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Review

The Netrin family of guidance factors: emphasis on Netrin-1 signalling

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Abstract

During the development of the nervous system, neurons respond to the coordinated action of a variety of attractive and repulsive signals from the embryonic environment. Netrins form a family of extracellular proteins that regulate the migration of neurons and axonal growth cones. These proteins are bifunctional signals that are chemoattractive for some neurons and chemorepellent for others. Netrins mainly interact with the specific receptors DCC and UNC-5 family. To date, several Netrins have been described in mouse and humans: Netrin-1, -3/NTL2, -4/β and G-Netrins.

Netrin-1 is the most studied member of the family. It is involved in the development many projections of the nervous system. When Netrin-1 interacts with its specific receptors, a cascade of local cytoplasmic events is triggered. Several signal transduction pathways and effector molecules have been implicated in the response to Netrin-1: small Rho-GTPases, MAP-Kinases, second messengers and the Microtubule Associated Protein 1B (MAP1B).

Theme: Development and regeneration
Topic: Axon guidance mechanisms and pathways

Keywords: Netrin-1; DCC receptor; UNC-5 family receptors; Axonal guidance; Neural migration; Intracellular signalling; GTPases; MAPKs

Contents

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1. Introduction

Information processing in the brain is determined, to a great extent, by an intricate network of neuronal connections. The sheer dimension of the task of connecting the neurons of the central nervous system (CNS) is amazing. In the adult human brain, each of its almost 10^{12} neurons connects to an average of 1000 target cells, thereby forming a specific circuit whose precise pattern is crucial for the correct function of the system. How is this pattern produced with the necessary precision and reliability during embryogenesis?

During morphogenesis of the nervous system, neurons are produced in specialized regions and then migrate through defined pathways until reaching their final location. Each neuron develops a group of dendrites that are characteristic of its phenotype and an axon that extends to form specific pathways to reach its synaptic target (Fig. 1). Precision is achieved through two kinds of processes: early neural activity-independent mechanisms and refinement mechanisms, which occur later and are activity-dependent [95,219,220,235]. This review will address the role of one family of guidance molecules, the Netrin family, in activity-independent mechanisms of neuronal organization.

1.1. General mechanisms of axon guidance

Neuronal migration and the guidance of axons towards their targets are regulated by mechanisms which, in many aspects, are similar to those that occur in leucocyte chemotaxis and *Dictyostelium discoideum amoebae* [38,61,66]. Neuroblasts and axons travel through the embryonic "milieu" and are guided by local signals [88] through the formation of specialized cellular structures that "explore" their surrounding environment: the growth cone in axons and the leading edge in migrating neurons [22]. These hand- or fan-like structures contain the machinery necessary to detect and respond to extracellular guidance cues and to provide the motor energy necessary for the growth of neurites. In spite of similarities, there are differences between neuroblast migration and growth cone navigation. In the former, the cell nucleus translocates in the same direction as the leading edge, retracting the posterior region of the cell body. In contrast, in growth cone navigation, the cell nucleus remains stationary and the advance of the

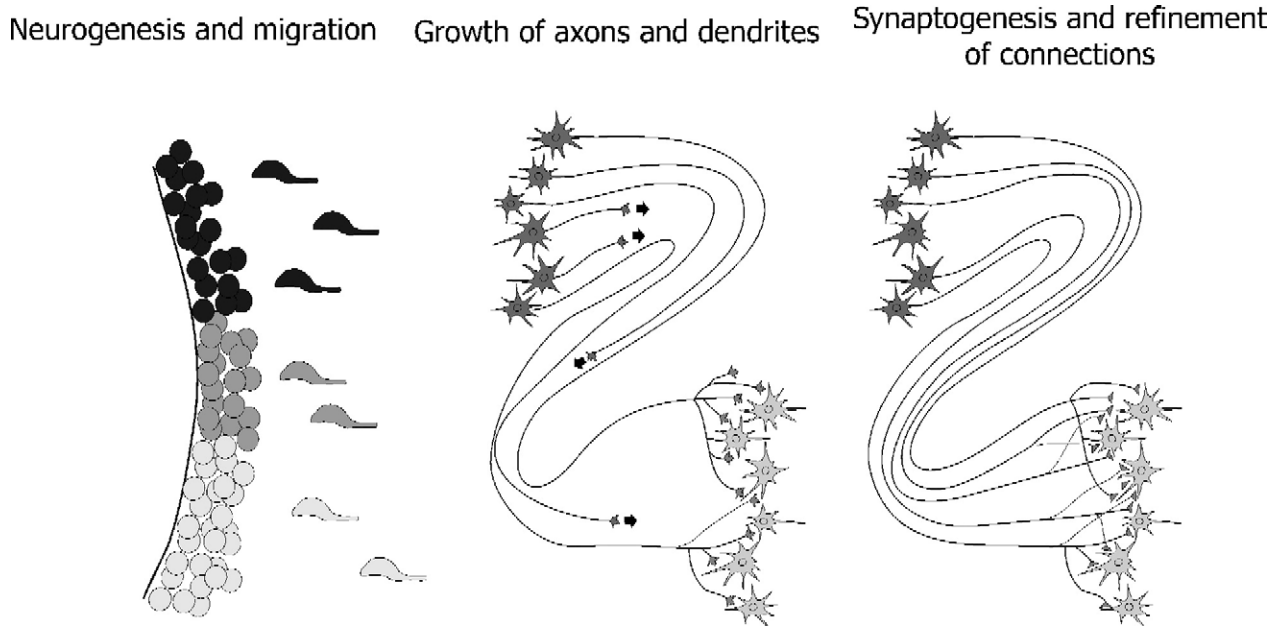

Fig. 1. Schematic representation of the main steps in nervous system development. The left panel shows a picture illustrating a region with three active neurogenetic areas. Newly generated neuroblasts migrate towards their final destination, directed by their leading process. Next (middle panel), axons grow toward their specific target regions. Finally (right panel), axons reach their target and establish specific synapses, some of which are refined at later stages.