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Review Article

PARP inhibitors: New partners in the therapy of cancer and inflammatory diseases

Andreína Peralta-Leal [a], José Manuel Rodríguez-Vargas [a], Rocío Aguilar-Quesada [a], María Isabel Rodríguez [a], José Luis Linares [b], Mariano Ruiz de Almodóvar [b], F. Javier Oliver [a]

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Abstract

Poly(ADP-ribose) polymerases (PARPs) are defined as cell signaling enzymes that catalyze the transfer of ADP-ribose units from NAD^+ to a number of acceptor proteins. PARP-1, the best characterized member of the PARP family, which currently comprises 18 members, is an abundant nuclear enzyme implicated in cellular responses to DNA injury provoked by genotoxic stress. PARP is involved in DNA repair and transcriptional regulation and is now recognized as a key regulator of cell survival and cell death as well as a master component of a number of transcription factors involved in tumor development and inflammation. PARP-1 is essential to the repair of DNA single-strand breaks via the base excision repair pathway. Inhibitors of PARP-1 have been shown to enhance the cytotoxic effects of ionizing radiation and DNA-damaging chemotherapy agents, such as the methylating agents and topoisomerase I inhibitors. There are currently at least five PARP inhibitors in clinical trial development. Recent in vitro and in vivo evidence suggests that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but also as single agents to selectively kill cancers defective in DNA repair, specifically cancers with mutations in the breast cancer-associated genes (BRCA1 and BRCA2). PARP becomes activated in response to oxidative DNA damage and depletes cellular energy pools, thus leading to cellular dysfunction in various tissues. The activation of PARP may also induce various cell death processes and promotes an inflammatory response associated with multiple organ failure. Inhibition of PARP activity is protective in a wide range of inflammatory and ischemia–reperfusion-associated diseases, including cardiovascular diseases, diabetes, rheumatoid arthritis, endotoxic shock, and stroke. The aim of this review is to overview the emerging data in the literature showing the role of PARP in the pathogenesis of cancer and inflammatory diseases and unravel the

solid body of literature that supports the view that PARP is an important target for therapeutic intervention in critical illness.

Introduction

The enzymatic activity responsible for the synthesis of poly(ADP-ribose) (PAR) polymers was originally described in the early 1960s in Paul Mandel's laboratory in Strasbourg [1]. This initial observation generated significant biological interest and started a rather competitive field of research in which laboratories from various disciplines involved in studies on genomic stability, posttranslational modification of proteins, transcription, cell cycle, cell survival, and cell death are still heavily involved.

In the course of the years the enzymes responsible for PAR synthesis have been given different acronyms but currently are called PAR polymerases (PARPs), a rather generally accepted term. In the past decade, genomic approaches have allowed the identification of 18 putative PARP sequences in the human genome, and a significant amount of information is available for at least 5 enzymes [2]: PARP-1 (113 kDa), PARP-2 (62 kDa), PARP-3 (60 kDa), PARP-4 (193 kDa), and PARP-5 (142 kDa) or Tankyrase 1 (TRF1-interacting, ankyrin-related ADP-ribose polymerase).

PARP-1 is the founding member and the most commonly studied of these enzymes. It is an abundant nuclear protein in which it is possible to distinguish three domains: first, a DNA-binding region able to recognize DNA strand breaks; second, a central automodification region rich in glutamic acid and containing a breast cancer-associated protein C-terminal motif; and third, a NAD-binding region with all the catalytic activities of the full-length enzyme. DNA strand breaks remarkably increase PARP-1 basal activity (up to 500 times) [3]. Compelling evidence suggests that PARP-1, through its physical association with or by the poly(ADP-ribosyl)ation of partner proteins, regulates chromatin structure, DNA metabolism, and gene expression [4]. PARP-1 accounts for at least 85% of maximally activated cellular PARP activity.

Section snippets

The development of PARP inhibitors

Most of the PARP inhibitors in development mimic the nicotinamide moiety of NAD^+. PARP catalyzes the cleavage of NAD^+ into ADP and ADP-ribose and attaches several molecules of the latter to the target protein in a process called poly(ADP-ribosyl)ation. Therefore, molecules that mimic NAD^+ block the binding of the NAD^+ to the enzyme, inhibiting PARP activity. The discovery of inhibitors of PARP was initially based on empirical, high-throughput screening, followed by optimization by chemical…

PARP and DNA repair

The genome is under constant mutational stress through exposure to exogenous and endogenous agents that damage DNA. In mammalian cells, more than 150 proteins have been described that are involved in the response to DNA damage [13]. These proteins coordinate the repair of DNA lesions by

different repair pathways [14], although there are also considerable overlap and interactions between mechanisms. In the absence of adequate detection and repair of DNA damage, these alterations can result in…

PARP inhibitors in the treatment of DNA repair deficiency-related cancers

Inhibition of PARP induces accumulation of large numbers of unrepaired SSBs, leading to the collapse of replication forks during S phase and the consequent generation of DSBs. Single-strand breaks are usually repaired by the base excision repair pathway; therefore, inhibition of this pathway greatly increases the number of unrepaired single-strand breaks, which subsequently leads to DSBs at replication forks. Therefore, cells deficient in DNA DSB repair are highly sensitive to chemical…

Other pathways involved in HR

Loss of PARP-1 has been shown to cause an increase in Rad51 foci and sister chromatid exchanges [54] as a result of an increase in the number of lesions normally repaired by HR. The sensitivity of cells deficient in proteins involved in HR to PARP inhibition suggests that treatment with PARP inhibitors maybe a useful therapeutic strategy for tumors displaying defects in the HR pathway other than BRCA defects. The observation that ATM and CHK2 depletion resulted in sensitivity to PARP inhibitors …

Mismatch-repair (MMR)-deficient cells

Mutations in genes involved in MMR or in their expression result in increased risk of tumor development and in increased resistance to many anticancer therapies [51], [57]. PARP inhibitors have been shown to sensitize resistant cells to alkylating agents [52], [58]; moreover, a PARP inhibitor (AG1461) enhanced temozolomide activity in MMR-proficient cells, but intriguingly, it was more effective in MMR-deficient cells [57]. It is likely that in MMR-deficient cells there is a switch in toxic…

PARP inhibitors as antiangiogenic agents

As has been described in the previous section, PARP inhibitors are being developed for the treatment of cancer, both in monotherapy and in combination with radiation and chemotherapeutic agents in humans. Recently, a number of reports from various laboratories, including ours, have led to a novel and unexpected effect of PARP inhibitors, showing a relationship between PARP and angiogenesis, and to the proposition of PARP inhibitors as antiangiogenic agents.

So far at least five PARP inhibitors…

Role of poly(ADP-ribose) polymerase in oxidative/nitrosative stress-related pathologies

It must be stressed that PARP-1 functions as a double-edged sword: on one hand, moderate activation of PARP can be of physiological importance via enhancement of DNA repair. On the other

hand, overactivation of PARP represents an important mechanism of tissue damage in various pathological conditions associated with oxidative and nitrosative stress, including myocardial reperfusion injury [68], [69], heart transplantation [70], and autoimmune β-cell destruction associated with diabetes mellitus …

Poly(ADP-ribosyl)ation inhibitors: promising drug candidates for a wide variety of pathophysiologic conditions

The “suicide hypothesis” is considered a key mechanism explaining the protective effects of PARP inhibition in various oxidative stress-induced diseases, involving overwhelming DNA damage (as result of ROS and RNS release during inflammation) and excessive activation of PARP leading to NAD and ATP depletion and necrotic cell death. The production of both NO (via the route of formation of peroxynitrite) and ROS induces damage in DNA and consequently leads to the activation of PARP-1 and PARP-2…

Perspectives

Pharmacological inhibition of key proteins involved in the response to DNA damage has emerged as an effective tool for cancer treatment, as the resistance of cancer cells to DNA-damaging agents originates from the modulation of DNA repair pathways. PARP has important prosurvival and protective functions in terms of DNA repair. A multitude of novel pharmacological inhibitors of PARP has entered clinical testing either as adjunct antitumor therapeutics or as monotherapy in familiar breast and…

Acknowledgments

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