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REGULATORY MECHANISMS IN OLFACTORY SYSTEM ASSEMBLY AND FUNCTION

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ABSTRACT

The mammalian sense of smell relies on the detection of odorants by a large family of G protein coupled receptors, encoded by ~1300 different genes in mice (Buck and Axel, 1991; Zhang et al., 2007). These odorant receptors (ORs) are expressed in olfactory sensory neurons (OSNs) in the main olfactory epithelium (MOE). A key feature of the mammalian olfactory system is that each OSN expresses only one of 2600 potential OR alleles (Chess et al., 1994; Malnic et al., 1999) such that the expression of a single specific OR protein establishes the odorant selectivity and identity of an OSN. Several layers of regulation control odorant receptor choice (Nguyen et al., 2007). Understanding this regulatory hierarchy of OR gene expression is critical in elucidating how odorant receptor choice is orchestrated and how ORs pattern the system.

Precise control of OR expression is fundamental for the assembly and operation of the MOE and the main olfactory bulb (MOB). ORs play an instructive role in OSN axon guidance and the generation of a topographic glomerular map in the MOB (Malnic et al., 1999; Ressler et al., 1994; Vassar et al., 1994; Mombaerts et al., 1996; Wang et al., 1998). This first order glomerular map resides on the surface of both olfactory bulbs and is mirror symmetric, i.e. each bulb is comprised of identical lateral and medial glomeruli (Ressler et al., 1994; Vassar et al., 1994; Mombaerts et al., 1996; Belluscio and Katz, 2001). These isofunctional glomeruli are precisely and reciprocally connected by a second order intrabulbar map directly beneath the surface glomerular map (Schoenfeld et al., 1985; Belluscio et al., 2002; Lodovichi et al., 2003). Neural activity plays an important role in establishing and shaping the connections within these olfactory maps and defines the functional organization of the system (Cummings and Belluscio, 2008). Olfactory maps likely result from a combination of neuronal activity and chemical guidance cues.

While many families of guidance molecules have been found to be expressed in the olfactory system, their role in organization and function are not determined. GDNF and its receptor GFRα1 have been detected in the main olfactory system (Cao et al., 2006; Maroldt et al., 2005; Nosrat et al., 1997; Paratcha et al., 2006; Trupp et al., 1997), but their specific cellular localization and importance in the functional organization of the olfactory system is still unknown. Understanding the functional roles of GDNF signaling may provide a molecular basis for factors that pattern the olfactory system.

This thesis investigates the mechanisms that regulate five fundamental components of olfactory system assembly and function: 1) odorant receptor expression, 2) odorant receptor choice, 3) OSN axon guidance, 4) olfactory maps, and 5) guidance molecules. Thematically specified, these mechanisms include the OR coding sequence in OR gene regulation, timing of OR expression, activity in the intrabulbar map, GDNF signaling in assembly and function, and GFRα1 in olfactory interneuron development.