PARways of Death

Rodrigo Durán

Introduction

Traditionally, three models of programmed cell death (PCD) have been proposed, according to the observations made during the second part of century XX: type I cell death associated with heterophagy (apoptosis), type II cell death associated with autophagy (autophagic death) and type III without digestion implicated (necrosis). However, different types of necrosis as a regulated process have been recently described, such as necroptosis, parthanatos, oxytosis/ferroptosis, (N)ETosis and pyroptosis. In general, regulated necrosis is described as a dysregulation of redox metabolome, which curses in an energetic depletion or a high level of redox species.

PARP1 (Poly-ADP-Ribose Polymerase 1) is a nuclear protein which catalyze formation of ADP-ribose from NAD^+. Under single or double strand breaks (SSB, DSB), PARP1 becomes active and recruits protein for DNA repairing by PAR adding (PARylation). Despiste this protective role, PARP1 has been related to several models of cell death, as well as some human diseases, such as neurodegeneration.

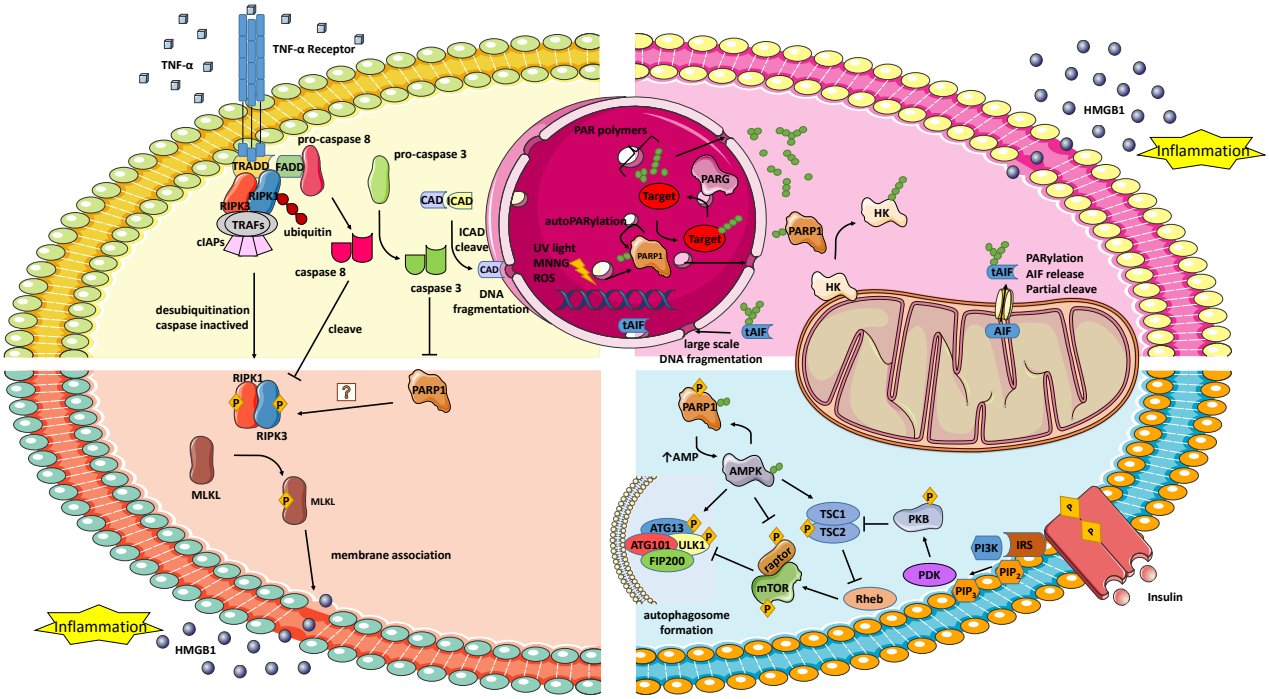
Role of PARP in cell death

Apoptosis

In spite of PAR formation can be occur prior to apoptosis to detecting DNA breaks, an excess of PARP1 activity and PAR prevents apoptosis, which is a highly expending process in terms of ATP Thus, inactivation of PARP1 by cleavage is necessary in order to activate and realize apoptosis, both intrinsic (not shown) and extrinsic pathway.

Parthanatos

Parthanatos is a new model of regulated necrosis characterized by the overactivation of PARP1. When DNA damage is profound, PARP-1 activated and produces long-chained, branched polymers of PAR, through the expenditure of ATP to regenerate NAD^+. This energy depletion leads to externalization of phosphatidylserine, dissipation of the mitochondrial membrane potential, translocation of AIF from the mitochondria to the nucleus, large-scale DNA fragmentation (~50 kb) and chromatin condensation, followed by cell death.



Necroptosis

The interplay between PAR and necroptosis is not fully understood, in spite of PAR enhances necroptotic death. Both necroptosis and parthanatos are inflammatory process, due to NF-κB activation (not shown) and release of Danger-associated molecular patterns (DAMPs), such as HMGB-1.

Autophagy

The expenditure of ATP during parthanatos leads to a higher AMP/ATP ratio and, thus, an increased AMPK activity. Completing a feedforward loop, AMPK can phosphorylate PARP1 and enhance its activity.

PARP in human disease

Parkinson

PARP is overexpressed in dopaminergic neurons, increasing susceptibility for parthanatos. Several hypothesis has been suggested to explain dopaminergic death in Parkinson involving PARP, such as (i) Glu-induced excitotoxicity leading to ROS formation, (ii) AIMP2 accumulation by Parkin inactivation promotes PARP activation and (iii) mitochondrial dysfuction leading to cell death by Parkin inactivation (damaged mitochondria can not be eliminated) and PARP activation (impaired genesis of new mitochondria).

Cancer

Currently, there are several PARP inhibitors in development as treatment against solid tumors, such as breast. BRCA and PARP allow repairing of DSB by homologous repair and SSB by base excision repair, respectively. If BRCA is mutated, PARP inactivation causes genomic instability, which leads to non-viable genetic errors and, finally, cell death. Furthermore, PARP inhibitors can be used as a complement or alternative to hormone-depending cancer treatments, since PARP interacts with Estrogen, Prostagen and Androgen receptors and promotes their function

Conclusions

In the last two decades, paradigm about cell death has changed from three well-differentiated models (apoptosis, autophagic death, necrosis) and added several subtypes of necrosis as a regulated process. The limits among them are diffused, due to sharing some features and interplay. PARP plays an important role by modulating several types of death and has been related to common human pathologies, as cancer or Parkinson. Therefore, understanding completely the role of PARP and parthanatos in human biology is needed to achieve a successful therapy.

Selected References

Berghe, T. Vanden, Linkermann, A., Jouan-Lanhouet, S., Walczak, H., & Vandenabeele, P. (2014). Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nature Reviews Molecular Cell Biology*, *15*(2), 135–147.

Virág, L., Robaszkiewicz, A., Rodriguez-Vargas, J. M., & Oliver, F. J. (2013). Poly(ADP-ribose) signaling in cell death. *Molecular Aspects of Medicine*, *34*(6), 1153–1167.

Bürkle, A., & Virág, L. (2013). Poly(ADP-ribose): PARadigms and PARadoxes. *Molecular Aspects of Medicine*, *34*(6), 1046–1065.

Fatokun, A. A., Dawson, V. L., & Dawson, T. M. (2014). Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities. *British Journal of Pharmacology*, *171*(8), 2000–16.

Figures were made by using Servier Medical Art (www.servier.com).