NEURONAL DEVELOPMENT AND SIGNAL TRANSDUCTION

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Neuronal differentiation is a complex neurobiological phenomenon that includes a series of events that are developmentally regulated. The first step in differentiation is a block of proliferation, leading from a round, cycling neuroblast to a flat quiescent neuron. This is followed by the process of extension of neurites, that represents the starting point for the morphological and functional polarization of the cell. Indeed, mature neurons are among the most highly polarized and compartmentalized of all cells.

As neurites start to grow, they are faced with the tremendous task to establish the appropriate pattern of connectivity. Following axon guidance and the specific fasciculation of processes traveling along the same pathways, the subsequent step is target selection, associated with field invasion, mapping and cell choice, with each neuron ultimately forming the appropriate synaptic architecture with its own specific target(s).

In the context of the developing embryo, extracellular guiding cues, cell-cell interactions and soluble factors create a network of interactions that, in a complex interplay with the genetic program of the cell, are responsible for neurite outgrowth, polarization, axon guidance to and from choice points, axonal fasciculation, and target selection.

The common theme emerging from the recent work has been the demonstration of the importance of a balance between positive and negative inputs, producing growth, collapse, attraction or repulsion of the growth cone. It is the integration of all these signals that determines the trajectory of the growing processes and allows a fine tuning of the directional responses through a continuous sampling of the environment. In addition, the dynamic regulation of the receptors for the extracellular cues contributes to extend the repertoire of possible responses of single growth cones.

Neurite outgrowth is also strongly influenced by signals coming form the extracellular matrix through adhesion receptors, in a complex interplay between adhesion and signaling.

The existence of multiple extracellular signals, interconnected with each other and modulated at multiple levels, account for the extreme complexity and precision in the pattern of connectivity observed in the nervous system. Together with the three-dimensional regulation of the process, also a fourth dimension - time - plays a crucial role in the building of the exact architecture of the nervous system, since the appropriate signals have to be present at critical stages of development. The same signaling molecules may in fact have opposing effects at different stages, depending on the subsets of receptors present on the neuron and on the concomitant presence of other signaling molecules. Thus, in most neurons of the central nervous system, axonal elongation is a phenomenon possible only during a restricted time-window in the course of development. The existence of this time-dependence explains the extreme difficulty of correctly repairing damages in the adult brain.

On the other hand, the existence of multiple signals and levels of integration also gives rise to redundance of information, an important security factor to cope with possible mistakes of various origin (mutations, toxicity...) which may occur in the course of neurogenesis.