TP53 Regulates Metabolic Genes


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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 72

This document contains 1 pathway and 34 reactions (see Table of Contents)

https://release.reactome.org
While the p53 tumor suppressor protein (TP53) is known to inhibit cell growth by inducing apoptosis, senescence and cell cycle arrest, recent studies have found that p53 is also able to influence cell metabolism to prevent tumor development. TP53 regulates transcription of many genes involved in the metabolism of carbohydrates, nucleotides and amino acids, protein synthesis and aerobic respiration.

TP53 stimulates transcription of TIGAR, a D-fructose 2,6-bisphosphatase. TIGAR activity decreases glycolytic rate and lowers ROS (reactive oxygen species) levels in cells (Bensaad et al. 2006). TP53 may also negatively regulate the rate of glycolysis by inhibiting the expression of glucose transporters GLUT1, GLUT3 and GLUT4 (Kondoh et al. 2005, Schwartzenberg-Bar-Yoseph et al. 2004, Kawauchi et al. 2008).

TP53 negatively regulates several key points in PI3K/AKT signaling and downstream mTOR signaling, decreasing the rate of protein synthesis and, hence, cellular growth. TP53 directly stimulates transcription of the tumor suppressor PTEN, which acts to inhibit PI3K-mediated activation of AKT (Stambolic et al. 2001). TP53 stimulates transcription of sestrin genes, SESN1, SESN2, and SESN3 (Velasco-Miguel et al. 1999, Budanov et al. 2002, Brynczka et al. 2007). One of sestrin functions may be to reduce and reactivate overoxidized peroxiredoxin PRDX1, thereby reducing ROS levels (Budanov et al. 2004, Papadia et al. 2008, Essler et al. 2009). Another function of sestrins is to bind the activated AMPK complex and protect it from AKT-mediated inactivation. By enhancing AMPK activity, sestrins negatively regulate mTOR signaling (Budanov and Karin 2008, Cam et al. 2014). The expression of DDIT4 (REDD1), another negative regulator of mTOR signaling, is directly stimulated by TP63 and TP53. DDIT4 prevents AKT-mediated inactivation of TSC1:TSC2 complex, thus inhibiting mTOR cascade (Cam et al. 2014, Ellisen et al. 2002, DeYoung et al. 2008). TP53 may also be involved, directly or indirectly, in regulation of expression of other participants of PI3K/AKT/mTOR signaling, such as PIK3CA (Singh et al. 2002), TSC2 and AMPKB (Feng et al. 2007).

TP53 regulates mitochondrial metabolism through several routes. TP53 stimulates transcription of SCO2
gene, which encodes a mitochondrial cytochrome c oxidase assembly protein (Matoba et al. 2006). TP53 stimulates transcription of RRM2B gene, which encodes a subunit of the ribonucleotide reductase complex, responsible for the conversion of ribonucleotides to deoxyribonucleotides and essential for the maintenance of mitochondrial DNA content in the cell (Tanaka et al. 2000, Bourdon et al. 2007, Kulawiec et al. 2009). TP53 also transactivates mitochondrial transcription factor A (TFAM), a nuclear-encoded gene important for mitochondrial DNA (mtDNA) transcription and maintenance (Park et al. 2009). Finally, TP53 stimulates transcription of the mitochondrial glutaminase GLS2, leading to increased mitochondrial respiration rate and reduced ROS levels (Hu et al. 2010).

The great majority of tumor cells generate energy through aerobic glycolysis, rather than the much more efficient aerobic mitochondrial respiration, and this metabolic change is known as the Warburg effect (Warburg 1956). Since the majority of tumor cells have impaired TP53 function, and TP53 regulates a number of genes involved in glycolysis and mitochondrial respiration, it is likely that TP53 inactivation plays an important role in the metabolic derangement of cancer cells such as the Warburg effect and the concomitant increased tumorigenicity (reviewed by Feng and Levine 2010). On the other hand, some mutations of TP53 in Li-Fraumeni syndrome may result in the retention of its wild-type metabolic activities while losing cell cycle and apoptosis functions (Wang et al. 2013). Consistent with such human data, some mutations of p53, unlike p53 null state, retain the ability to regulate energy metabolism while being inactive in regulating its classic gene targets involved in cell cycle, apoptosis and senescence. Retention of metabolic and antioxidant functions of p53 protects p53 mutant mice from early onset tumorigenesis (Li et al. 2012).

**Literature references**


**Editions**

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TP53 binds the TIGAR gene

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