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Review

P53 and Sirt1: Routes of metabolism and genome stability

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ABSTRACT

The tumor suppressor p53 is a transcription factor that regulates key processes. But, the outcomes of the p53 response go beyond its role as a nuclear transcription factor. Sirtuin (SIRT1) regulates p53 functions as transcription factor. At the same time, SIRT1 protects the genome under stress conditions. The link between p53 and SIRT1 responses is unique. Both regulate metabolism, stress signaling, cell survival, cell cycle control and genome stability. Recent studies have proposed cancer as a metabolic disease. This is due to the switch from aerobic to anaerobic metabolism during tumor development. Yet, the complex molecular circuits (in and out of the nucleus) of tumor progression remain elusive. In this review, we will focus on the interplay between p53 and SIRT1. We will discuss their roles as nodes for possible therapeutic intervention.

Contents

1. P53, effect on metabolism and oxidative stress

Metabolic changes take place with tumor progression. Cancer cells often rewire their metabolic pathways to promote fast growing and genomic instability. The best-understood function of p53 is its central role as tumor suppressor. Emerging evidence indicates a role of p53 in monitoring/modulating cell metabolism [1]. Cell fate depends either by p53 transcription-dependent or -independent responses within mitochondria. P53 regulates many

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proteins required for metabolism and reactive oxygen species (ROS) production. Besides, p53 controls redox signaling, through the modulated expression of pro-and anti-oxidant proteins [2].

1.1. The Warburg effect and p53

Transformed cells get a series of features to proliferate fast and to escape from programmed cell death. In 1927 Otto Warburg demonstrated that tumor progression takes place together with metabolic changes [3]. Warburg observed that cancer cells shift from oxidative phosphorylation (OXPHOS) to glycolysis. This occurs even in presence of oxygen. This process is now recalled as the "Warburg effect". Glycolysis takes part in the cytoplasm. It leads to the NADH and ATP production through conversion of glucose into pyruvate. Oxidative phosphorylation generates ATP into mitochondria. In resting conditions OXPHOS is predominant and more efficient. Even if, cells with high rates of proliferation tend to switch to glycolysis. Cancer cells make use of the pentose phosphate pathway (PPP), which originates from a bypass in the glycolysis [4]. PPP is necessary for lipid and nucleic acid synthesis and represents an important source of NADPH. NADPH is also necessary for the production of glutathione (GSH), the major intracellular antioxidant. Thus, the PPP leads to proliferate fast and to protection against oxidative stress [5].

P53 is the most important obstacle for tumor progression. The p53 homologue is present in unicellular organisms. This indicates that the tumor suppression may not be p53's original function [6]. Besides DNA damage and oncogene activation, nutrient flow changes activate p53 [7]. Recent studies show that p53 controls the metabolic switch between glycolysis and oxidative phosphorylation.

1.2. P53 and glucose metabolism

P53 inhibits glycolysis by acting at different levels. It has been demonstrated that p53 decreases glucose import by reducing the expression of GLUT1 and GLUT4 glucose transporters [8]. P53, through the inhibition of IKK, also regulates the GLUT3 expression [9]. Bensaad and co-workers demonstrated that p53 reduces glycolysis by promoting TIGAR expression [5]. TIGAR dephosphorylates fructose-2,6-bisphosphate to fructose-6-phosphate and blocks the breakdown of glucose into pyruvate. This in turn promotes the switch to the oxidative pentose phosphate pathway (ox-PPP). The latter leads to NADPH production and to a more effective protection against oxidative stress. P53-independent TIGAR accumulation is a hallmark of several tumors. Yet, the scenario is complex since p53 inhibits the glucose-6-phosphate dehydrogenase (G6PDH) expression. G6PDH takes part in the first and limiting step of the ox-PPP [4]. The mechanism by which p53 inhibits G6PDH represents a way to block ox-PPP in case of accumulation of TIGAR in cancer cells. TAp73, a member of the p53 family, induces the expression of G6PDH genes and leads to cell proliferation [10]. In mouse embryonic fibroblasts, p53 inhibits glycolysis. In these cells, P53 reduces the protein levels of the glycolytic enzyme phosphoglycerate mutase (PGM). PGM converts 3-phosphoglycerate into 2-phosphoglycerate [11]. However, p53 promotes glycolysis in muscle by inducing the expression of PGM M isoform [12] and of hexokinase II (HK2) [13]. The latter converts glucose into glucose-6-phosphate in the first step of glycolysis. This indicates that the effects of p53 on glycolysis are remarkable and tissue-specific.

1.3. P53 modulates the glucose metabolism while controlling the gluconeogenesis

Gluconeogenesis produces glucose and is essential for tumor cell growth. P53 represses the gluconeogenesis by promoting the expression of histone deacetilase sirtuin 6 (SIRT6). SIRT6 deacetylates forkhead box protein O1 (FOXO1). In turn, this represses the expression of glucose-6-phosphatase (G6PC) and of phosphoenolpyruvate carboxykinase (PCK1). Both enzymes are rate-limiting proteins for gluconeogenesis [14].

1.4. P53 and oxidative phosphorylation

While repressing glycolysis, p53 promotes oxidative phosphorylation at distinct levels. In presence of oxygen, the pyruvate derived from glycolysis is converted in Acetyl coenzyme A (Acetyl-CoA). The latter takes part in the tricarboxylic acid (TCA) cycle. In TCA cycle, ATP is generated through oxidative phosphorylation. Besides, TCA cycle provides precursors for anabolic pathways, so supporting cell growth and proliferation. P53-deficient cells produce less ATP from the TCA cycle compared to control cells [15]. In detail, p53 promotes TCA cycle by reducing the pyruvate dehydrogenase kinase 2 (PDK2) expression. PDK2 inactivates the pyruvate dehydrogenase complex (PCD). In turn this promotes the conversion of pyruvate into lactate instead of Acetyl-CoA[16].

P53 enhances gene transcription of mitochondrial components, including subunit 1 of cytochrome c oxidase (COI) [17], and cytochrome c oxidase 2 (SCO2). SCO2 in turn regulates the subunit 1 of complex IV [15]. Besides, p53 induces the expression of the mitochondrial apoptosis-inducing factor (AIF) [18]. AIF acts as NADH/NADPH oxidase. AIF is also essential for the proper functioning of complex I.

P53 reduces the expression of the TCA cycle-associated malic enzymes ME1 and ME2. These enzymes are important for NADPH production, lipogenesis and glutamine metabolism. Thus, P53 regulates both the progression of biosynthetic pathways and the antioxidant response [19]. Besides, p53 enhances OXPHOS by promoting the transcription of glutaminase 2 (GLS2) [20,21]. GLS2 stimulates the production of glutamate and α-ketoglutarate. The latter is a key component of the TCA cycle involved in ATP production and the antioxidant response.

1.5. P53 lipid metabolism and mitochondrial homeostasis

Besides alterations in glycolysis and oxidative phosphorylation, cancer cells show a deregulated lipid metabolism. In particular, cancer cells synthesize fatty acids. The fatty acids are the main reserve of lipids. Lipids are necessary for membrane formation and signaling transduction [22]. Breast, colon and prostate cancer cells [23–25] have high levels of fatty acids synthases (FASN). This observation supports the role of FASN in tumorigenesis. In line with this, FASN inhibition counteracts cellular transformation (reviewed in [26]). FASN deficiency counteracts cancer growth in cells with activated PI3K signaling. Yet, blocking FASN in K-Ras-driven cancer cells has no effect on proliferation [27].

P53 attenuates the fatty acids synthesis, repressing the expression of the transcriptional regulator SREBP-1 (sterol regulatory element-binding protein 1c). The latter promotes the expression of triglyceride synthesis and lipogenic enzymes [28]. Thus, p53 inhibits the expression of FASN and (ATP citrate lyase) ACLY genes. Thereby, p53 may repress tumor proliferation while inhibiting the fatty acids synthesis. The fatty acid oxidation leads to the formation of Acetyl-CoA, which takes part in the TCA cycle, producing ATP, NADPH and FADPH. As mentioned above, TCA cycle is active in resting conditions. While, NADPH is necessary for the cellular protection against oxidative stress. Upon glucose deprivation, p53 induces the expression of Lpin1. This in turn stimulates the fatty acids oxidation [29]. Lpin1 is a nuclear transcriptional co-activator. Following glucose starvation Lpin1 induces the expression of genes involved in fatty acids oxidation. But, Lpin1 inhibits the fatty acid oxidation at high glucose.

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