A molecular link between distinct neuronal asymmetries

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Striking functional lateralization of the human brain across the left–right axis has long been known, the most notable of which is the localization of language to the left side of the brain. Mechanisms used to establish brain asymmetry have remained elusive due to the difficulty of identifying molecular correlates of functional asymmetries. The nematode Caenorhabditis elegans has been a valuable system to address molecular mechanisms used to confer asymmetry on a largely symmetric nervous system; it is one of the few organisms in which clear molecular-to-functional asymmetric correlates have been identified.

Two pairs of C. elegans sensory neurons display morphological and functional asymmetries: AWC olfactory neurons and ASE taste neurons.1,2 Each pair of these neurons expresses a different set of chemoreceptor genes such as str-2 (Fig. 1).2 AWCOff is a default fate and is specified by a calcium-activated CaMKII–MAPK cascade. Intracellular calcium signaling between the 2 AWC and other neurons in a network connected via NSY-5 gap junctions establish stochastic AWC asymmetry during late embryogenesis.4,6 Differential calcium levels between the 2 AWC neurons are essential for asymmetric AWC differentiation. The cell with a higher calcium level remains as the default AWCOff fate, while the cell with a lower calcium level becomes the induced AWCOn fate.6 Several mechanisms have been identified to inhibit the calcium–kinase pathway to induce AWCOn. For example, the NSY-5 gap junction protein and NSY-4 claudin-like protein act in parallel to inhibit the calcium-activated kinase pathway in the induced AWCOn fate (Fig. 1).5,7

In contrast to AWC neurons, ASE asymmetry is established at the 4-cell stage and is lineage-dependent. ASE left (ASEL) and ASE right (ASER) neurons express different putative chemoreceptors of the receptor-type guanylyl cyclase family in a directionally asymmetric manner. Notch signaling and priming of the chromatin of a microRNA (miRNA) locus in the early lineage of ASEL and ASER are crucial for ASE asymmetry and result in a complex transcriptional regulatory network and a bi-stable negative feedback loop. In ASEL, the DIE-1 transcription factor and lsy-6 miRNA suppress expression of the COG-1 transcription factor to promote ASEL-specific genes. In ASER, COG-1 represses DIE-1 at a transcriptional and post-transcriptional level (Fig. 1).

Although AWC and ASE neurons appear to use distinct mechanisms to establish asymmetry, a recent study discovered an interesting molecular link between these 2 types of asymmetries.3 The zinc finger transcription factor DIE-1 has long been known to be important for ASE asymmetry, but its role in AWC neurons was not known. In a study aimed at examining the regulation of directionally asymmetric die-1 expression in ASEL, it was discovered that die-1 is also asymmetrically expressed in AWC neurons. Intriguingly, asymmetric expression of die-1 in ASE neurons is stochastic, reflective of the stochastic nature of AWC asymmetry.

Expression of die-1 is regulated in distinct ways in AWC and ASE neurons. In ASE neurons, 3 phases of die-1 regulation have been identified:3 (1) the early bilateral phase, during which die-1 is initially expressed in both ASE neurons; (2) restriction of die-1 to only ASEL through transient activity of the afore-mentioned cog-1, which suppresses die-1 in ASER; (3) maintenance of asymmetric die-1 expression in ASEL using a transcription factor called CEH-35 as well as DIE-1 to maintain its own expression in ASEL. Asymmetric expression of die-1 is also maintained using the FOZI-1 transcription factor, which represses die-1 in ASER throughout life.

In AWC neurons, die-1 is expressed in a stochastically asymmetric fashion in the AWCOff neuron; antisymmetric die-1 expression is dependent on NSY-4 tight junctions and NSY-5 gap junctions. Consistent with asymmetric die-1 expression in AWCOff, die-1 is required for the
calcium-activated CaMKII-MAPK pathway to specify the AWC<sup>OFF</sup> fate in a cell autonomous fashion (Fig. 1).<sup>3</sup> Although hypomorphic alleles for <i>die-1</i> affect ASE asymmetry, only <i>die-1</i>-null mutants affect AWC asymmetry, suggesting a differential requirement for <i>die-1</i> activity in AWC and ASE neurons.

Overall, <i>die-1</i> is essential for the establishment of 2 distinct forms of neuronal asymmetries. Although the mechanisms used to regulate <i>die-1</i> are distinct in the 2 pairs of neurons described, this molecular link may represent an evolutionary tie between stochastic and directional asymmetries, in which directional asymmetry is perhaps a more evolved system used to confer functional diversity on a largely symmetric nervous system.

**References**

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**Figure 1.** Schematic of AWC and ASE asymmetry. Intercellular communication mediated by gap junctions (GJ) and claudins coordinates asymmetric expression of chemosensory receptor genes in AWC. Directional ASE asymmetry is established through transcriptional and posttranscriptional regulatory cascades. Not all molecules involved are listed. Molecules in black or red are active and gray are less active or inactive.