

26. Transcription Chapter

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INTRODUCTION

THE TRANSCRIPTIONAL PROCESS

REGULATION OF TRANSCRIPTION BY TRANSCRIPTION FACTORS

STRUCTURAL FEATURES OF TRANSCRIPTION FACTORS

CO-ACTIVATORS

CO-REPRESSORS

COMPLEXITY OF TRANSCRIPTION FACTOR INTERACTIONS

METHODS FOR ASSESSING TRANSCRIPTION FACTOR ACTIVITY

EXAMPLES -

GLUCOCORTICOID AND MINERALOCORTICOID RECEPTORS AS
TRANSCRIPTION FACTORS

Corticosteroid receptors regulate transcription in the nervous system

The mechanisms of corticosteroid receptor regulation of transcription have been elucidated

cAMP REGULATION OF TRANSCRIPTION

cAMP controls phosphorylation of the cAMP response element-binding protein

The cAMP response element-binding protein is a member of a family containing interacting proteins

The function of the cAMP response element-binding protein has been modeled in transgenic organisms

HOMEODOMAIN TRANSCRIPTION FACTORS AND BRAIN DEVELOPMENT

Homeodomain proteins regulate brain region development

TRANSCRIPTION AS A TARGET FOR DRUG DEVELOPMENT

REFERENCES

27. GROWTH FACTORS

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GROWTH FACTORS ARE ESSENTIAL FOR NERVOUS SYSTEM DEVELOPMENT AND FUNCTION

1. Growth factors are proteins that stimulate cellular proliferation and promote cellular survival.
2. Growth factors activate multiple signal transduction pathways required for survival and differentiation.
3. Growth factors activate multiple signal transduction pathways required for survival and differentiation.

CLASSES OF GROWTH FACTORS ACTING IN THE NERVOUS SYSTEM

1. The neurotrophins comprise a family of highly related molecules which act to support the survival and phenotypic specificity of select subsets of neurons.

Nerve Growth Factor.

Brain-Derived Neurotrophic Factor

Neurotrophin 3

Neurotrophin 4/5

Neurotrophins, synaptic plasticity and neurotransmission

2. Neurotrophic Cytokines are a small group of cytokine-like molecules that act in the nervous system.

Ciliary Neurotrophic Factor

Leukemia Inhibitory Factor

Interleukin 6

Cardiotrophin 1

Other Cytokines

3. The fibroblast growth factors comprise a gene family of nine members which share substantial sequence homology and have diverse effects in the nervous system.

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4. Transforming growth factors b are the prototypic members of a large family of related factors which have a diverse roles both in development and in the mature animal.

TGF β subfamily

Bone Morphogenetic Protein Subfamily

5. Glial-Derived Neurotrophic Factor family represents a newly recognized family of target-derived neurotrophic factors.

Glial-Derived Neurotrophic Factor

Neurturin

Artemin

Persephin

6. Epidermal Growth Factor and related factors have a diverse range of actions in the nervous system.

Epidermal Growth Factor and TGF α

Neuregulins

7. A number of other growth factors act in the nervous system:

Platelet-Derived Growth Factor

Insulin-Like Growth Factor I

Hepatocyte growth factor

Macrophage stimulating factor

GROWTH FACTORS ACT COMBINATORIALLY AND SEQUENTIALLY TO REGULATE NERVOUS SYSTEM DEVELOPMENT

References

Tables-1 and 2

Figure 1-4

29. Stem Cells

Outline for Basic Neurochemistry: 6/18/03

Alison K. Hall

- 1) There are different types of stem cells
 - i) Stem cell is multipotent and self renewing
 - ii) Embryonic stem cells are origin of all cells
 - iii) Fetal stem cells build tissues
 - iv) Adult stem cell replenish tissues
 - (a) Hematopoietic, mesenchymal, neural
 - (b) Concept of cell fate restriction

- 2) Lessons from the hematopoietic stem cell
 - i) Reconstitutes all cells in blood
 - ii) Few stem cells present in bone marrow, peripheral blood
 - iii) Growth factors regulate survival, amplification of stochastically generated cells

- 3) Stem cells contribute to the developing nervous system
 - i) Neural crest stem cell
 - (1) Environmental cues determine cell fate
 - (a) Different from hematopoietic stem cells
 - (b) Concept of induction, instructive cues
 - (2) Role of intrinsic transcription factors
 - ii) CNS stem cells (eg Jessell)

- 4) Neural stem cells offer potential for repair in the adult nervous system.
 - i) Neurons postmitotic, neurodegeneration results in cell, functional loss
 - ii) Fetal neural stem cells for therapy
 - (a) Stem cells can be propagated as neurospheres
 - iii) Adult neural stem cells for therapy
 - iv) The developmental biology: is this selection or instruction?
 - v) Insert Box example: Promise for Parkinson's?

- 5) Brain cells can be derived from non-brain stem cells
 - i) In vitro/in vivo issue?
 - ii) Bone marrow stem cell therapy for leukodystrophy
 - iii) Concept of injury signals that guide homing

- 6) Common stem cell therapy challenges
 - i) Sufficient number of single population
 - ii) Effective connectivity, survival, function
 - iii) Ethical issues
 - iv) Tumor formation?

30. Axonal Growth in the Adult Nervous System

Wendy.Kartje and Martin Schwab

I. Background:

- a) CNS and PNS axonal regeneration; increased after PNS injury, limited after CNS injury.

II. Regeneration in the PNS after lesion:

- a) Remodeling of the nerve-muscle endplate in normal and d. muscle (role of activity in shaping circuitry).
- b) Injury to peripheral nerve:
 1. Wallerian degeneration, schwann cells and glial cells remove myelin/schwann cells go back to early developmental stages/increase in trophic factors, ECM factors
 2. Proximal nerve stump: sprouting and elongation/ cell bodies increase growth associated proteins, ie GAP-43, others.
 3. Crush injury: basement membrane stays intact, good regeneration and pathfinding vs nerve cut, with scar, worse pathfinding.
 4. Recovery of function: animal models vs. clinical/crush vs. cut (aberrant connections)

III. CNS injuries:

- a) Stroke, traumatic head injuries/loss of nerve cell bodies
 1. Transplants, stem cells as cellular replacements/not very successful
 2. Compensatory sprouting of spared neurons/probably underlying spontaneous (but limited) recovery of function.
- b) SCI (trauma,bleeding,MS-plaques)/ axonal tract lesions
 1. Distal to lesion: Wallerian degeneration (by microglia/macros):slow
 2. proximal stump sprouting/limited: 4 possible reasons:
 - i.) adult neurons do not grow well although there is spontaneous increase of GAP-43, Aguayo experiments, ie growth response of CNS neurons to lesions can be enhanced, GAP/CAP (Caroni-Skene)/Inosine (Benowitz)/Trophic factors
 - ii.) Inhibitors, especially in myelin, ie Nogo, MAG, etc in-vitro studies/ IN-1, anti-Nogo antibodies in-vivo application leading to regeneration, anatomical plasticity and functional recovery.
 - iii.) Inhibitors in scars, CS-PGS (Silver-Fawcett)
 - iv.) Insufficient trophic support, trophic factors in SCI, ie NT-3 (Tetzlaff, etc).

IV. Two ways to functional recovery: regeneration and compensatory neurite growth

- a) Target finding, specific synapse formation
 1. guidance factors: present in adult nervous system but function not know.
 2. activity-dependent stabilization

- b) Partial lesions to long tracts frequent/or parallel tract systems/spared fibers take over targets by compensatory sprouting.