**Networks, Structures and Evolution of Extracellular Interactions in Driving Neuronal Connectivity**

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Molecular recognition lies at the heart of axon guidance mediated by guidance cues and their interactions with cell surface guidance receptors. Major guidance receptor-cue complexes were identified using genetic and biochemical means nearly three decades ago, which were established to function in several guidance model systems, such as midline attraction and repulsion in bilaterians, and visual and olfactory circuits. Recent advances have increased this repertoire, but the general rules of recognition – pairs of cues and receptors – have remained mostly unchanged. Here, we question and update these interactions for the Robo, Ephrin, Eph, Semaphorin and Plexin classes of proteins: Robo interactions with their newly discovered ligands, NELLs, are important for midline axon guidance. We reveal and chart the interactions of bilaterian Robos and NELLs with insights into the evolution of this binding. We show that recent conformational changes in Robo receptors may be controlling their responsiveness to NELLs as guidance cues. Similarly, we reveal the evolutionary steps in the de novo rise of specificity in Kirrels, which are axon coalescence receptors during wiring of olfactory receptor neurons, using ancestral reconstructions and high-resolution structures. Finally, we present an expanded network of interactions among nematode guidance receptors and cues and demonstrate novel high-affinity interactions, which rationalize previously observed genetic interactions in axon guidance, synaptic targeting and morphogenesis.