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DNA damage response upon environmental contaminants: An exhausting work for genomic integrity

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Abstract

Following exposure to xenobiotics, cellular mechanisms will take place to prevent damages relative to i) DNA, to maintain genome integrity, ii) proteins, to maintain their activities, iii) lipids, to limit peroxidation. This system of cellular defence and resistance is energetically costly. In this commentary review, we discuss the impact of DNA damage and the DNA damage response (DDR) on energetic metabolism. Conversely, we address the question about how energetic metabolism would influence DDR. These points will be highlighted in the context of cancer, in which genome instability and aerobic glycolysis are cancer hallmarks.

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1. DNA damage response: an expensive energetic system

DDR is fined-tuned by energetic metabolism to maintain genomic integrity. For this purpose, metabolic and DNA damage checkpoints are the surveillance molecular mechanisms, which induce the coordination of DNA repair with bioenergetics to limit the survival and proliferation of damaged cells and metabolic collapse. The DNA damage checkpoints, characterized in the 90's, include DNA damage sensors, signaling transducers and effectors [1], in order to stop cell cycle to perform repair. The metabolic checkpoints, initially identified in 1974 have been recently revived. They are multiple and specific of the cell type and the environmental context (like AMPK or p53). They sense nutrient depletion and adapt metabolic reactions to the cellular needs, in relationship with cell cycle. The coupling DDR/metabolism is barely described in toxicology but literature is growing and open new doors for discovery.

The impact of DNA damage and its impact on energy metabolism was firstly evidenced with the DNA damage sensor PARP-1 (poly(ADP-ribose) polymerase 1) [2]. Activated by numerous genotoxic stresses (by physical or chemical agents, upon acute or chronic exposure), PARP-1 triggers ATP and NAD^+ depletions, associated by mitochondrial depolarization, reactive oxygen species (ROS) production and apoptosis. NAD^+ resynthesis after PARP-1 overactivation induces a metabolic collapse. It is important to note that PARP-1 is a major caspase target, in order to promote apoptosis induction, a mechanism that also requires energy. Otherwise, due to energy drop, it induces necrosis [3]. However, recent findings underline that an adaptive metabolism can occur, with a stimulation of AMPK (AMP-activated protein kinase), leading to an increase in fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) following DNA damage and PARP-1 activation [2] (Fig. 1). Induced by multiple genotoxic stresses (ultraviolet radiation, crosslink agents and ionizing radiation), it could be interesting to study such effects at low doses with environmental contaminants.

PARP-1 also regulates metabolism by interacting with different metabolic partners: SIRT1 (sirtuin 1), nuclear factors and energy sensors (AMPK) [4], showing the possible dialogues between DNA damage and metabolic checkpoints.

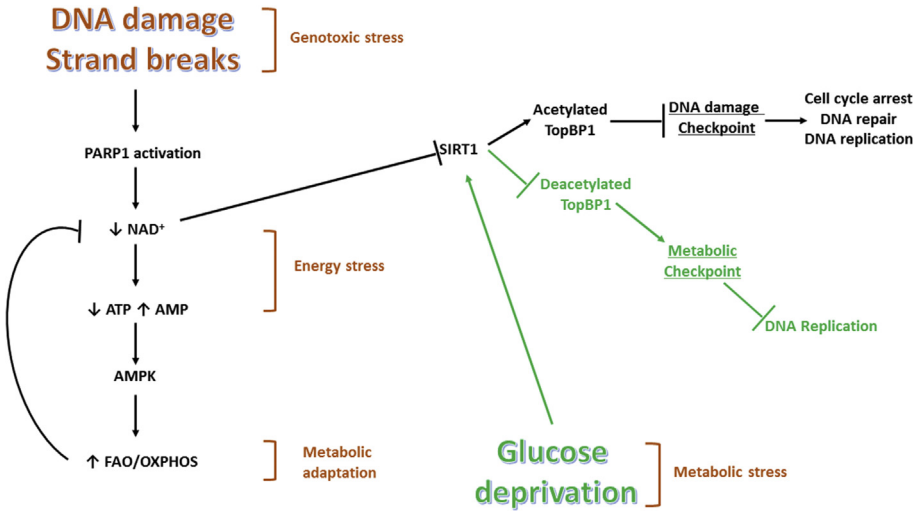
2. When DNA damage checkpoints regulate metabolic pathways

Genotoxicity and bioenergetics upon exposure to contaminants were separately studied for years. Recently, there is growing evidence supporting that DNA damage and metabolic response are interacting networks. When DNA damage occurs, the checkpoints that regulate cell arrest and cell repair are orchestrated by metabolic checkpoints.

2.1. SIRT1

SIRT1 is a member of sirtuin family of NAD^+-dependent histone deacetylase, involved in cell resistance, survival and longevity. It regulates energy sensing and is

Fig. 1



From genotoxic stress to metabolic adaptation and the feedback regulation including SIRT1 intervention. After DNA damage, the strong activation of PARP1 depletes cells from NAD+. This energy stress could activate AMPK and stimulate FAO and OXPHOS to encompass NAD + drop. SIRT1 and PARP1 compete for NAD+. This feedback regulates the activity of TopBP1 by acetylation/deacetylation and the consecutive cell cycle arrest, DNA repair and DNA replication after DNA damage checkpoint or inhibition of DNA replication after metabolic checkpoint following glucose deprivation. AMPK (AMP-activated protein kinase), FAO (fatty acid oxidation), PARP-1 (poly(ADP-ribose) polymerase 1), OXPHOS (oxidative phosphorylation), SIRT1 (sirtuin 1), TopBP1 (DNA topoisomerase II binding protein 1).

activated by nutrient depletion (including reduction in glucose access). SIRT1 was recently described as a switch of metabolic and DNA damage checkpoints. Precisely, SIRT1 regulates the acetylation/deactelyation of DNA topoisomerase II binding protein 1 (TopBP1) [5]. On the one hand, glucose deprivation induces SIRT1 activation, transducing ToBP1 deacetylation and thereby inhibiting DNA replication. In contrast, DNA damage inhibits SIRT activity, resulting in TopBP1 acetylation that constitutes DNA damage checkpoint and promote repair. SIRT1 pathway would deserve attention as a target for environmental contaminants (Fig. 1). Furthermore, a downregulation of SIRT 1 may be induced through the activation of AhR, a crucial sensor of xenobiotics. It leads to a downregulation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) levels together with an increase of its acetylation (inactive fraction of PGC1α), followed by a decreased expression of the levels of phosphoenolpyruvate carboxykinase (PEPCK-C) and glucose-6-phosphate dehydrogenase (G6Pase) [6]. Altogether, these observations provide evidence of a role of SIRT1 in glucose homeostasis.

2.2. p53

The transcription factor p53 was firstly characterized as the guardian of genome, and thus, as a major regulator of DNA damage checkpoint. When activated by DNA damage, p53 induces cell arrest and DNA repair or in some cases, autophagy induction. If the damages are abundant, it can directly trigger apoptosis. Others stresses also activate p53 such as hypoxia and oxidative stress. The p53-activated cellular responses play a pivotal role in DNA repair, tumorigenesis, cell death and survival. Knowing the multiple functions of p53 as an integrator/checkpoint regulator of DNA damage and metabolic homeostasis, single mutation can promote tumorigenesis and p53 is a major driver suppressor of tumors [7].

For ten years, many works attribute an important role of p53 in the regulation of cellular metabolism of cancer cells, especially in the regulation of glycolysis and OXPHOS (for review [8]). In cancer cells, cells yield high level of aerobic glycolysis and a drop of OXPHOS. This phenomenon, termed as « Warburg » effect (for review [9,10]), has been identified as a major hallmark of malignancy. It have been recently described that p53 positively upregulates OXPHOS and respiration through upregulation of SCO2 (synthesis of cytochrome c oxidase). Moreover, p53 negatively regulates glycolysis through the induction of TIGAR (tumor protein 53 induced glycolysis regulator). Then, the loss of function of p53 by mutations could contribute to the Warburg effect through a metabolic reprogramming that favor glycolysis.

Beyond its activity as a transcription factor, p53 also regulates mitochondria homeostasis during apoptosis, by interacting with pro- and anti-apoptotic Bcl2 members. Thus, the disturbances of p53 pathway by xenobiotics would trigger extensive and various effects.

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