RETINAL ABNORMALITIES IN NEURODEGENERATIVE DISEASES

Maté Goldar, Carla

Bachelor´s Degree in Biomedical Sciences, Universitat Autònoma de Barcelona

Universitat Autònoma de Barcelona

Introduction

♦ Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive dysfunction, degeneration and death of neural cells. They lead to irreversible functional loss and represent a major concern in our current society due to their high and increasing incidence. Some of the main neurodegenerative disorders, such as Alzheimer, Parkinson and Multiple sclerosis, present visual disturbances and structural changes within the retina.

♦ Eye as a window to the brain [1]: changes in the retina of patients can help to predict changes in the brain, since the retina is a direct extension of the CNS. This early diagnosis can help solving the current lack of reliable non-invasive diagnostic techniques, limiting the application of an effective treatment.

♦ Stem cell research offers the possibility of developing new therapeutic approaches to prevent and restore neuronal cell loss at the retina.

Methods

Data displayed in this poster has been obtained from scientific literature research of recent papers and reviews using the searching engine Pubmed-NCBI and the scientific journals Nature and Science. Selection of papers mainly based on date of publication and quality of journal.

♦ Keywords: neurodegenerative diseases, retina, Alzheimer´s disease, Parkinson´s disease, multiple sclerosis, stem cell therapies, cell reprogramming

Aims

♦ Describing retinal abnormalities in the main neurodegenerative diseases

♦ Presenting OCT as the major approach available for non-invasive retinal imaging methods and its potential application for early diagnosis, treatment monitoring and study of neurodegenerative diseases

♦ Speculating about the potential use of stem cells as a tool for future effective therapies

Retinal abnormalities in neurodegenerative diseases

Alzheimer

♦ Primary neurodegenerative disorder and most common form of dementia. Most common symptoms are memory impairment, language deficits and a gradual loss of bodily function.

♦ Etiology on debate. Two major lesions: extracellular beta-amyloid (A-β) neuritic plaques and p-tau intracellular neurofibrillary tangles.

♦ Difficulty with reading, finding objects and recognizing colors, abnormalities in depth and motor perception and reduced spatial contrast sensitivity → RNFL and macular thinning, vacuolar degeneration and reduced numbers of RGCs, an increase in the optic disc cupping, reduced retinal blood flow, a pathological accumulation of A-β and p-tau, hypertrophy and proliferation of astrocytes and an amyloid precursor protein (APP) immunoreactivity [2]

♦ OCT to determine RNFL and macular thickness, Detection of apoptosing retinal cells (DARC) for assessing treatment efficacy and evaluation of ocular vascular function in correlation with cognitive decline.

Parkinson

♦ Second most common neurodegenerative disorder. Main motor symptoms are tremor, bradykinesia rigidity and postural instability, also non-motor symptoms

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♦ Largey idiopathic. It shows a progressive depletion of the neurotransmitter dopamine in the *pars compacta* of the substantia nigra. Major alteration: Lewy bodies

♦Visual acuity is diminished, visual hallucinations, `motion blur´ in contrast perception, disturbed color vision, inappropriately `dark-adapted´ state → swelling of photoreceptors and RGCs, pale intracellular inclusions in the outer plexiform layer, morphological deterioration of the perifoveal dopaminergic plexus and RNFL and macular thinning [3,4]

♦OCT to determine RNFL thinning and correlate it with disease severity

Multiple sclerosis

♦ Chronic immune-mediated disease of the CNS which affects the myelin sheath of the nerves at the brain and the spinal cord, showing heterogeneous decline in motor and cognitive functions. Two phenotypes: relapsing remitting MS (RR MS) and secondary progressive (SP) MS.

♦Demyelinating lesions in the white (WM) and grey matter (GM) of the CNS are the classical hallmark of the disease.

♦Decrease in visual acuity and contrast sensitivity, defects in binocular and color vision, diplopia and blurred vision, photophobia, excessive glare, photopsias, oscillopsia, abnormal eye movements → retinal atrophy and inflammation, RNFL and macular thickness, loss of RGCs, amacrine and bipolar cells, astrocyte hypertrophy and proliferation, abnormalities in the iris in chronic cases, pathological cupping of the optic disc, retinal periphlebitis and in 20% of the cases optic neuritis [5]

♦OCT shows RNFL, macular, RGCs layer and inner plexiform layer thickness, which can be correlated with the level of brain atrophy and nerve damage. Low-contrast letter acuity (LCLA) and alteration of the visual evoked potential (VEP) latencies also useful for early diagnosis

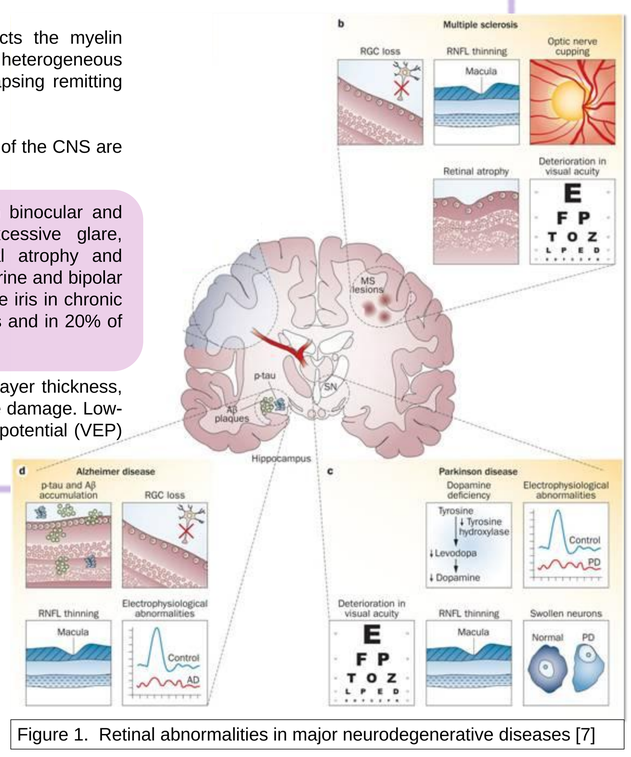

Figure 1. Retinal abnormalities in major neurodegenerative diseases [7]

Stem cell–based therapies

Stem cells are unspecialized and capable of giving rise to any type of cell by renewing themselves through cell division in response to external (microenvironment) and internal (genes) signals, remaining meanwhile in a quiescent state

- ESCs
- iPSCs
- Adult SC

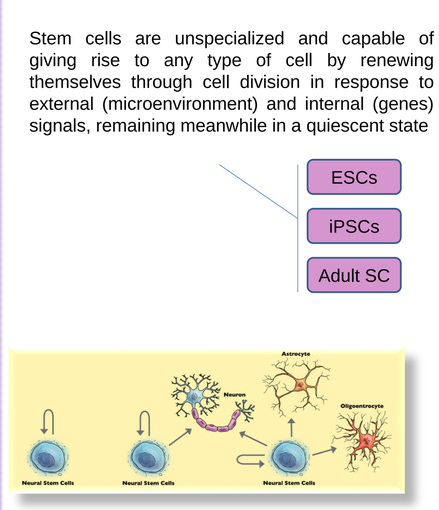

Figure 2 Classification of stem cells. Adapted from Human *Anatomy and Physiology, an OpenStax College* resource

Neural stem cells (NSCs) are a potential therapeutic tool for neurodegenerative diseases. In the adult brain they´re mainly restricted ~~in~~ to two tissue niches: the subventricular zone (SVZ) and the subgranular zone (SGZ). They can give rise to neurons (neurogenesis) and astrocytes and oligodendrocytes (gliogenesis) [6]

- **AD**: genetically-modified NSCs overexpressing choline acetyltransferase (ChAT) and the A-β degrading enzyme neprilysin[19] (sNEP) enhance regeneration, memory restoration and target AD pathology
- **PD**: transplantation of human brain-derived NSCs and NSCs derived from human ESCs establish synaptic connections with host cells and release dopamine
- **MS**: Oligodendrocyte progenitor cells (OPCs) and NSCs transplantation promote endogenous remyelination and neuronal regeneration, blocking also the uncontrolled inflammation

Potential applications of stem cells			
Cell replacement approaches	Disease modeling	Neuroprotection	Neuroregeneration

Cell reprogramming enables the generation of any somatic cell type by genetic manipulation in a cell culture dish [7]

♦ Induced pluripotent stem cells (iPSCs): derived from patient somatic cells using four transcription factors Oct4, Sox2, Klf4, c-Myc and Fbx15

♦Induced retinal progenitor cells (iRPCs) and induced retinal neurons (iRN): only one reprogramming step, transcriptional factors: Brn2, Ascl1, Myt1l, NeuroD1 (human models)

♦Adult stem cells physiologically generate the cell types of the tissue in which they reside at the body

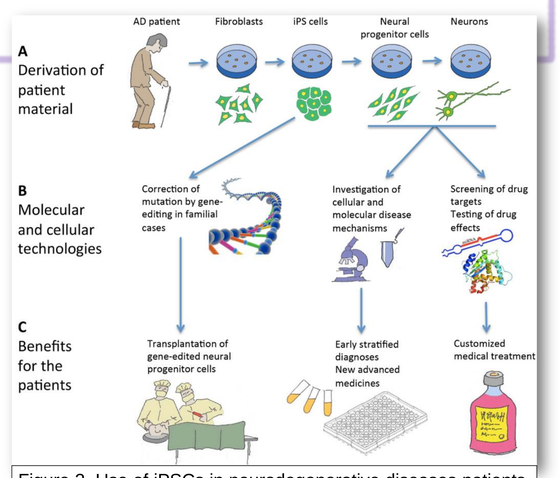

Figure 3. Use of iPSCs in neurodegenerative diseases patients. Freude K. et al. (2014) Induced pluripotent stem cells derived from Alzheimer´s disease patients: the promise, the hope and the path ahead. J. Clin. Med 3(4) 1402-1436

Conclusions

♦ Neurodegenerative diseases are considered as incurable

♦ The eye and the neurons of the retina of these patients represent a potential location for new therapies and early diagnosis

♦ OCT appears to be the main potential technique for this early diagnosis and disease study purpose

♦ Stem cell-based therapies and cell reprogramming techniques offer the potential to generate human retina cells, to develop specific human-cell-based retina disease models and to open up new therapeutic strategies for the major neurodegenerative disorders

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