla neurons do not express ORs, with one exception (OR35a) (Couto et al., 2005; Yao et al., 2005). There are two other sensory structures on the antenna: the arista, a feather-like projection (Foelix et al., 1989), and the sacculus, a multichambered "pit" (Shanbhag et al., 1995), whose neurons express neither ORs nor GRs.

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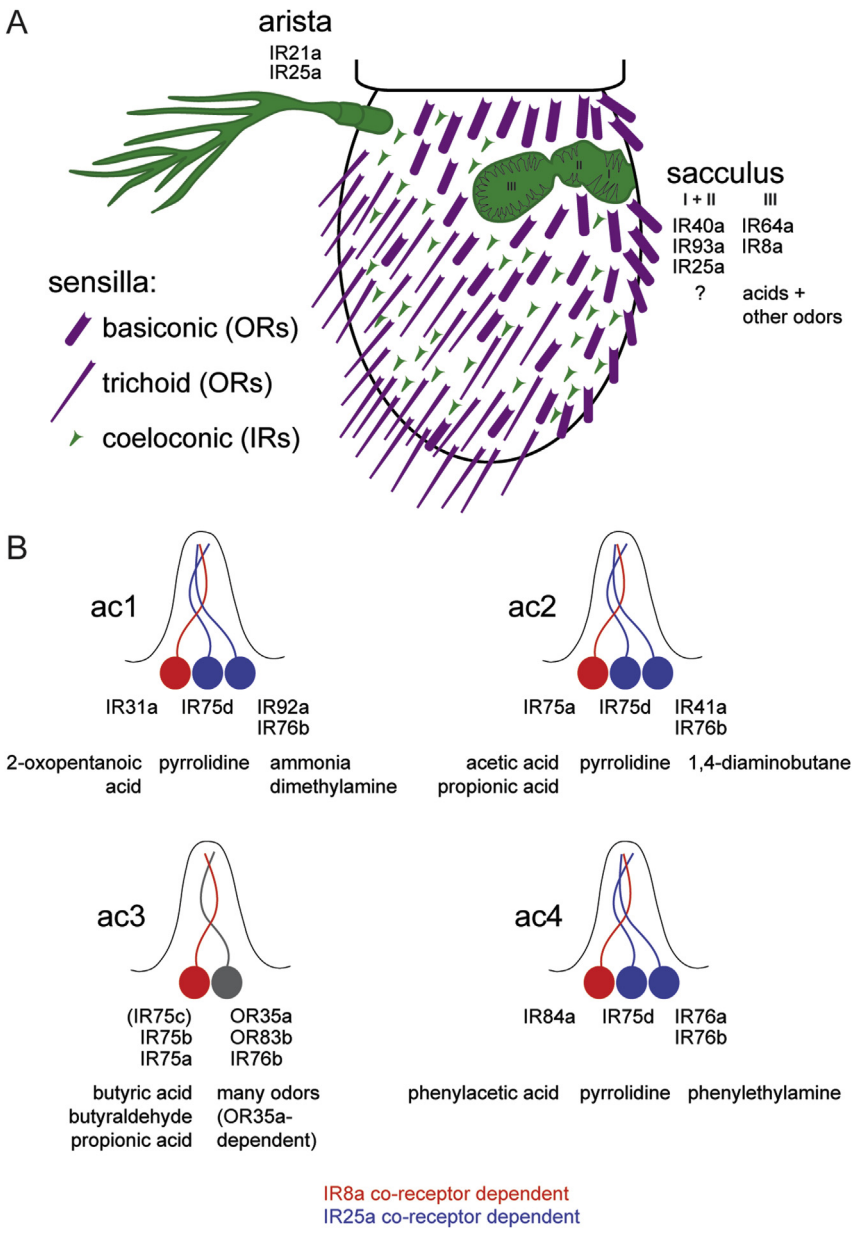

Fig. 1. Expression and odor ligands of antennal IRs. (A) Schematic representation of sensory structures on the olfactory third antennal segment of *Drosophila melanogaster*, color coded for their expression of ORs (magenta) or IRs (green). (B) IR expression in OSNs innervating antennal coeloconic (ac) sensilla. The best identified ligands for each neuron are indicated. Expression of the broadly-expressed co-receptors IR8a and IR25a is not shown, but OSNs shaded red require IR8a and mainly respond to acids/aldehydes, while OSNs shaded blue require IR25a and mainly respond to amines.

Genomic analysis has identified 66 IR genes (including 9 putative pseudogenes) in *D. melanogaster* (Benton et al., 2009; Croset et al., 2010). Comprehensive expression analysis of these genes by RT-PCR, fluorescence RNA *in situ* hybridization and/or using transgenic reporters has shown that 16 of these are expressed in the antenna. Ten of these IRs are expressed in selective subsets of coeloconic sensilla OSNs (Benton et al., 2009; Croset et al., 2010), either uniquely, or co-expressed with 1–2 other IRs (Fig. 1B). Pioneering electrophysiological characterization of odor evoked-responses of coeloconic sensilla OSNs (see Section 3) defined the existence of four sensilla classes (ac1–ac4) with different response profiles and distinct but overlapping distributions on the surface of the antenna (Yao et al., 2005). The spatial map yielded by expression analysis of IR genes corresponded closely with the spatial distribution of the physiologically defined coeloconic classes (Yao et al., 2005), providing a compelling, though indirect, line of evidence that the receptors define the odor response profiles of these neurons (Benton et al., 2009). One neuronal class in ac3 sensilla co-expresses OR35a and IR76b, but the characterized odor responses in these neurons depend solely on the OR gene (Benton et al., 2009; Yao et al., 2005).

Two IRs, IR8a and IR25a, are expressed – at somewhat heterogeneous levels – in many of the coeloconic OSNs (Benton et al., 2009). Consistent with this broad expression, these receptors appear to function as co-receptors with several different, selectively expressed IRs (see Section 4) (Abuin et al., 2011; Benton et al., 2009). IR25a is additionally expressed, more weakly, in basiconic and trichoid OSNs, but its function in these cells, if any, is unclear (Benton et al., 2009).

The four remaining antennal IRs – IR21a, IR40a, IR64a and IR93a – are not found in coeloconic sensilla. IR21a is expressed, together with IR25a, in aristal neurons (Benton et al., 2009)