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Introduction

Jiang et al., previously found that p53 inhibits the important NADPH producer glucose-6-phosphate dehydrogenase. As this did not fully explain the effect of p53 on NADPH, here further investigated whether p53 controls the expression of malic enzymes, which catalyse the oxidative decarboxylation of malate to generate pyruvate and either NADPH or NADH. In mammalian cells, three malic enzyme isoforms have been identified: a cytosolic $NADP^+$-dependent isoform (ME1), a mitochondrial $NAD(P)^+$-dependent isoform (ME2) and a mitochondrial $NADP^+$-dependent isoform (ME3), of which ME1 and ME2 are the main isoforms. By recycling the tricarboxylic acid (TCA) cycle intermediate malate into the common TCA cycle carbon source pyruvate, malic enzymes may have a regulatory role in matching TCA flux to cellular demand for energy, reducing equivalents and biosynthetic precursors

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Reciprocal regulation of p53 and malic enzymes modulates metabolism and senescence

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Abstract

Cellular senescence both protects multicellular organisms from cancer and contributes to their ageing. The pre-eminent tumour suppressor p53 has an important role in the induction and maintenance of senescence, but how it carries out this function remains poorly understood. In addition, although increasing evidence supports the idea that metabolic changes underlie many cell-fate decisions and p53-mediated tumour suppression, few connections between metabolic enzymes and senescence have been established. Here we describe a new mechanism by which p53 links these functions. We show that p53 represses the expression of the tricarboxylic-acid-cycle-associated malic enzymes ME1 and ME2 in human and mouse cells. Both malic enzymes are important for NADPH production, lipogenesis and glutamine metabolism, but ME2 has a more profound effect. Through the inhibition of malic enzymes, p53 regulates cell metabolism and proliferation. Downregulation of ME1 and ME2 reciprocally activates p53 through distinct MDM2- and AMP-activated protein kinase-mediated mechanisms in a feed-forward manner, bolstering this pathway and enhancing p53 activation. Downregulation of ME1 and ME2 also modulate the outcome of p53 activation, leading to strong induction of senescence, but not apoptosis, whereas enforced expression of either malic enzyme suppresses senescence. Our findings define physiological functions of malic enzymes, demonstrate a positive-feedback mechanism that sustains p53 activation, and reveal a connection between metabolism and senescence mediated by p53.