Systematic identification of wiring specificity molecules using single-cell genomics

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EDITORIAL

Our human brain consists of billions of neurons, and each neuron forms about one thousand synaptic connections with other neurons, providing cellular basis for us to sense, think, and act. My research interest falls into two fundamental questions: How are different neuronal subtypes specified during development? What controls neuronal wiring specificity? Understanding these two questions is the key to understand how the brain develops and functions. Precise neural circuit assembly is critical for appropriate function of the nervous system. Neural circuit assembly comprises multiple processes, including cellular specification, axon/dendrite targeting, and synaptic partner matching. These steps must be highly coordinated and tightly controlled to ensure precise neural circuit assembly. Accordingly, many studies have focused on understanding the developmental mechanisms underlying those processes. Over the past several decades, numerous molecular and cellular mechanisms playing roles in neural cell fate specification, axon guidance and dendrite morphogenesis have been identified.

Synaptic partner matching, the last step in circuit assembly, is relatively poorly understood, and underlying molecules and mechanisms are just being revealed. I am using *Drosophila* olfactory circuit as a model to study neuronal fate determination and wiring specificity, aiming to find common principals that govern those two processes in higher organisms. *Drosophila* olfactory system consists of ~50 classes of olfactory receptor neurons and ~50 classes of projection neurons, which form one-to-one connections in the antennal lobe, providing a powerful model to study mechanisms for neuronal specification and wiring specificity. The olfactory circuit organization shares high similarities between flies and mammals. In *Drosophila*, each class of ORN expresses a single olfactory receptor (OR) gene and sends its axons to a specific glomerulus in the antennal lobe, where the corresponding class of PN arborize dendrites in the same glomerulus to make synaptic connections with ORN axons. PNs receive olfactory information directly from ORNs through ORNàPN synapses, and send the information to higher brain centers, including the mushroom body calyx and lateral horn, through PN axons. The development of ORN-PN connections can be roughly divided into three phases: i) PN dendrites begin to innervate the antennal lobe from 0 hour after pupae formation (APF) and, by 18h APF, have occupied the coarse positions of their future glomeruli; ii) ORN axons begin to arrive at the edge of the antennal lobe at 18h APF and further converge onto subregions near their final target area; iii) Between 26h and 48h APF, ORN axons invade the antennal lobe and connect with corresponding PN dendrites to form individual glomeruli. These three steps can be simplified as PN targeting, ORN targeting and ORN-PN matching. How are these stereotyped events controlled at the molecule level? Previous studies have identified a number of molecules and mechanisms that control neuronal fate determination and wiring specificity in *Drosophila* olfactory system, some of which have been shown to play conserved roles in mammalian neuronal systems. However, our understanding of those mechanisms is far from complete. Most of previous findings have used genetic approaches, e.g., loss-of-function and gain-of-function screen and RNAi screen. There are several limitations using genetic approaches. First of all, most of the genetic screens, largely depending on available reagents (e.g., transgenic animals), could not cover all genes of the fly genome, or even all genes encoding cell surface molecules which are likely to mediate most of above processes. Secondly, in most cases, only one gene is investigated at one time, such that if a combination of two or more genes act redundantly to control neuronal specification or wiring specificity, it will be very difficult to reveal these gene combinations. I am interested in applying genomic approaches, single-cell RNA sequencing for example, to addressing those question. Currently, we have established a reliable single-cell RNA-seq platform for collecting single-cell transcriptomes and processing data for *Drosophila* neurons. Based on this, I aim to study how lineage-specific factors, specifically transcription factors (TFs) and cell surface molecules (CSMs), regulate neuronal identity and wiring specificity, as TFs and CSMs are generally considered to control those two processes, respectively. My research has broad significance beyond olfactory circuit wiring. The wiring principles we learn from flies are likely generalizable to more complex circuits in the mammalian brain. Understanding the basic mechanisms of wiring specificity is a prerequisite to understanding how mis-wiring may contribute to neurological and psychiatric disease.

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