

Chapter 2

Programmed Cell Death During Retinal Development of the Mouse Eye

Barbara M. Braunger, Cora Demmer and Ernst R. Tamm

Abstract Similar to other parts of the central nervous system, there are two types of programmed cell death during retinal development. In early development, the neuronal progenitor population is affected. In the mouse eye, this kind of programmed cell death begins at around embryonic day (E) 12.5 and peaks between E14.5 and E16.5. The second phase of programmed cell death occurs during synaptogenesis within the first 2 postnatal weeks. Important signaling mechanisms that induce programmed cell death of retinal progenitors appear to involve nerve growth factor acting on the proapoptotic receptor to p75 neurotrophin receptor (p75^{NTR}) and transforming growth factor- β .

Keywords Retina · Programmed cell death · Neuronal development · Apoptosis

2.1 Introduction

Programmed cell death constitutes an important element of the morphogenetic processes during development of the central nervous system in which up to 70 % of neurons that have been generated do not survive until adulthood. This article will briefly review the process of programmed cell death in the mouse retina.

2.2 Programmed Cell Death in the Mouse Retina

Similar to other parts of the central nervous system, there are two types of programmed cell death during retinal development. In early development, the neuronal progenitor population is affected. In the mouse eye, this kind of programmed cell

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J. D. Ash et al. (eds.), *Retinal Degenerative Diseases*, Advances in Experimental Medicine and Biology 801, DOI 10.1007/978-1-4614-3209-8_2,
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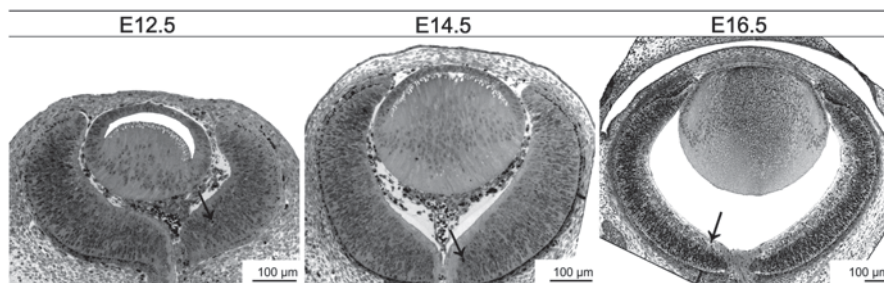


Fig. 2.1 Retinal development: semithin sections of the mouse eye at different embryonic time-points (*E*). The *arrows* indicate pycnotic cell nuclei

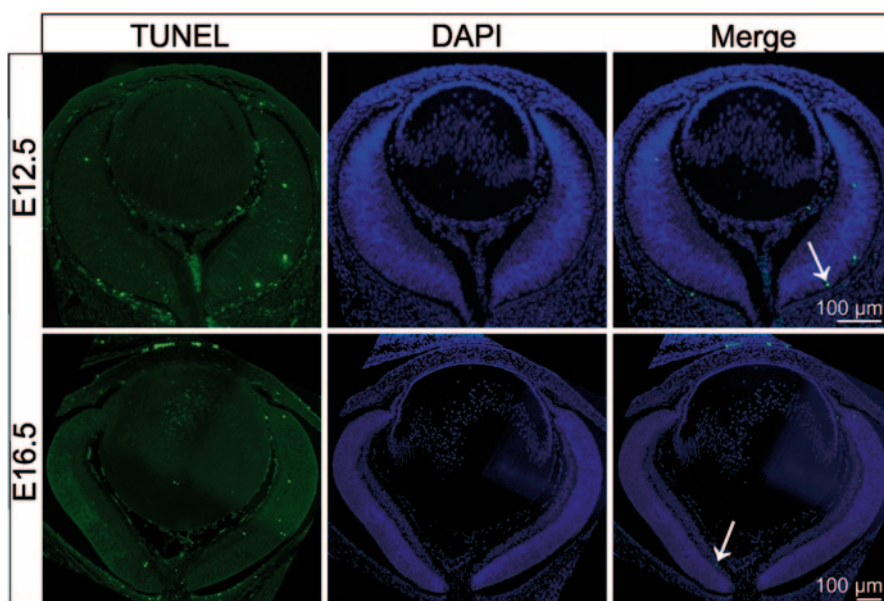


Fig. 2.2 Apoptotic cell death during embryonic retinal development. TUNEL staining visualizes apoptotic cells (*arrows*). Paraffin sections of mouse embryonic eyes at embryonic day (*E*) 12.5 and E16.5

death begins at around embryonic day (*E*) 12.5 [1] and peaks between E14.5 and E16.5, a period where numerous pycnotic or TUNEL-positive progenitor cells can be identified (Figs. 2.1 and 2.2). It has been discussed that the advantage of this kind of cell death is the adaptation of the size of the progenitor cell population [2, 3]. The second phase of programmed cell death in the developing central nervous system occurs during synaptogenesis. The cells are sorted out in order to promote optimal target innervation. According to the neurotrophin hypothesis, neurons that are in the process to seek connectivity compete with other neurons for a limited supply of neurotrophic factors provided by the target cell. The winner cell will survive, while those cells that are unsuccessful in this competition will die [4–6].

In the mouse retina, programmed cell death during synaptogenesis occurs during the first 2 postnatal weeks. Young et al. [7] showed that degenerating cells were found in all layers of the retina at the day of birth, but they were distributed unevenly. Retinal ganglion cells die during the first 11 days of life with a peak between postnatal (P) days 2–4. Death of amacrine cells takes place during the first 11 days, with its peak during P4–5. Bipolar and Müller cells die between P5–18 with highest cell death between P8–9. Inner rods die between P5–10 with the peak at P7, whereas outer rods undergo programmed cell death during P5–24, and the peak at P11 [7]. Overall, photoreceptors are affected less than other retinal neurons by programmed cell death [8].

2.3 Neurotrophins

Neurotrophins constitute a family of secreted proteins which are involved in proliferation, growth, and maintenance of neurons. Family members are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), and neurotrophin-4 (NT4). In the adult rodent retina, NGF is expressed in astrocytes, retinal ganglion cells, Müller cells, and the retinal pigment epithelium [9], while BDNF is detected in Müller cells [10], retinal ganglion cells, and cells of the inner nuclear layer [11, 12]. NT-3 is expressed in a small subset of cells in the inner nuclear layer and the ganglion cell layer, and NT-4 in the inner and outer nuclear layer of the retina [13]. Neurotrophins mediate their function through binding to the family of tropomyosin related kinase receptors (Trk) and the p75 neurotrophin receptor (p75^{NTR}) [14]. NGF binds to TrkA, BDNF and NT-3 to TrkB and NT-4 to TrkC. Nevertheless, there is some crossreactivity, e.g., NT-3 is able to bind to TrkA and TrkB. The classic view is that through binding to their Trk receptors, neurotrophins primarily mediate their neurotrophic functions like promoting axonal and dendritic growth, synapse formation, neuroprotection, and maintenance [15]. After receptor binding, the receptor dimerizes and autophosphorylates the cytoplasmatic kinase domain. Briefly, this results in an activation of Ras, which then triggers PI3K, p38MAPK, and c-Raf/ERK pathways [15].

The p75^{NTR} receptor, which belongs to the tumor necrosis factor superfamily, was the first receptor identified for NGF. All neurotrophins can bind to p75^{NTR} with similar affinity [16–18].

2.4 Signaling Mechanisms During Programmed Cell Death of the Mouse Retina

In the retina of birds, programmed cell death of progenitors is under control of NGF released from microglia: NGF acts on those neuronal progenitors that express p75^{NTR}, but not TrkA [17]. P75^{NTR} is a proapoptotic receptor in the absence of TrkA, and NGF induces programmed cell death in this context [17, 19]. The relevance

of this mechanism for development of the mammalian retina is unclear. There is a significant decrease in programmed cell death of neuronal progenitors during early embryonic development of p75^{NTR}-deficient retinæ [20, 21]. Still, this appears to be a transitory event which does not result in obvious changes in retinal morphology of p75^{NTR}-deficient mice past E15 [21].

In addition, TGF- β signaling appears to modulate programmed cell death of neuronal progenitors in the avian retina as the application of antibodies that neutralize signaling of all three avian TGF- β isoforms (TGF- β 1, - β 2, - β 3) reduces programmed cell death of neuronal progenitors in treated embryos, effects that appear to be independent from the action of NGF and its binding to p75^{NTR} [22]. Again, the relevance of these findings in birds for the development of the mammalian retina is unclear. Embryos of double TGF- β 2/TGF- β 3-deficient mice show a reduction of neuronal progenitors undergoing programmed cell death at E 14.5 [23], but die around E 15.5, a time when programmed cell death of retinal progenitors has reached its peak and well before the time when death of differentiated retinal neurons begins [7, 24].

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Retinal Degenerative Diseases

Mechanisms and Experimental Therapy

Ash, J.; Grimm, C.; Hollyfield, J.G.; Anderson, R.; LaVail, M.M.; Rickman, C.B. (Eds.)

2014, LXI, 862 p. 188 illus., 187 illus. in color.,

Hardcover

ISBN: 978-1-4614-3208-1