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Parthanatos as a Cell Death Pathway Underlying Retinal Disease

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Abstract

Parthanatos is a programmed cell death pathway mediated by the effects of pathogenically high levels of poly(ADP-ribose) polymerase 1 (PARP1) activity. This process underlies a broad range of diseases affecting many tissues and organs across the body, including the retina. This chapter reviews mechanisms that are currently understood to drive parthanatos in the context of retinal diseases associated with this form of cell death. Toxicity of upregulated PAR content, NAD^+ and ATP depletion, translocation of apoptosis-inducing factor (AIF) to the nucleus, and loss of glycolytic function are discussed. Since therapies that preserve vulnerable cells remain elusive for the vast majority of retinal diseases, pharmacologically blocking parthanatos may be an effective treatment strategy for cases in which this process contributes to pathogenesis.

Keywords

Parthanatos; Programmed cell death; PARP1; PAR; NAD^+; Apoptosis-inducing factor; Bioenergetics

53.1. Introduction

Retinal diseases vary considerably in regard to severity, progression, genetic predisposition, and association with environmental/non-genetic risk factors. However, a common feature is that cellular dysfunction progresses to cell death. Retinal cell degeneration is most commonly attributed to apoptosis or necrosis, but this view is now being challenged in some instances as alternative forms of cell death are identified that more accurately fit the specific disease profile (Sancho-Pelluz et al. 2008). As examples, pyroptosis, necroptosis, autophagic cell death, and apoptosis may each play a role in the death of separate classes of cells in diabetic retinopathy (Feenstra et al. 2013), and retinal ischemia/reperfusion associated with glaucoma may kill ganglion cells by triggering autophagy and paraptosis (Wei et al. 2015).

Parthanatos is a form of programmed cell death that is also gaining attention in the retinal disease field (Arango-Gonzalez et al. 2014; Liu et al. 2015; Jang et al. 2017), particularly in relation to certain inherited retinal diseases (IRDs), age-related macular degeneration (AMD) (Jang et al. 2017), and ischemia/reperfusion of the retina (glaucoma, diabetic retinopathy, and vascular diseases of the eye) (Liu et al. 2015). This process is characterized

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by an overproduction of poly(ADP-ribose) (PAR) by hyperactivated PARP enzymes, particularly PARP1, and it similarly has been implicated in various non-ocular diseases such as stroke, Alzheimer's disease, Parkinson's disease, diabetes, arthritis, neurotrauma, multiple sclerosis, heart attack, and liver damage (Virag and Szabo 2002; Kim et al. 2005).

53.2. PARP1 Function and Structure

PARP1 is one of eighteen members of the PARP superfamily (Dawson and Dawson 2004). This nuclear enzyme surveilles the genome for damage and cleaves nicotinamide adenine dinucleotide (NAD^+) into ADP-ribose and nicotinamide when activated by, for example, DNA strand breaks (Shall and de Murcia 2000). PARP1 then catalyzes the polymerization and transfer of ~50–200 ADP-ribose molecules onto target proteins as a posttranslational modification referred to as poly(ADP-ribosyl)ation or parylation (Yu et al. 2003). A primary purpose of parylation is to facilitate DNA repair, and it may also alter chromatin structure in a manner that supports gene transcription (Lindahl et al. 1995).

PARP genes are categorized together based on sequence homology rather than function, and some lack parylation activity (Ame et al. 2004). PARP1, responsible for >95% of all PAR generated (Dawson and Dawson 2004), has highly conserved motifs that include an N-terminal DNA-binding domain (DBD), a nuclear localization signal, an automodification domain, and a C-terminal catalytic domain (Kraus and Lis 2003). This enzyme targets numerous nuclear proteins that include histones, transcription factors, topoisomerases I and II, helicases, singlestrand break repair factors, base excision repair factors, and PARP1 itself (Wang et al. 1995; Kim et al. 2005). Although parylation may serve as a cell survival mechanism under normal circumstances, extreme conditions in which PARP1 is overactivated (e.g., extensive genotoxic stress) conversely promote cell death (Burkle 2001) via parthanatos.

Parthanatos is separate from apoptosis and necrosis despite sharing some morphological features (David et al. 2009). This pathway is caspase-independent, making it distinct from apoptosis, although it was commonly referred to as a caspase-independent form of apoptosis (Cande et al. 2002) prior to "parthanatos" being coined in 2007 (Golstein and Kroemer 2007). Similarly, parthanatos has characteristics that overlap with necrosis such as the loss of membrane integrity and depletion of cellular energy stores (Yu et al. 2003). However, unlike in canonical necrosis, cells dying by parthanatos undergo chromatinolysis as a regulated process without swelling and rupture of cell membranes (Andrabi et al. 2008).

53.3. PAR Structure and Regulation

PAR polymers may be comprised of just a few ADP-ribose molecules to as many as ~200 with a new branch typically established every 20–50 residues (D'Amours et al. 1999), or they can be linear. These differences appear to have functional consequences. For example, histones have the highest affinities for PAR polymers that are branched, lower affinities for those that are long and linear, and the lowest affinities for those that are short and linear (Panzeter et al. 1992). Evidence also suggests that PAR structure, along with rate of

production/concentration, serves as a signal directing whether pathways promoting cell survival versus cell death are activated (Andrabi et al. 2006).

In the absence of DNA damage, the basal rate of PARP1 catalytic activity is very low. However, when PARP1 binds to structural defects in the genome or encounters other activators such as nucleosomes, PAR production may increase as much as 500× (Ferro and Olivera 1982). During physiological conditions in which PARP1 is activated, several mechanisms counterbalance increased PAR production to maintain cellular homeostasis. First, typically within 1 minute of synthesis, a PAR molecule is catabolized by poly-(ADP-ribose) glycohydrolase (PARG) and ADP-ribosyl protein lyase (de Murcia and Menissier de Murcia 1994). Second, autoparylation of PARP1 downregulates its own activity by interfering with interactions between the DNA and DBD (D'Amours et al. 1999). Third, accumulation of the nicotinamide by-product from the consumption of NAD^+ by PARP1 may act as a negative feedback signal (Hageman and Stierum 2001).

53.4. PAR Toxicity via Apoptosis-Inducing Factor

A mechanism by which high PAR levels lead to cell death is that it indirectly causes peripheral chromatin condensation and genomic DNA fragmentation in the nucleus via AIF. This process is initiated when excess PAR polymers enter the cytosol from the nucleus and consequently induce translocation of AIF from the mitochondria to the nucleus (Susin et al. 1999). Consistent with parthanatos being distinct from apoptosis, the actions of both PAR and AIF are caspase-independent (Andrabi et al. 2006). However, under certain forms of oxidative stress, PARP1 activity may be regulated by physical interaction with nuclear RIPK1, a mechanism that overlaps with necrosis (Jang et al. 2018).

Rod photoreceptor death in certain genetic forms of retinitis pigmentosa (RP) may be caused by release of AIF under conditions of excessive PAR. In the rd1 mouse model of RP, expression of *Parp1* was equivalent between mutant and wild-type retinas while PAR upregulation was apparent only in the mutant retinas after the onset of degeneration. Immunolabeling showed that PAR colocalizes in the outer nuclear layer with both oxidative DNA damage and AIF. Conversely, cultured rd1 mouse retinal explants treated with a PARP inhibitor showed evidence of decreased cell stress and lower reactivity to cell death markers (Paquet-Durand et al. 2007). The research group also found evidence in mouse models of eight other IRDs supporting the role of parthanatos, rather than apoptosis (Arango-Gonzalez et al. 2014).

53.5. Cell Death by NAD^+ Depletion

While the actions of excess PAR and nuclear AIF have gained acceptance as canonical mechanisms underlying parthanatos, they may not be necessary for initiating cell death. Instead, overactivation of PARP1 can be sufficient to kill cells through NAD^+ depletion (Alano et al. 2010). PARP1 is the most potent consumer of nuclear NAD^+ (Bai and Canto 2012), and generation of PAR under physiological conditions causes a transient decrease in the content of this metabolite pool (Ding et al. 1992). During extreme PARP1 activation, nuclear NAD^+ can become depleted such that neither PARPs nor other downstream

consumers can function properly. For example, nuclear sirtuins require nuclear NAD^+ to deacetylate histones (Ying 2013).

NMNAT1-asssociated retinal degeneration (LCA9) is an early-onset, severe IRD caused by mutations in the enzyme required to generate nuclear NAD^+ (Falk et al. 2012). In a mouse model of this disease (Greenwald et al. 2016), the NAD^+ content in neural retina appears to be decreased while the level of the NAD^+ precursor nicotinamide mononucleotide is increased, and ATP levels remain unaffected in comparison to littermate controls (Greenwald et al., RD2018). Mutant NMNAT1 cannot adequately regenerate NAD^+ under ordinary levels of PARP1 activation, and the net effect is presumably the same as if PARP1 were to have been overactivated.

53.6. Cell Death by NAD^+ Depletion and Low ATP

Since both consumption of NAD^+ by PARP1 and regeneration of NAD^+ by NMNAT1 require ATP, overactivation of PARP1 may produce a bioenergetic collapse of the cell as ATP stores are depleted (Pieper et al. 1999). NAD^+/ATP depletion has been considered as an underlying cause of dry AMD, and this hypothesis was tested using a human-derived retinal pigment epithelium cell line (ARPE-19) that was subjected to oxidative stress (Jang et al. 2017). Challenged ARPE-19 cells showed an increase in PARP1 activity while NAD^+ and ATP levels were lower than normal. However, translocation of AIF to the nucleus was not observed, and depleting the cells of this factor did not impact cell viability. Mitochondrial dysfunction, detected as depolarization of the organelle, could be reversed by supplementation with NAD^+ or by pharmacological inhibition of PARP1, which also restored NAD^+ and ATP levels (Jang et al. 2017).

53.7. PAR Toxicity via Defects in Glycolysis

More recently, PAR toxicity by interference with glycolysis was presented in opposition to NAD^+ depletion being the executioner of parthanatos (David et al. 2009). Parylation inhibits hexokinase 1, a critical enzyme in glycolysis, and this blockade occurs prior to NAD^+ depletion during genotoxic stress (Andrabi et al. 2014). However, Andrabi et al. do not exclude the possibility that NAD^+ depletion caused by PAR synthesis may contribute to and sustain the existing glycolytic defects; in primary astrocyte cultures, supplementation with exogenous NAD^+ can entirely restore glycolytic capacity and cell viability (Ying et al. 2003). Since AIF and hexokinase 1 interact, the release of AIF from the mitochondria could play a role in bioenergetic failure in the context of glycolysis (Andrabi et al. 2014).

53.8. Concluding Remarks

Retinal degenerations are highly variable in etiology and the locus of disease can be within one or across multiple cell types. For such reasons, developing therapies that target the primary defect can be challenging. Therefore, investigating whether some retinal diseases are associated with less familiar programmed cell death pathways outside of apoptosis and necrosis may reveal promising therapeutic targets (Morris et al. 2018). Such interventions could be effective for treating clusters of diseases based on the common cell death pathway,

independent of the primary gene defect(s) or insult(s) (Marigo 2007). Likewise, given the emerging evidence that parthanatos underlies various retinal diseases that are currently untreatable, it would be reasonable to explore therapies that target this form of cell death such as PARP inhibitors, NAD^+ and NAD^+ precursor supplementation, and therapies that restore hexokinase activity.

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