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Polymorphic receptors: neuronal functions and molecular mechanisms of diversification

Dietmar Schreiner, Thi-Minh Nguyen and Peter Scheiffele

The formation of neuronal circuits is driven by complex developmental programs. A key feature of such programs is the precise spatiotemporal control of cell surface recognition molecules in genetically defined cells. Moreover, epigenetic modifications and alternative splicing processes have emerged that are not genetically predetermined but stochastic in nature. Recent studies have highlighted critical functions of such stochastic processes in neuronal wiring and neuronal self-recognition. In this review, we will illustrate recently identified principles that control the molecular diversity of neuronal cell surface receptors, and the function of such receptors in encoding a dynamic or stable neuronal identity.

Addresses
Biozentrum, University of Basel, 4056 Basel, Switzerland

Corresponding author: Scheiffele, Peter (peter.scheiffele@unibas.ch)

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Introduction

One of the most impressive aspects of nervous systems is the perplexing morphological and functional diversity of their cells. The reproducibility of neuronal connectivity that arises during development has long led to the proposal that there should be molecular recognition cues that engrave a certain identity into each class of neurons or even each single neuron in the brain. In particular for more complex nervous systems, the total number of neuronal cells and the multitude of recognizable neuronal sub-classes pose the question to what extent such cellular diversity can be matched by molecular cues. Over the past decade, several polymorphic receptor families with considerable molecular diversity have been characterized that contribute to specific aspects of neuronal identity. In this review, we will discuss recent progress in identifying the mechanisms underlying the molecular diversification of such polymorphic receptors and their functions in neuronal recognition and wiring.

Single cell identity

Neuronal self-avoidance has emerged as a key mechanism for shaping neuronal morphology and connectivity. During the elaboration of axonal and dendritic processes, neurons express unique sets of self-repulsive receptors at their cell surface. These cues confer a molecular cell surface identity that prevents self-fasciculation, promotes axonal bifurcation and dendritic branching, and contributes to the appropriate pairing of dendritic processes from multiple different cells in a multi-synaptic complex [1–4]. Recent studies in vertebrate and invertebrate systems uncovered gene families with considerable molecular diversity that are essential for neuronal self-avoidance and thus appear to specify neuronal identity at the level of single neurons.

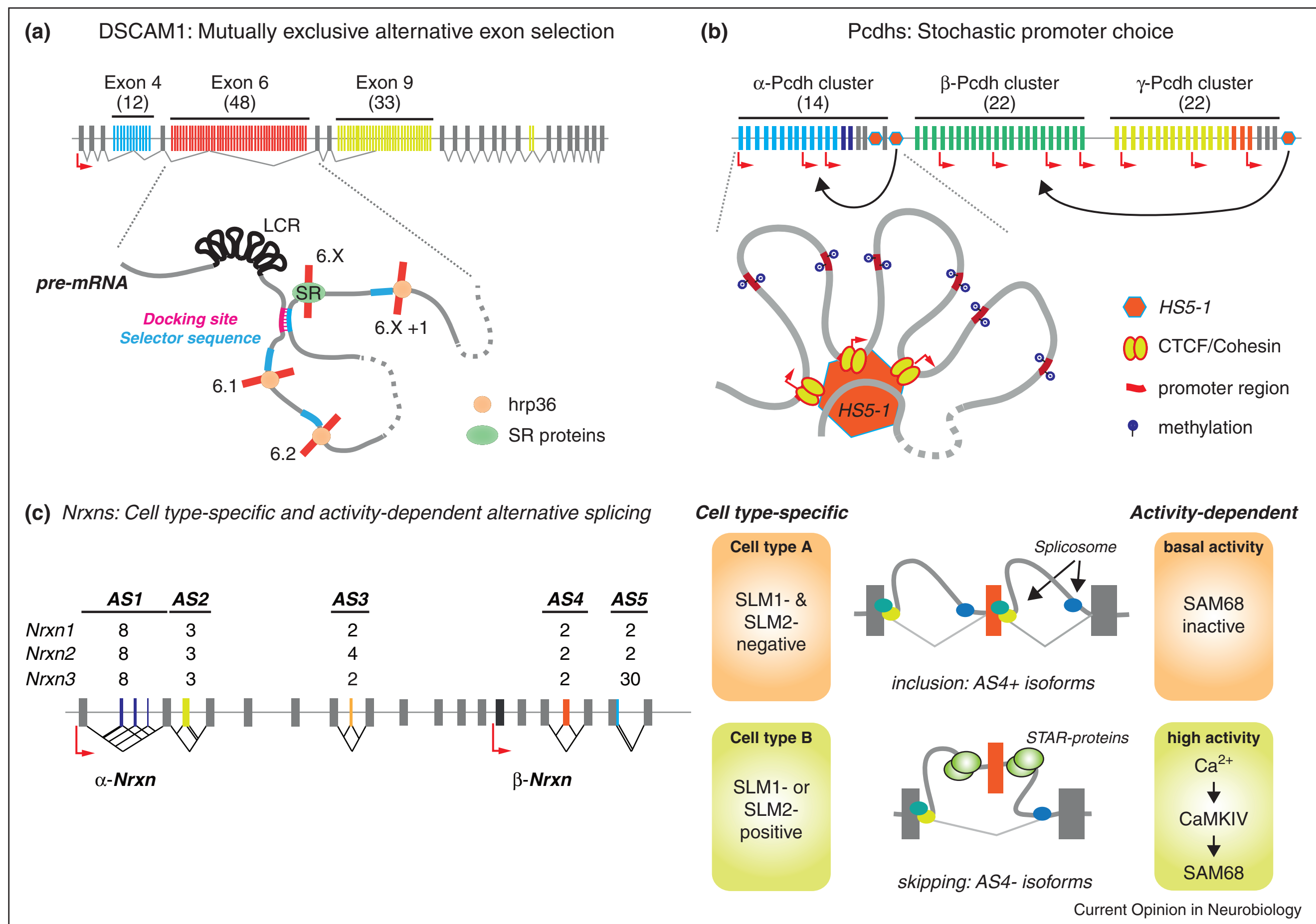
Amplification of molecular diversity by alternative splicing of DSCAM1

Providing each individual neuronal cell within a brain area with a unique molecular identity demands a receptor system with a high coding capacity. In *Drosophila melanogaster* neuronal self-avoidance is controlled by the Down's Syndrome Cell Adhesion Molecule, DSCAM1, a polymorphic receptor with potentially more than 38 000 isoforms. DSCAM1 is a transmembrane protein containing immunoglobulin (Ig) and fibronectin type II domains. The molecular diversification is derived from extensive combinatorial alternative splicing. There are three clusters of alternatively spliced exons (exon 4.1–12, exon 6.1–48, and exon 9.1–33), containing 12, 48 or 33 alternative exons, respectively. From each of these three clusters a single exon is selected and incorporated into the mature mRNA. Importantly, a second-generation sequencing analysis of DSCAM1 transcripts revealed that, indeed, almost all permutations of alternative exon combinations can be detected *in vivo* [5••]. The alternative exons encode parts or entire Ig domains of DSCAM1 [6] (Figure 1a), note that a fourth alternatively spliced segment encodes variable transmembrane domains). Hence, nearly 19 000 DSCAM1 protein isoforms can be generated that differ in their extracellular domains. Remarkably, these isoforms engage in exclusively homophilic binding that drives contact-mediated repulsion [7,8••]. Thus, the cell surface of a single neuron contains a unique DSCAM1 repertoire which recognizes the identical DSCAM1 repertoire on axon and dendrite from the same cell and converts this recognition into self-avoidance.

Mutually exclusive alternative exon selection

The complex alternative splicing of DSCAM1 pre-mRNA poses several important questions regarding its

Figure 1



Molecular mechanisms of receptor diversification. **(a)** Schematic depiction of Drosophila DSCAM1: alternative exon clusters 4, 6, 9 and 17 are colored. Alternatively spliced segments 4,6 and 9 contain 12, 48 or 33 alternatively spliced exons. At each cluster mechanisms ensure that only one alternative exon is included into the mature mRNA. The model for alternative segment 6 suggests that a selector sequence (blue) located upstream of each alternative exon in the cluster interacts in a stochastic manner with a docking site (pink). This leads to the release of the hrp36 RNA-binding protein, binding of SR proteins, and enables the splicing of the particular exon. The selector/docking duplex positions a locus control region (LCR) enhancer in the proximity of the chosen exon, which promotes incorporation into mature transcript (adapted from Graveley [9], Olson *et al.* [11] and Wang *et al.* [10]). **(b)** Simplified model of the clustered protocadherin locus (Pcdh). Each of the 58 potential alpha-Pcdh, beta-Pcdh, and gamma-Pcdh transcripts is expressed from individual promoters preceding the variable exons (exons in blue, green and yellow, respectively; some selected promoters indicated as red arrows). The choice of a particular promoter is determined by long-range interactions with so-called DNase-I-hypersensitivity elements (red hexagon, e.g. HS51-1) that recruit the CTCF/cohesin complex. The CTCF/cohesin complex association with DNA is regulated by methylation. CTCF/cohesin complex binds simultaneously to unmethylated promoters and the HS5-1 enhancer region located at the 3′ end of each Pcdh cluster (Guo *et al.* [27]). **(c)** Molecular diversity of neurexins is generated by alternative splicing at 5 alternatively spliced segments (AS1-5). Alternative exons are shown in color, constitutive exons in gray. Some segments consist of simple cassette exons, whereas others contain multiple alternative acceptor and/or donor splice sites. Alternative splicing at AS4 is regulated by SLM1 and SLM2 in a cell type-specific manner. SAM68 activity toward *Nrxn1 AS4* requires activation by neuronal calcium signaling.

regulation and logic. A key feature of DSCAM1 alternative splicing is the mutually exclusive selection of single alternative exons from each of the three alternative exon clusters. For cluster 6, this selection relies on three key components: a conserved intronic secondary structure (LCR) upstream of the cluster 6, docking–selector sequences associated with each of the exon 6 variants, and the RNA binding protein hrp36 which binds to all exon 6 variants and represses their inclusion [9–11]. The current model proposes that hrp36 binds throughout the entire exon 6 cluster and functions as a splice repressor preventing the splicing of exons located in this cluster. Stochastic interaction of the docking site preceding the exon 6 cluster and a selector sequence of an exon 6 variant results in displacement of the splicing repressor and brings the LCR element in the proximity to the selected exon 6 variant. The presence of a single docking sequence ensures that only one exon 6 variant can be incorporated, hence, ensuring mutually exclusive selection of the alternative exons (Figure 1a). Interestingly,

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