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Review article

PARP1 promoter links cell cycle progression with adaptation to oxidative environment

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ABSTRACT

Although electrophiles are considered as detrimental to cells, accumulating recent evidence indicates that proliferating non-cancerous and particularly cancerous cells utilize these agents for pro-survival and cell cycle promoting signaling. Hence, the redox shift to mild oxidant release must be balanced by multiple defense mechanisms. Our latest findings demonstrate that cell cycle progression, which dictates oxidant level in stress-free conditions, determines *PARP1* transcription. Growth modulating factors regulate CDK4/6-RBs-E2Fs axis. In cells arrested in G1 and G0, RB1-E2F1 and RBL2-E2F4 dimers recruit chromatin remodelers such as HDAC1, SWI/SNF and PRC2 to condense chromatin and turn off transcription. Release of retinoblastoma-based repressive complexes from E2F-dependent gene promoters in response to cell transition to S phase enables transcription of *PARP1*. This enzyme contributes to repair of oxidative DNA damage by supporting several strand break repair pathways and nucleotide or base excision repair pathways, as well as acting as a co-activator of transcription factors such as NRF2 and HIF1a, which control expression of antioxidant enzymes involved in removal of electrophiles and secondary metabolites. Furthermore, PARP1 is indispensible for transcription of the pro-survival kinases MAP2K6, ERK1/2 and AKT1, and for maintaining MAPK activity by suppressing transcription of the MAPK inhibitor, MPK1. In summary, cell cycle controlled *PARP1* transcription helps cells to adapt to a pro-oxidant redox shift.

1. Pro-oxidant physiology of proliferating cells

Human cells proliferate in a variety of contexts. Controlled cell divisions play a particular function for development of the embryo, while in the adult organism mainly stem and some immune cells retain the ability to proliferate. Cancer cells, as a special type of transformed cells, are capable of unlimited and uncontrolled growth. Regardless of the type of dividing cell, proliferation imposes a requirement for energy and reducing power. Although mitochondrial oxidative phosphorylation is the most efficient source of ATP, it can cause extensive release of $O_2^{\bullet-}$, which is dismutated to H_2O_2 either in mitochondria (by SOD2) or in the cytoplasm (by SOD1). Therefore, above some critical threshold value of this oxidant in cell compartments, aerobic glycolysis becomes more favorable than oxidative phosphorylation in order to limit the hazardous waste products resulting from the mitochondrial metabolic pathway [1]. During fatty acid oxidation, $O_2^{\bullet-}$ and H_2O_2 can also be produced by xanthine oxidase in peroxisomes, which duplicate and are segregated between progeny cells. Although metabolically unrelated, NADPH oxidases act as a primary source of oxidants in macrophages and some cancer cells [2].

Depending on the cell type, proliferation-inducing agents such as growth factors (platelet-derived, fibroblast, epidermal, insulin-like and transforming growth factor β), cytokines (type I interferons, granulocyte-macrophage colony-stimulating factor), mutant K-ras or small GTPase Rac-1 elevate intracellular $O_2^{\bullet-}$ through NADPH oxidase and/or mitochondria [3,4]. Due to pressure induced by an elevated and sustained redox shift to a mild oxidative environment, cells have developed efficient mechanisms of adaptation and functional transformation of „bad" to „good" molecules, which promote cell proliferation and survival at different signaling levels [5].

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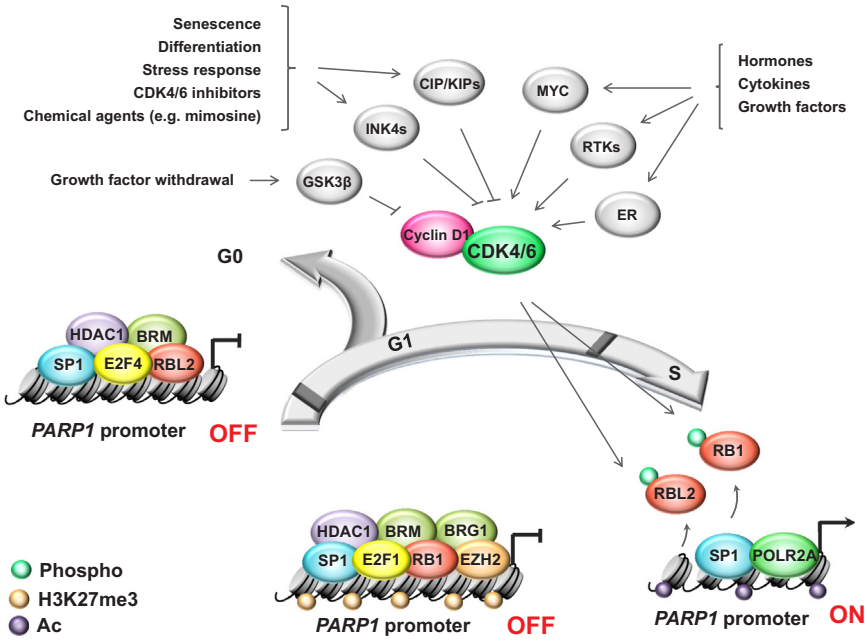

Fig. 1. Cell cycle progression dictates *PARP1* transcription via growth factors/inhibitors-G1/G0-CDK4/6-RBs axis. Cell cycle machinery is controlled by external signals in order to adapt cells to environmental requirements and conditions. Stimulation of receptor tyrosine kinases (*RTKs*), MYC protooncogene or estrogen receptor (ER) in response to peptide and non-peptide growth-promoting agents activates cyclin-dependent kinase 4 and 6 (CDK4/6), which associate with cyclin D1 and phosphorylate retinoblastoma proteins (RB1, RBL2). This modification keeps retinoblastoma proteins released from promoters of PARP1 and cell cycle promoting genes, thereby allowing active gene transcription and enabling cell transition from G1 to S phase. Upon cell growth arrest in G1 or cell cycle exit to G0, CDK4/6 inhibition results in hypophosphorylation of retinoblastoma proteins, their binding to E2F-driven gene promoters and recruitment of chromatin remodelers, which are capable of inactivating gene expression by removing transcription-promoting indicators and/or inserting transcription-inhibiting histone modification(s). It leads to an increase in nucleosome density and chromatin condensation. Notably, composition of the repressive complex varies between cells arrested in G1 and in G0. Limiting PARP1 expression in G0 is achieved solely by histone deacetylase 1 (HDAC1) for histone deacetylation, while in G1 HDAC1 additionally requires PRC2 (polycomb repressor complex 2) activity and trimethylation of H3K27 by enhancer of zeste homolog 2 (EZH2) to repress PARP1 transcription. Cell cycle arrest in G2 does not affect the mRNA and protein levels of PARP1.

2. Cell cycle progression regulates PARP1 transcription

Poly-ADP-ribose polymerase 1 (PARP1) is a multitasking enzyme that regulates many intracellular processes, including DNA repair, metabolism, signaling and transcription, by direct interaction with other proteins and DNA, involving their ADP-ribosylation and auto-ADP-ribosylation of PARP1. The data acquired and published in the EMBL-EBI Expression Atlas indicate high PARP1 abundance in proliferating cancerous and non-cancerous cells (e.g. macrophages) [6]. In search for the link between *PARP1* transcription and cell cycle progression, we recently revealed that cell arrest in G1 or exit to G0 lead to *PARP1* repression by retinoblastoma-based multiprotein complexes, which are also known to repress transcription of E2F-dependent genes encoding proteins responsible for cell transition to S phase [7]. The mode of growth inhibition determines the composition of the repressive complex at the *PARP1* promoter, giving priority to E2F1-RB1 dimers under G1 arrest in cancer, as well as in CD34 + hematopoietic progenitor/stem cells treated with cyclin-dependent kinases 4 and 6 (CDK4/6) pharmacological inhibitors or depleted of nucleotides by mimosine. E2F4-RBL2-based complexes were found to be prevalent in differentiated cells (Fig. 1). Since PARP1 is involved in cell protection against oxidants, one may think that *PARP1* repression in response to proliferation arrest may sensitize cells to agents that challenge redox homeostasis. Some ongoing and recruiting clinical trials have been testing FDA approved CDK4/6 inhibitors Palbociclib (IBRANCE®, PD0332991) and Ribociclib (LEE011, Kisqali) in combination with drugs such as doxorubicin, carboplatin and paclitaxel, which trigger acute redox imbalance [8].

Furthermore, PARP1 enhances cell proliferation. Hormone-activated cyclin-dependent kinase 2 (CDK2) phosphorylates and activates PARP1, thereby facilitating H1 displacement and transcription of the majority of hormone-responsive genes in breast cancer [9]. In urinary bladder carcinoma cells, PARP1 regulates cyclin E expression, cell cycle re-entry and G1/S progression [10]. Thus, high levels of PARP1 in cancer cells promote cell cycle progression, which is associated with an increased level of oxidants, thereby maintaining PARP1 transcription and creating a self-promoting cycle.

3. PARP1 co-activates expression of proteins that enzymatically decompose oxidants and remove secondary metabolites

The primary role in antioxidant defense and in cell adaptation to excessive oxidant or electrophile production is fulfilled by enzymatic antioxidant defense, which comprises direct scavengers of electrophiles, but also enzymes that detoxify the secondary metabolites. Many such enzymes are under transcriptional control of nuclear factor erythroid 2 (NFE2)-related factor 2 (NRF2), a basic leucine zipper (bZIP) protein, which dissociates from its repressor Keap1 and translocates to nucleus in response to a physiological shift in redox homeostasis towards oxidant production. NRF2 requires PARP1 for full transcriptional activity, because PARP1 facilitates interaction of NRF2 and NRF2-partner (small MAF protein; MAFG) with the antioxidant response element (ARE) (Fig. 2) [11]. An inhibitory effect of PARP1 knockdowns was found in breast cancer cells and proliferating mouse fibroblasts. Although in normal cells NRF2 suppresses tumor promotion and progression, this pathway is constitutively activated in various cancers by mutation and transcriptional repression of Keap-1, accumulation of Keap-1-NRF2 disruptors, transcriptional and post-translational NRF2 induction. In view of NRF2 targets, this transcription factor provides chemoresistance and, like PARP1, has become a target for anticancer interventions [12].

Another oxidant-counteracting mechanism that involves PARP1 is represented by its interaction with the transcription factor hypoxia-inducible factor 1-alpha (HIF1α), which undergoes activation during hypoxia and hypoxia-triggered redox imbalance [13,14]. PARP1 co-activates HIF1α-dependent transcription of genes, which promotes cell survival. In murine embryonic fibroblasts, PARP1 caused accumulation of HIF1α via upregulation of NO and oxidant production in cells treated with deferoxamine [15]. In addition to PARP1, HIF1α binds EP300/CBP acetylase(s) for full transcriptional activity. A similar observation was made for nuclear factor kappa B (NF-κB), activation of which required synergistic interaction with PARP1 and EP300/CBP. However, for HIF1α mutual dependence between these two types of co-activators has not been documented yet.

Promoters of some antioxidant enzymes such as catalase, SOD1 or SOD2 carry the binding motif for NF-κB, but the role of PARP1 in transcription activation of these genes has not been confirmed. Instead,