Development of the Cerebral Cortex: VII. Growth Factors: II

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Scientists have been surprised by their findings when they attempt to link intellectual ability among people of normal intelligence to the number of neurons in the brain. Contrary to popular belief, there is no observable correlation between the number of neurons and one's intelligence or ability. Yet it is remarkable that most of the idiopathic cases of mental retardation are associated with smaller head size as well as smaller brain size compared to age- and sex-matched normal subjects. It is likely that some of these cases of idiopathic mental retardation arise through disturbances in the birth of neurons and their subsequent differentiation and migration. However, it is also important to consider not only the total number of neurons that are born but also how they are connected and the ability of these neurons to communicate with each other and process information through neural networks.

In previous columns, we reviewed the birth of neurons and their migration to their final cortical destinations. A later maturational event is the development of interneuronal synaptic connections. In the final stage of development, large groups of neurons are eliminated by programmed cell death. Growth factors have been implicated in all of these phases. In this column, we discuss how growth factors mediate these effects.

Certain growth factors have been shown to increase the number of progenitors if added to cells in tissue culture.

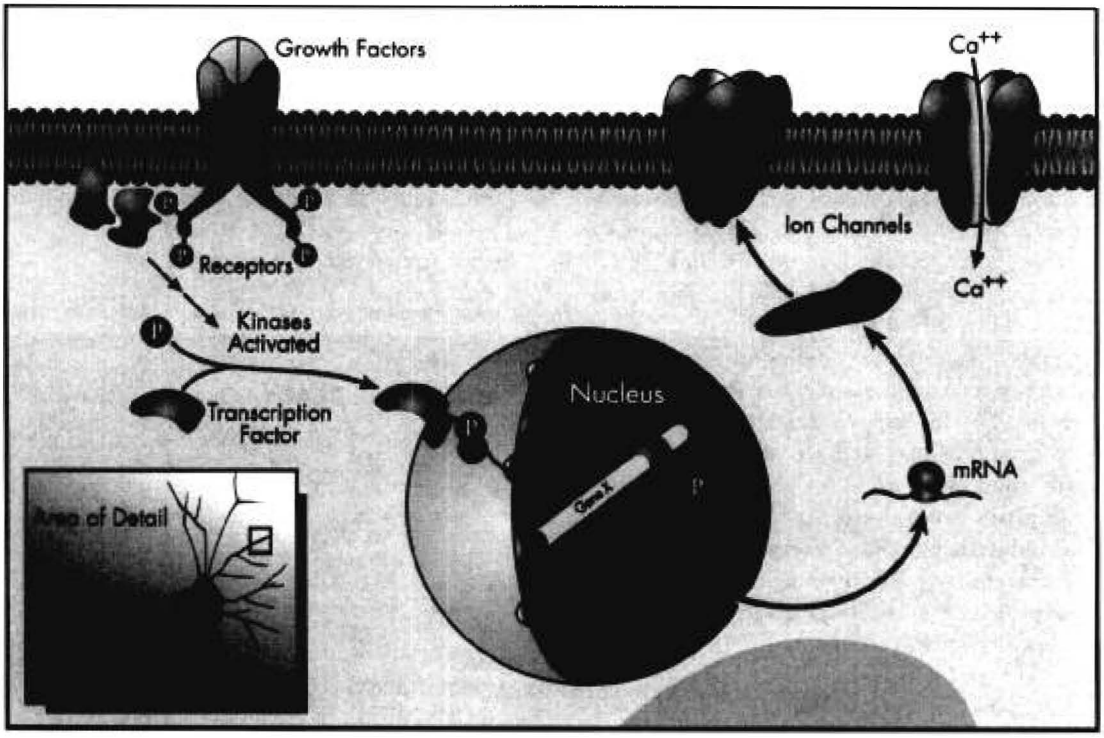

Fig. 1 Growth factors send signals from the surface of a neuron into the cell. Two molecules of a growth factor are shown binding to their receptor. The receptors are transmembrane tyrosine kinase receptors that become phosphorylated after binding to a variety of growth factors. In their phosphorylated state, the receptors attract other signaling proteins. The newly formed complex of proteins activates several kinase pathways, one of which is shown here. In this pathway, transcription factors are phosphorylated, move into the nucleus, and initiate the transcription of genes that are needed by the neuron at that moment. The mRNA messages are transported back into the cytoplasm and translated into proteins, such as the ion channels shown. In this example, increased intracellular levels of the second messenger, Ca^{++}, result from the increased production of ion channels.

Among these factors, fibroblast growth factor (FGF) is active during the early phases of neurogenesis. A minute amount of FGF microinjected in the cerebral ventricles of a rat embryo results in large increases in the volume of the cerebral cortex and a nearly twofold increase in the number of neurons generated. The increase is retained into adulthood and thus appears to be permanent. The effects of FGF result in an increase in the surface area rather than the thickness of the cerebral cortex. This result is particularly interesting from an evolutionary standpoint, since cortical surface area greatly increases over the course of vertebrate evolution, with a 1,000-fold change occurring between mouse and human. FGF or related factors are likely candidates to regulate cortical surface area in different mammalian species. Several related FGF molecules, as well as specific FGF receptors, have been identified. Some of these receptors have been shown to increase cell proliferation and thus may be involved in the increase in cell number described above.

A second family of growth factors implicated in these events are the neurotrophins, and these consist of four family members: NGF, BDNF, NT-3, and NT-4. Three receptors have been identified that bind these growth factors. They are called TrkA, TrkB, and TrkC, for tyrosine receptor kinases. There is some overlap in the affinities of each of the neurotrophins for these receptors. NGF specifically binds to TrkA, BDNF and NT-3 both bind to TrkB, and NT-4 binds to TrkC and to some extent TrkB.

How does the binding of a growth factor to its receptor lead to the activation of intracellular signals? Many receptors take advantage of two distinct protein domains: an extracellular component that binds to the signaling molecule and an intracellular domain that passes the signal on to cytoplasmic proteins. For the FGFs, neurotrophins, and many other growth factors, the binding of a ligand to its receptor causes two receptor molecules to come together and form a dimer (Fig. 1). This brings the catalytic domain of the receptors into close proximity and promotes an interaction. The catalytic domain of many of these growth factor receptors comprises protein kinases that add phosphate groups to their substrate proteins. Protein kinases regulate the activity of intracellular proteins and, in fact, the phosphorylation of proteins is probably the single most important mechanism by which growth factors, hormones, and neurotransmitters exert their biological effects.

Several events occur in rapid succession after the binding of a growth factor to its receptor (Fig. 1). The two receptors dimerize, and there is a rapid phosphorylation of the receptor molecules. Proteins that are normally nearby in the cytoplasm are now attracted to the receptors and bind tightly to the newly phosphorylated site. Complexes are thus formed with an activated receptor kinase at the core. The associated proteins are often themselves phosphorylated after binding to the receptor kinase, and their own activity level is thereby regulated. Through this mechanism, a cascade of signals is generated.

Growth factors activate a crucial pathway that leads directly to the nucleus and the transcription of genes. Transcription factors in the cytoplasm are phosphorylated and rapidly transported into the nucleus. There they bind to promoter regions of specific genes and initiate the transcription of these genes. In this way, an external signal is able to alter gene expression and often leads to the synthesis of new proteins in response to that signal. This pathway is used by all neurons, and we will see in future columns how it is implicated in the acquisition and maintenance of cognitive skills, such as learning and memory.

In summary, the binding of a growth factor to its receptor leads to the rapid transmission of a signal from the outside of a neuron to its inside through a process termed *signal transduction*. The phosphorylation and dephosphorylation of proteins is one of the most important mechanisms cells use to regulate their growth, differentiation, and proliferation. Mutations in proteins involved in signal transduction cascades lead to a number of clinical disorders. For example, the molecular basis for certain cancers was discovered only after the discovery and study of protein kinases. We now understand that mutations of these proteins disrupt the regulation of the cell cycle that is so critical for normal cellular growth.

WEB SITES OF INTEREST

http://www.cryst.bbk.ac.uk/%7Eubcg09j/sigtrans/siggroup.html
http://www.cryst.bbk.ac.uk/~ubcg09j/neurotrophins/nt_new.html#top

ADDITIONAL READINGS

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