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Major review

Trophic factors in the pathogenesis and therapy for retinal degenerative diseases

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ABSTRACT

Trophic factors are endogenously secreted proteins that act in an autocrine and/or paracrine fashion to affect vital cellular processes such as proliferation, differentiation, and regeneration, thereby maintaining overall cell homeostasis. In the eye, the major contributors of these molecules are the retinal pigment epithelial (RPE) and Müller cells. The primary paracrine targets of these secreted proteins include the photoreceptors and choriocapillaris. Retinal degenerative diseases such as age-related macular degeneration and retinitis pigmentosa are characterized by aberrant function and/or eventual death of RPE cells, photoreceptors, choriocapillaris, and other retinal cells. We discuss results of in vitro and in vivo animal studies in which candidate trophic factors, either singly or in combination, were used in an attempt to ameliorate photoreceptor and/or retinal degeneration. We also examine current trophic factor therapies as they relate to the treatment of retinal degenerative diseases in clinical studies.

1. Introduction

Since the identification of nerve growth factor (NGF) in the early 1950s by Dr. Rita Levi-Montalcini, and characterization of its activity and discovery of epidermal growth factor (EGF) by Dr. Stanley Cohen, both awarded the 1986 Nobel Prize in Medicine or Physiology,[A] many other trophic molecules have been discovered and studied in the laboratory as well as in clinical settings as a possible treatment modalities to increase proliferation and survival of target cells and tissues. In the last few decades these studies have focused largely on prevention of neurodegeneration (e.g., delayed death of dopaminergic neurons to ameliorate Parkinson disease) and delayed degeneration of photoreceptors and the neural retina in the treatment of retinal degenerative diseases.[54,307] We shall describe preclinical studies of the use of several trophic factors to improve photoreceptor and/or retinal survival in culture and in various animal models of retinal degenerations. Furthermore, we outline current and potential clinical therapies utilizing trophic factors and, based on the literature, draw conclusions about the possible directions of this burgeoning field.

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2. Trophic factors

2.1. Definition of a trophic factor

Trophic (derived from the Greek τροφη meaning "nourishment") or growth factors are endogenously produced substances (either proteins or steroid hormones) that bind to cell surface or nuclear receptors and generally function to promote cell proliferation, maturation, survival, and/or regeneration.[322,358] Cytokines represent a subtype of growth factors. These small (<30 kDa) cell-signaling molecules (polypeptides or glycoproteins) are specifically produced by, and are functionally associated with, hematopoietic and immune cells, thereby acquiring the descriptor "immunomodulating agents". Cytokines mainly function over short distances, have a short half-life, and are produced at low concentrations.[86] Neurotrophic factors are neuron-specific. These secreted proteins are critical during neuronal development and prevent nerve cell death. They regulate neuronal growth and protein synthesis and also increase neurite outgrowth and neurotransmitter synthesis in specific circumstances.[196] In order to be classified as a neurotrophic factor, a molecule must: 1) keep neurons alive (withdrawal results in cell death); 2) be synthesized in a biologically active form by the neuron requiring it for survival; 3) be present in target tissue in very small amounts; and 4) affect in vivo neuronal development.[27]

2.2. Cell types involved in trophic factor production in the retina–retinal pigment epithelium–choroid complex

Neurons are not the only cells with the ability to secrete trophic factors. In the eye the retinal pigment epithelium (RPE) and Müller cells are the main producers of these substances.[98,108] Additionally, choroidal endothelial cells have been shown to express trophic factor mRNA and/or secrete several trophic factors.[135]

The RPE is a monolayer of hexagonal, cuboidal, pigmented cells, 10–14 μm in diameter, that grows on Bruch membrane. Bruch membrane is a pentalaminar collagenous tissue interposed between the choroid (a highly vascular tissue) and the RPE.[13] Maintenance of normal retinal physiology relies in part on a wide variety of RPE function—such as preservation of the blood–ocular barrier, phagocytosis of shed photoreceptor outer segments, absorption of scattered light to enhance visual acuity, protection against toxic and oxidative damage, selective transport of substances to and from the neural retina, dehydration of the subretinal space, processing of vitamin A metabolites in the visual cycle, development of immune and inflammatory responses, and secretion of growth factors.[307] The RPE cells interact intimately with photoreceptors and are vital to photoreceptor homeostasis and survival.[330] A number of critical functions attributed to the RPE seem to occur as a result of appropriate RPE growth factor secretion: regulation of angiogenesis (e.g., vascular endothelial growth factor [VEGF] and pigment epithelium-derived factor [PEDF])[35,345] and apoptosis (e.g., basic fibroblast growth factor [bFGF]),[40] prevention or promotion of cell differentiation and maturation (e.g., platelet-derived growth factor [PDGF]),[136] and provision of trophic support to photoreceptor cells and the choroid (e.g., PEDF, ciliary neurotrophic factor [CNTF], brain-derived neurotrophic factor [BDNF], neurotrophin-3 [NT-3], and others).[7,121,164,165] Although aberrant growth factor production has been linked with age-related macular degeneration (AMD),[141,203] these substances have a potential role in treating degenerative retinal diseases through exogenous administration, which may result in expression of pro-survival factors by the target cells.[383]

The Müller cells are the predominant glial cells in the retina. Some of their functions and characteristics include expression of voltage-gated ion channels and neurotransmitter receptors, synthesis and release of synaptic mediators, regulation of the extracellular concentration of neuroactive substances (i.e., modulation of activity of the surrounding cell types), control of synaptogenesis and differentiation, secretion of numerous trophic factors and expression of their cognate receptors, and others.[77,242] Upon injury to the retina, the Müller cells undergo significant morphologic, cellular, and molecular changes such as increased expression of growth factor receptors and secretion of growth factors and other molecules that may mitigate the neuronal insult, facilitating neovascularization in response to hypoxia and differentiation of neuronal cell types to aid in retinal regeneration after damage.[108] For example, after prolonged or high-intensity visible light exposure to the retina, activated microglia grow into the degenerating photoreceptor layer and alter NGF, BDNF, CNTF, bFGF, and glial-derived neurotrophic factor (GDNF) expression by Müller cells, thereby affecting photoreceptor survival.[124]

2.3. Signaling mechanisms

Signal transduction after binding of a growth factor to its cognate receptor involves receptor dimerization, activation, and rapid trans-autophosphorylation at tyrosine residues.[28] Numerous downstream signaling molecules, such as adaptor proteins and kinases, specifically interact with these phosphorylated sites and in turn are activated (often becoming phosphorylated themselves), which results in an activation of various distinct downstream cascades with specific biological effects. The three major cell survival mechanisms activated by growth factor binding include the Jak/STAT, the PI3K/Akt, and the Ras/MAPK pathways.[85,272,313,341,359] Alternatively, activation of the death receptor (e.g., FasL/Fas interaction) signaling or c-Jun N-terminal kinase, or insufficient activation of numerous other survival signal transduction factors (e.g., NF-kappaB, neuronal and endothelial nitric oxide (NO), Notch, c-fos, cAMP-response-element-binding protein (CREB1), ATF1, heat shock proteins (HSPs), and apoptosis-inducing factor) leads to inactivation of pro-survival factors (e.g., Bcl-2), release of cytochrome c from the inner mitochondrial space, caspase activation, and cell death.[30,48,68,127,234,315,357]

There are two classic neurotrophic families. The first is the neurotrophins, including NGF, BDNF, NT-3, and NT-4/5.[102] NGF binds the p75NTR and the p140trk (trkA) receptors; BDNF and NT-4/5 bind the trkB receptor, and NT-3 primarily binds the trkC receptor (reviewed by Ebadi et al[86]). The second is the GDNF-family consisting of GDNF, neurturin, artemin,