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Mitochondrial Liaisons of p53

Lorenzo Galluzzi,[1–3,*] Eugenia Morselli,[1–3,*] Oliver Kepp,[1–3] Ilio Vitale,[1–3] Marcello Pinti,[4] and Guido Kroemer[1,5–8]

Abstract

Mitochondria play a central role in cell survival and cell death. While producing the bulk of intracellular ATP, mitochondrial respiration represents the most prominent source of harmful reactive oxygen species. Mitochondria participate in many anabolic pathways, including cholesterol and nucleotide biosynthesis, yet also control multiple biochemical cascades that contribute to the programmed demise of cells. The tumor suppressor protein p53 is best known for its ability to orchestrate a transcriptional response to stress that can have multiple outcomes, including cell cycle arrest and cell death. p53-mediated tumor suppression, however, also involves transcription-independent mechanisms. Cytoplasmic p53 can physically interact with members of the BCL-2 protein family, thereby promoting mitochondrial membrane permeabilization. Moreover, extranuclear p53 can suppress autophagy, a major prosurvival mechanism that is activated in response to multiple stress conditions. Thirty years have passed since its discovery, and p53 has been ascribed with an ever-increasing number of functions. For instance, p53 has turned out to influence the cell's redox status, by transactivating either anti- or pro-oxidant factors, and to regulate the metabolic switch between glycolysis and aerobic respiration. In this review, we will analyze the mechanisms by which p53 affects the balance between the vital and lethal functions of mitochondria. *Antioxid. Redox Signal.* 15, 1691–1714.

Introduction

According to the endosymbiotic theory, mitochondria originated from separate proteobacteria (in particular Rickettsiales or close relatives) that were engulfed by other prokaryotes >2 billion years ago (75). This hypothesis is supported by several lines of evidence, including (but not limited to) (i) the double-membraned structure and the size of mitochondria; (ii) the persistence of mitochondrial DNA (mtDNA) and of a proficient machinery for protein synthesis; (iii) the closer resemblance of several mitochondrial proteins including specific enzymes and transport systems, as well as of mitochondrial ribosomes, to their prokaryotic (rather than eukaryotic) counterparts; (iv) the lipid composition of the mitochondrial inner and outer membranes (IM and OM, respectively); and (v) the parallelism between mitochondrial fission and the binary fission of bacteria (75).

In a hypothetical scenario, the precursors of modern mitochondria, protomitochondria, would have avoided expulsion and/or degradation by the host cell *via* a finely regulated strategy, which has been proposed as the precursor of one of the mechanisms by which mitochondria now regulate cell death (see below). In particular, it has been suggested that the ancestors of mitochondria were able to generate cytotoxic products but also their direct antagonists. Such cytotoxic molecules would have been characterized by an increased half-life as compared to that of their antidotal partners, or they would have been held under control only in the actual presence of protomitochondria, resulting in the addiction of host cells to the intrinsic prosurvival function of endosymbionts (62, 101, 103). Speculatively, certain parallels between mitochondrial fission (which occurs in multiple instances of mitochondrial apoptosis in mammalian cells) and bacterial sporulation (which represents a primordial response of prokaryotic organisms to stress) have also been put forward in support of the endosymbiotic theory (63).

Throughout coevolution with their host cells, protomitochondria have progressively lost a series of functions that were futile for intracellular life but required for autonomous survival outside of the host, thereby becoming obligate

[1]INSERM, U848, Villejuif, France.
[2]Institut Gustave Roussy, Villejuif, France.
[3]Université Paris Sud-XI, Villejuif, France.
[4]Dipartimento di Scienze Biomediche, Università degli studi di Modena e Reggio Emilia, Modena, Italy.
[5]Metabolomics Platform, Institut Gustave Roussy, Villejuif, France.
[6]Centre de Recherche des Cordeliers, Paris, France.
[7]Pôle de Biologie, Hôpital Européen Georges Pompidou, Paris, France.
[8]Université Paris Descartes, Paris, France.
*These two authors equally contributed to this article.

cytoplasmic symbionts (65). In a parallel process, host cells have gradually adapted to the continuative presence of the proto-mitochondrial endosymbionts, first taking advantage from them and eventually becoming dependent on them for the execution of ever more complex biochemical pathways (64). These processes have been paralleled by a bi-directional transfer of genetic material between the mitochondrial ancestors and their host cells (114). Nowadays, mitochondria are indispensable for the survival of higher eukaryotic cells, and, vice versa, mitochondria cannot survive outside the cytoplasm. Intracellular parasitism has evolved to mutually advantageous and obligate symbiosis, explaining why the fates (life or death) of mitochondria and of their host cells are intimately interwoven.

Vital functions of mitochondria

The importance of mitochondria for higher eukaryotes has been recognized >1 century ago. Originally dubbed bioplasts (6), these organelles were soon rebaptized because of their threadlike appearance in the course of spermatogenesis (mitos = thread, chondros = granule) (11). Pioneering attempts to isolate mitochondria were undertaken during the 1930s (54), approximately when Otto Warburg was recognizing the essentials of cancer cell metabolism (247, 248). Starting with the 1940s, the fundamental biochemical reactions underlying mitochondrial respiration were elucidated, culminating in Mitchell's chemiosmotic theory on the conservation of energy as an electrochemical gradient across the IM (54, 157).

The peculiar biochemical properties of mitochondria, which are intimately linked to their compartmentalized ultrastructure, provide an optimal microenvironment for a large number of bioenergetic and biosynthetic metabolic pathways. The most significant metabolic circuitry confined to mitochondria is aerobic respiration (also known as oxidative phosphorylation), consisting in a synchronized sequence of redox reactions that are catalyzed by the cooperative activity of five multisubunit enzymes embedded in the IM (*i.e.*, respiratory complexes I-IV and the F_1F_O-ATP synthase) and two soluble factors (*i.e.*, cytochrome *c*, CYTC; coenzyme Q_{10}), which function as electron shuttles within the mitochondrial intermembrane space (IMS). Collectively, these enzymes are also known as the electron transfer chain. Respiratory complexes actively extrude protons from the mitochondrial matrix, thereby generating an electrochemical gradient (intrinsically associated with the so-called mitochondrial transmembrane potential, $\Delta\psi_m$) that is dissipated by the F_1F_O-ATP synthase to produce the vast majority of intracellular ATP (157, 199) (Fig. 1). Averagely, an healthy eukaryotic cell contains around 2.000 mitochondria, which produce >90% of intracellular ATP (182, 241). Although these values may vary quite consistently depending on both cell-intrinsic variables (*e.g.*, cell type, cell cycle phase, and transformation) and cell-extrinsic parameters (*e.g.*, availability of nutrients, and oxygen tension), they provide a tangible estimation on the importance of mitochondria for the physiology of eukaryotic cells.

Another important metabolic pathway that is virtually confined to the mitochondrial matrix is the Krebs cycle, also known as tricarboxylic acid (TCA) cycle, citric acid cycle, or, more rarely, Szent-Györgyi-Krebs cycle (241). In aerobic conditions, pyruvate (the end-product of glycolysis) is rapidly taken up by mitochondria *via* a high-affinity transporter and is oxidized to acetyl-CoA and CO_2 by the pyruvate dehydrogenase complex. Acetyl-CoA is the actual fuel for the TCA cycle, through which it gets fully oxidized to CO_2, while three reduced nicotinamide adenine dinucleotide (NADH), one reduced flavine adenine dinucleotide ($FADH_2$), and one GTP (or ATP) molecules are generated (Fig. 1). The reducing equivalents of NADH and $FADH_2$ can be used by the electron transport chain to create further ATP as part of oxidative

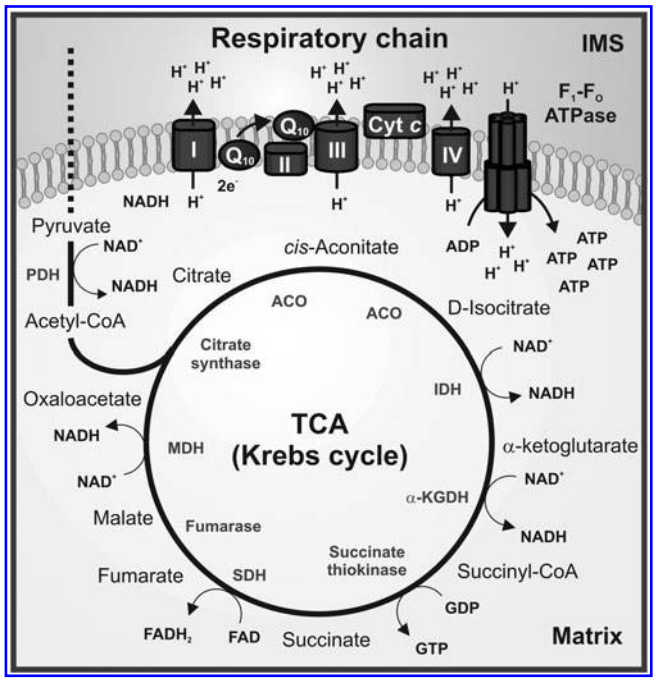

FIG. 1. Vital functions of mitochondria. One of the most prominent vital functions exerted by mitochondria is aerobic respiration (also known as oxidative phosphorylation), consisting in a synchronized sequence of redox reactions that are catalyzed by five multisubunit enzymes (*i.e.*, respiratory complexes I–IV and the F_1F_O-ATP synthase) that are embedded in the IM and two soluble factors (*i.e.*, CYTC; coenzyme Q10), which function as electron shuttles within the IMS. Respiratory complexes actively extrude protons from the mitochondrial matrix, thereby generating an electrochemical gradient that is dissipated by the F_1F_O-ATP synthase to generate ATP. The TCA cycle (also known as Krebs cycle) is another bioenergetic pathway that is virtually confined to the mitochondrial matrix. In normoxic conditions, the end-product of glycolysis (pyruvate) is taken up by mitochondria, promptly converted to acetyl-CoA and CO_2 by the PDH complex, and feeds into the TCA cycle. Through the TCA, acetyl-CoA is fully oxidized to CO_2, whereas three NADH, one $FADH_2$, and one GTP (or ATP) molecules are generated. Of note, the reducing equivalents provided by NADH and $FADH_2$ can be used by respiratory complexes to produce ATP as part of oxidative phosphorylation. Mitochondria provide an optimal biochemical microenvironment for (at least part of) several other biochemical cascades, including the urea cycle, gluconeogenesis, and ketogenesis (not shown). α-KGDH, α-ketoglutarate dehydrogenase; ACO, aconitase; CYTC, cytochrome *c*; $FADH_2$, reduced flavine adenine dinucleotide; IDH, isocitrate dehydrogenase; IM, mitochondrial inner membrane; IMS, mitochondrial intermembrane space; MDH, malate dehydrogenase; NADH, reduced nicotinamide adenine dinucleotide; PDH, pyruvate dehydrogenase; SDH, succinate dehydrogenase; TCA, tricarboxylic acid.

phosphorylation. Altogether, the breakdown of one molecule of glucose by aerobic glycolysis allows for the generation of 38 molecules of ATP. Only 2 of these ATP molecules are the net result of the cytosolic glucose → pyruvate conversion (anaerobic glycolysis). The other 36 derive (either by direct substrate-level phosphorylation of ADP or indirectly, *via* oxidative phosphorylation) from pyruvate decarboxylation (2 NADH = 6 ATP) and the TCA cycle (since one glucose molecule generates 2 pyruvate molecules, the global yield is 2 ATP, 6 NADH equivalent to 18 ATP, 2 $FADH_2$ equivalent to 4 ATP). Thus, mitochondrial respiration finalizes glucose oxidation by generating a greater amount of ATP than glycolysis. However, since the latter is completed in a few metabolic steps and hence is much faster than aerobic respiration (186), glycolysis may become preferable under some conditions that require either rapid energy release (*e.g.*, contraction of muscle cells) (170) or massive biosynthesis of intracellular structures in rapidly proliferating (including cancer) cells (9, 108). This also reflects the fact that, in rapidly dividing cells, there is a high demand for metabolic intermediates to feed anabolic reactions (*e.g.*, citrate and glycerol for the biosynthesis of lipids, and ribose sugars for the generation of nucleotides), some of which originate from the TCA cycle (178).

Additional metabolic pathways that proceed within mitochondria include heme biosynthesis, β-oxidation of fatty acids, steroidogenesis, the metabolism of some amino acids (aa), and the generation of Fe/S clusters (199). Further, mitochondria host the first steps of the urea cycle (also known as Krebs-Henseleit cycle, which mediates ammonium detoxification), as well as reactions belonging to gluconeogenesis and ketogenesis (153).

Lethal functions of mitochondria

Programmed cell death (PCD) can be mediated by several distinct (though sometimes partially overlapping) signal transduction pathways, which can be classified according to morphological and/or biochemical criteria (69, 104, 106). One of the most prominent PCD subroutines is apoptosis, which manifests with rounding-up of the cell, retraction of pseudopodes, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), usually no (or very slight) modifications of cytoplasmic organelles, plasma membrane blebbing (but persistence of its integrity until the final stages of the process), and engulfment of apoptotic bodies by local phagocytes (*in vivo*) (69, 104, 106). Biochemical features that have been used to define apoptosis include the exposure of the phospholipid phosphatidylserine on the outer leaflet of the plasma membrane and the massive activation of caspases (69, 104, 106), evolutionarily conserved serine proteases cleaving after an Asp residue (39) that also participate in many cell death-unrelated processes (66, 116). During the first phases of apoptosis, the observation of mitochondria by light microscopy reveals very little (if any) obvious morphological changes, in overt contrast with nuclei (which undergo impressive structural rearrangements). For this reason, mitochondria were initially thought not to participate in the regulation of PCD, or (at best) they were ascribed with a minor role within positive feedforward loops for the amplification of the apoptotic signal (3, 52). During the 1990s, it has progressively become accepted that mitochondrial membrane permeabilization (MMP) represents a critical checkpoint in the cascade of events leading to cell death *via* intrinsic apoptosis (105, 128, 267–269). Later, it has been demonstrated that MMP is also crucial for the execution of PCD through nonapoptotic cell death subroutines (68, 69, 165). Thus, MMP has been added to the most prominent biochemical manifestations of PCD.

Cells respond to a wide array of adverse conditions (including DNA damage, nutrient and/or growth factor deprivation, endoplasmic reticulum stress, and lysosomal damage) by igniting signal transduction pathways that have lethal consequences, but also by activating a number of prosurvival mechanisms by which they attempt to cope with stress. Most often, such prodeath and prosurvival signals converge to and are opposing each other at the level of mitochondrial membranes. When lethal stimuli prevail, mitochondrial membranes become irreversibly permeabilized, resulting in a series of catastrophic consequences, including (but not limited to) $\Delta\psi_m$ dissipation, which is paralleled by an abrupt arrest of mitochondrial ATP generation and of several other biosynthetic pathways, and the release into the cytosol of multiple proteins that are usually retained within the IMS, where they mediate vital functions (72, 105). These factors can be classified into three large categories: direct activators of caspases (*e.g.*, CYTC), indirect activators of caspases (*e.g.*, SMAC/DIABLO and OMI/HTRA2), and caspase-independent cell death executioners (*e.g.*, apoptosis-inducing factor [AIF] and endonuclease G). Once in the cytosol, IMS proteins ignite caspase-dependent and caspase-independent mechanisms that altogether seal the cell's fate (105) (Fig. 2).

Lethal MMP can be executed by two distinct, though partially overlapping, molecular mechanisms, which originate either at the OM or at the IM (105). On one hand, in response to stress, multidomain proapoptotic members of the BCL-2 protein family can assemble into large homo- or heteromeric channels that render the OM permeable to (at least some) proteins. This process is commonly known as mitochondrial outer membrane permeabilization (MOMP) and results in the cytosolic spillage of IMS proteins, including the soluble component of the respiratory chain CYTC, whose depletion (eventually) leads to mitochondrial uncoupling and $\Delta\psi_m$ loss (Fig. 2). Antiapoptotic members of the Bcl-2 protein family (*e.g.*, BCL-2 and BCL-X_L) also (but not only) exert prosurvival functions by sequestering their proapoptotic counterparts into inactive complexes (204). In this context, some BH3-only proteins (which are known as activators, *e.g.*, BID) mediate proapoptotic effects by physically interacting with (and hence activating) BAX and/or BAK, whereas others (known as derepressors, *e.g.*, BAD) act by displacing BAX and BAK from BCL-2/X_L-mediated inhibition, thereby unleashing their lethal potential (35, 251).

An alternative route to MMP originates at the IM, after the opening of a multiprotein structure that is built up at the OM-IM junctions and that is known as the permeability transition pore complex (PTPC). In physiological conditions, the PTPC exhibits a low-conductance conformation and likewise grants the exchange of small metabolites and ions between the cytosol and the mitochondrial matrix. However, in response to some proapoptotic stimuli, including reactive oxygen species (ROS) overgeneration and cytosolic Ca^{2+} overload, the PTPC assumes a high-conductance state that allows for the rapid and unregulated entry of solutes into the mitochondrial matrix driven by the $\Delta\psi_m$. Such an abrupt loss of the IM

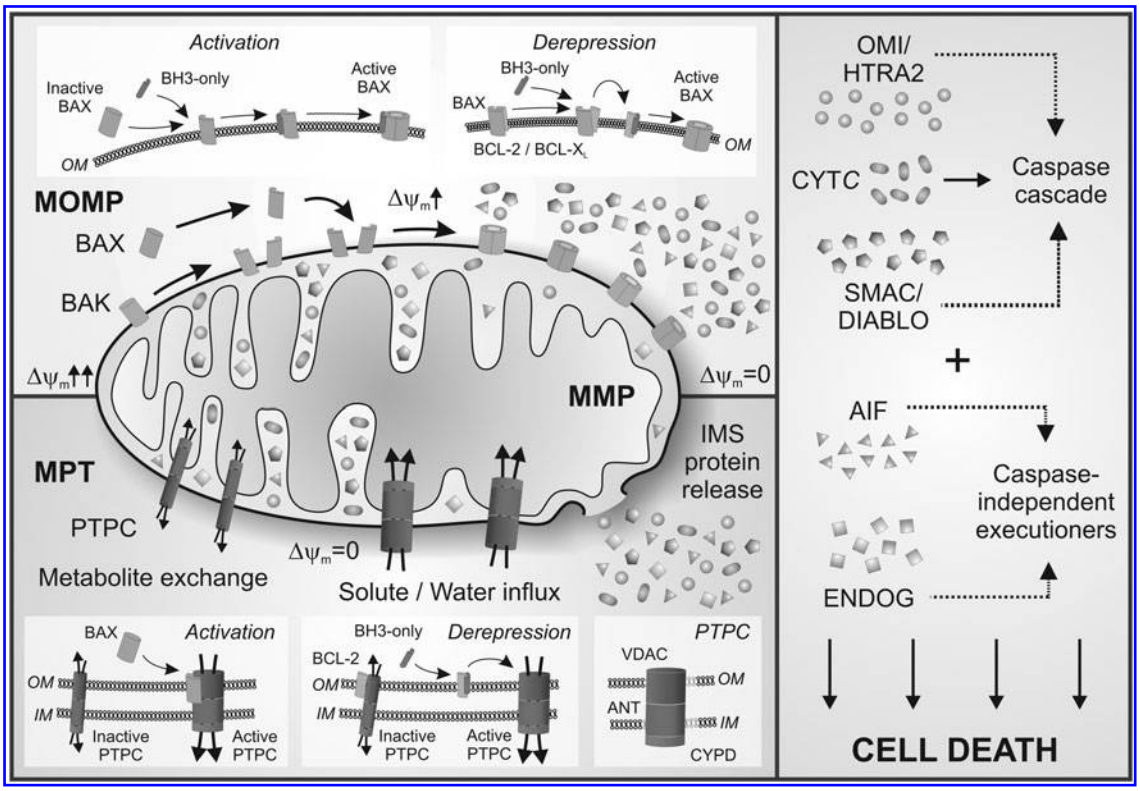

FIG. 2. Lethal functions of mitochondria. MMP is widely considered as a point-of-no-return in multiple signal transduction cascades that lead to cell death. MMP can derive from either of two distinct, though partially overlapping, molecular mechanisms. On one hand, protein-permeable channels generated by multidomain proapoptotic proteins from the BCL-2 family (*e.g.*, BAX and BAK) may ignite MMP at the OM, thereby promoting MOMP. Although MOMP allows for the early release into the cytosol of cytotoxic proteins that are normally retained within the IMS, it initially affects the $\Delta\psi_m$ to limited extents. Because of MOMP, however, the IMS becomes depleted for soluble components of the electron transfer chain such as CYTC, leading to respiratory uncoupling and (finally) $\Delta\psi_m$ loss. In this scenario, antiapoptotic members of the BCL-2 protein family (*e.g.*, BCL-2 and BCL-X_L) exert cytoprotective functions by sequestering their proapoptotic counterparts into inactive supramolecular complexes. As an alternative, MMP can originate at the IM, due to the opening of a supramolecular complex known as PTPC. In physiological conditions, the PTPC exhibits a low-conductance state and mediates the exchange of small metabolites between the cytosol and the mitochondrial matrix. The precise molecular composition of the PTPC remains unclear, though some consensus is growing on its backbone structure, comprising the VDAC (in the OM), ANT (in the IM), and CYPD (in the mitochondrial matrix). Multiple interactors modulate the activity of the PTPC, including both pro- and antiapoptotic members of the BCL-2 protein family. In response to specific cell death inducers, the PTPC assumes a high-conductance state allowing for the deregulated entry of small solutes and water into the mitochondrial matrix, a process that is known as MPT. MPT leads to immediate $\Delta\psi_m$ dissipation and to a progressive osmotic swelling of the mitochondrial matrix, which eventually results in OM breakdown and in the unselective release of IMS proteins into the cytosol. Irrespective of the initiating stimulus and transduction mechanism, MMP is paralleled by a bioenergetic/biosynthetic catastrophe and by the cytosolic translocation of direct and indirect caspase activators (*e.g.*, CYTC, SMAC/DIABLO, and OMI/HTRA2) as well as of caspase-independent cell death executioners (*e.g.*, AIF and ENDOG), which altogether seal the cell fate. BH3-only proteins have been proposed to modulate both MOMP and MPT by acting either as direct activators of proapoptotic BCL-2 family members (or of the PTPC) or by functioning as derepressors, thereby displacing BAX, BAK, activator BH3-only proteins, or PTPC components from BCL-2/BCL-X_L-mediated inhibition. AIF, apoptosis-inducing factor; ANT, adenine nucleotide translocase; CYPD, cyclophilin D; $\Delta\psi_m$, mitochondrial transmembrane potential; ENDOG, endonuclease G; MMP, mitochondrial membrane permeabilization; MOMP, mitochondrial outer membrane permeabilization; MPT, mitochondrial permeability transition; OM, mitochondrial outer membrane; PTPC, permeability transition pore complex; VDAC, voltage-dependent anion channel.

impermeability to solutes is known as mitochondrial permeability transition (MPT) and results in the immediate dissipation of the $\Delta\psi_m$ as well as in the osmotic swelling of the mitochondrial matrix. Because of its highly convoluted nature, the surface of the IM largely exceeds that of the OM, implying that MPT eventually results in the breakdown of the OM, in turn allowing for the unspecific spillage of IMS proteins into the cytosol (105) (Fig. 2). The PTPC is a highly dynamic entity (240), and its precise composition has been subject of an intense debate (21). Nevertheless, some consensus has emerged concerning the proteins that would constitute the PTPC scaffold structure, which include the voltage-dependent anion channel, in the OM, the adenine nucleotide translocase in the IM, and cyclophilin D in the mitochondrial matrix. Several proteins (as well as endogenous small molecules, including ATP, ADP, NADH, and nitric oxide) have been shown to interact with components of the PTPC, thereby modulating either its vital or lethal functions (105, 240, 275).

Table 1. Links Between p53 and the Vital Functions of Mitochondria

Protein	*Link(s) to p53*	*Function*	*Ref.*
AIF	p53 target gene (activator RE)	IMS protein required for complex I assembly/stability	(66, 194, 222, 236)
ALDH4	p53 target gene (activator RE)	Antioxidant enzyme involved in proline degradation	(260)
AMID	p53 target gene (activator RE)	Redox-active mitochondrial flavoprotein	(143, 255)
AMPK β1	p53 target genes (activator RE)	Positive regulators of autophagy (mitophagy) in response to decreased energy levels	(58, 59)
AMPK β2	p53-phosphorylating kinase		
BAD	p53 target gene (activator RE)	BH3-only protein involved in mitophagy	(130, 134)
BAX	p53 target gene (activator RE)	Proapoptotic BCL-2-like protein involved in mitophagy	(130, 258)
BCL-2	p53 target gene (inhibitor RE) p53-interacting protein	Antiapoptotic member of the BCL-2 protein family that also exerts antiautophagic functions	(130, 158)
BCL-X_L	p53 target gene (inhibitor RE) p53-interacting protein	Antiapoptotic member of the BCL-2 protein family that also exerts antiautophagic functions	(130, 224)
BNIP3	p53 target gene (activator RE)	BH3-only protein involved in mitophagy	(130, 271)
CAT	p53 target gene (activator RE)	Antioxidant enzyme	(173)
CKB	p53 target genes (activator RE)	Buffer ATP levels at the expenses of phosphocreatine	(7, 249)
CKM			
COX1	p53 target gene (activator RE)	Main subunit of the respiratory chain complex IV	(176)
CPEB	Enhancer of *TP53* mRNA translation	Widely affects the p53 system by modulating *TP53* mRNA polyadenylation-induced translation	(26, 77)
DAPK1	p53 target gene (activator RE)	Stimulator of autophagy (mitophagy)	(144, 264, 265)
DRAM	p53 target gene (activator RE)	Proautophagic and proapoptotic lysosomal protein	(43, 44)
GLUT1	p53 target gene (inhibitor RE)	Plasma membrane glucose transporters	(213)
GLUT4			
GLUT3	p53-responsive gene (indirect)	Plasma membrane glucose transporter	(98)
GPX1	p53 target gene (activator RE)	Antioxidant enzyme	(86, 225)
HK2	p53 target gene (activator RE)	Catalyzes the rate-limiting step of glycolysis Interacts with the PTPC, thereby inhibiting apoptosis	(67, 147, 148, 183)
MCL-1	p53 target gene (inhibitor RE)	Antiapoptotic member of the BCL-2 protein family that may exert indirect antiautophagic functions	(187)
MnSOD	p53 target gene (activator RE)	Antioxidant enzyme	(86)
PGM	p53 target gene (inhibitor RE)	Glycolytic enzyme, converts 3PG into 2PG	(100, 208)
p53R2	p53 target gene (activator RE)	Contributes to maintenance/biogenesis of mitochondria	(15)
PTGES (PIG12)	p53 target gene (activator RE)	Prostaglandin-isomerizing and antioxidant enzyme	(92, 191)
PUMA	p53 target gene (activator RE)	BH3-only protein involved in mitophagy	(130, 258)
SESN1 (PA26)	p53 target genes (activator RE)	Components of the peroxiredoxin regeneration system	(22, 23, 136)
SESN2 (HI95)		Positive regulators of autophagy (mitophagy)	
SCO2	p53 target genes (activator RE)	Key regulator of mitochondrial respiration	(150)
TFAM	p53-interacting protein	Cooperates with p53 for mtDNA maintenance	(253, 261)
TIGAR	p53 target gene (activator RE)	Inhibitor of glycolysis with antioxidant properties	(12)
TP53INP1	p53 target gene (activator RE)	Antioxidant protein	(30)
TSC2	p53 target gene (activator RE)	Proautophagic signal transducer	(58, 89)

2PG, 2-phosphoglycerate; 3PG, 3-phosphoglycerate; AIF, apoptosis-inducing factor; ALDH4, aldehyde dehydrogenase 4; AMID, AIF-homologous mitochondrion-associated inducer of death; AMPK, AMP-modulated protein kinase; CAT, catalase; CKB, creatine kinase (brain); CKM, creatine kinase (muscle); COX, CYTC oxidase; CPEB, cytoplasmic polyadenylation element-binding protein; CYTC, cytochrome *c*; DAPK1, death-associated protein kinase 1; DRAM, damage-regulated autophagy modulator; GLUT, glucose transporter; GPX, glutathione peroxidase; HK2, hexokinase II; IMS, mitochondrial intermembrane space; MnSOD, manganese superoxide dismutase; PGM, phosphoglycerate mutase; PIG, p53-induced gene; PTGES, prostaglandin E synthase; PTPC, permeability transition pore complex; PUMA, p53-upregulated modulator of apoptosis; RE, responsive element; SCO2, synthesis of COX2; SESN, sestrin; SOD, superoxide dismutase; TFAM, mitochondrial transcription factor A; TIGAR, TP53-induced glycolysis and apoptosis regulator; TP53INP1, tumor protein p53-inducible nuclear protein 1; TSC, tuberous sclerosis complex.

Importantly, PTPC interactors include both anti- and proapoptotic BCL-2-like proteins, such as BAX (10, 20, 145, 214, 215, 235), BAK (214, 235), BID (266), BCL-2 (10, 20, 146, 214, 235), and BCL-X_L (215, 235), suggesting some degree of crosstalk between MOMP and MPT.

The p53 system

The transcription factor p53 presumably is the most extensively studied protein ever. Its discovery dates back to 1979, representing the culmination of two methodologically distinct (namely, one virological and one serological) approaches. Thus, p53 was first identified as a polypeptide of ~53–55 kDa that coimmunoprecipitated with the large-T antigen in SV40-transformed cells (32, 102, 113, 126, 152). The same polypeptide was then found to be overexpressed in a wide variety of murine SV40-transformed cells as well as in uninfected embryonic carcinoma cells (126), suggesting that it would be encoded by the cellular genome and upregulated by SV40 infection or oncogenic transformation. Practically at the same time, antibodies directed against p53 were detected in serum samples from mice xenografted with several tumor cell

Table 2. Links Between p53 and the Lethal Functions of Mitochondria

Protein	*Link(s) to p53*	*Function*	*Ref.*
AIF	p53 target gene (activator RE)	Caspase-independent executioner of intrinsic apoptosis	(105, 222)
AMID	p53 target gene (activator RE)	AIF homolog mediating caspase-independent cell death	(254, 255)
APAF1	p53 target gene (activator RE)	Postmitochondrial mediator of intrinsic apoptosis	(105, 162, 202)
BAD	p53 target gene (activator RE) p53-interacting protein	BH3-only protein of the derepressor type	(35, 96, 251)
BAK	p53 target gene (activator RE) p53-interacting protein	Proapoptotic member of the BCL-2 protein family	(105, 120, 184, 188, 190)
BAX	p53 target gene (activator RE) p53-interacting protein	Proapoptotic member of the BCL-2 protein family	(37, 105, 158, 184)
BCL-2	p53 target gene (inhibitor RE) p53-interacting protein	Antiapoptotic member of the BCL-2 protein family	(105, 158, 161)
BCL-X_L	p53 target gene (inhibitor RE) p53-interacting protein	Antiapoptotic member of the BCL-2 protein family	(105, 161, 224)
BID	p53 target gene (activator RE) p53-interacting protein	BH3-only protein of the activator type	(35, 211, 218, 251)
BIRC5 (Survivin)	p53 target gene (inhibitor RE)	Caspase-inhibitor of the IAP family	(5, 85)
BOK	p53 target gene (activator RE)	Proapoptotic member of the BCL-2 protein family	(105, 256)
CASP-3, −6 and −7	p53-cleaving enzymes	Postmitochondrial executioner caspases	(105, 212)
CASP-6	p53 target gene (activator RE) p53-cleaving enzyme	Postmitochondrial executioner caspase	(105, 133, 212)
CASP-8	p53-cleaving enzyme	Premitochondrial initiator caspase (*via* BID)	(105, 212)
DAPK1	p53 target gene (activator RE)	Stimulates apoptotic membrane blebbing and a feedforward loop for the activation of p53	(82, 144)
FDXR	p53 target gene (activator RE)	Pro-oxidant enzyme	(88, 127)
HAUSP	p53-deubiquitinating enzyme	Mitochondrial deubiquitinating enzyme, stabilizes the mitochondrial pool of p53	(124, 139)
MCL-1	p53 target gene (inhibitor RE)	Antiapoptotic member of the BCL-2 protein family	(105, 187)
MnSOD	p53 target gene (inhibitor RE) p53-interacting protein	Antioxidant enzyme	(51, 273)
MSL2	p53-ubiquitinating enzyme	Modulates p53 localization (but not its stability)	(110)
NOXA (PMAIP1)	p53 target gene (activator RE)	BH3-only protein of the derepressor type	(35, 174, 251, 256)
NRF2	p53 target gene (inhibitor RE)	Antioxidant transcriptional factor	(56)
OSGIN1 (OKL38, BDGI)	p53 target gene (activator RE)	Localizes at mitochondria and stimulates CYTC release	(246, 257)
p53AIP1	p53 target gene (activator RE)	Localizes at mitochondria and mediates $\Delta\psi_m$ loss	(151, 175)
$p66^{SHC}$	p53 target gene (activator RE)	Adaptor protein involved in the regulation of mitochondrial ROS production and lifespan	(155, 181, 234)
PRODH (PIG6)	p53 target gene (activator RE)	Enzyme with proline oxidase activity, mediates the p53-induced proapoptotic activation of calcineurin	(191, 201)
PUMA	p53 target gene (activator RE)	BH3-only protein of the activator type	(35, 168, 251)
SCO2	p53 target gene (activator RE)	Indirectly favors ROS overgeneration	(26, 150, 245)
TP53I3 (PIG3)	p53 target gene (activator RE)	Quinone oxidoreductase involved in the early cellular response to DNA damage	(61, 119, 191, 193)
VDAC	p53-interacting protein	Backbone component of the PTPC	(105, 252)

APAF1, apoptotic peptidase activating factor 1; BDGI, bone marrow stromal cell-derived growth inhibitor; BIRC5, baculoviral IAP repeat-containing 5; CASP, caspase; $\Delta\psi_m$, mitochondrial transmembrane potential; FDXR, ferredoxin reductase; HAUSP, herpesvirus-associated ubiquitin-specific protease; IAP, inhibitor of apoptosis protein; NRF2, nuclear factor-E2-related factor 2; OSGIN1, oxidative stress-induced growth inhibitor 1; p53AIP1, p53-regulated apoptosis-inducing protein 1; PIG, p53-induced gene; PRODH, proline dehydrogenase (oxidase) 1; ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.

lines of distinct origin (45, 102, 152, 206), and a few years later similar circulating antibodies were identified in breast cancer patients (41) and in children with a wide variety of cancers (31).

The human *TP53* gene is located on the short arm of chromosome 17 (17p13.1) and codes for an mRNA of 11 kb that is translated (starting from exon 2) into a polypeptide of 393 aa with a predicted molecular weight of 43.7 kDa (90, 99, 149). This value is significantly lower than the molecular weight exhibited by p53 upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis (from which the name p53 originated), most likely as a result of the high number of proline residues that slow down the electrophoretic migration of the protein and hence make it appear heavier than it actually is (274). Alternative splicing of the human *TP53* gene leads to the synthesis of at least eight distinct p53 isoforms, whose tissue specificity, functions, and mutual interactions remain largely unknown (16, 40, 197, 203). The p53 protein contains five distinct functional domains: (i) an N-terminal acidic transactivation domain (aa 1–42), where also the binding site for MDM2 (the most important negative regulator of p53, see below) is located; (ii) a proline-rich region (aa 40–92), which is conserved in p53 from several species and also contains a second transactivation domain; (iii) a central DNA-binding domain (DBD, aa 101–306), which is the target of >90% of p53 mutations found in human tumors; (iv) an oligomerization domain (aa 307–355) consisting of a β-strand followed by an α-helix (which is necessary for dimerization); and (v) a C-terminal domain (aa 356–393) that contains a nonspecific DBD (which recognizes damaged DNA) and that is involved in the negative regulation of the central DBD (80). Two nuclear export signals are located at aa 11–27 (transactivation domain) and at aa 340–351 (oligomerization domain), whereas three nuclear localization signals have been identified at aa 316–324 (oligomerization domain), aa 370–376, and aa 380–386 (both in the C-terminal domain) (125, 223).

In physiological conditions, p53 is kept under control by MDM2, an E3 ubiquitin ligase that is overexpressed by genetic and/or epigenetic mechanisms in multiple tumors (91) (Fig. 3). The intracellular levels of MDM2 are critical in determining p53 fate. Indeed, whereas low amounts of MDM2 stimulate (poly)-monoubiquitination and nuclear export of p53, high levels promote its polyubiquitination and degradation (123). In turn, *MDM2* is regulated by p53 *via* a transcriptional feedback loop [*i.e.*, p53 transactivates *MDM2*, thereby self-restraining its own activity (81)], as well as by another oncosuppressor protein, ARF, which acts by sequestering MDM2 in the nucleolus (therefore preventing the MDM2/p53 interaction) (91). Additional MDM2-like proteins have been described that regulate p53 functions, in particular MDMX (also known as MDM4) (216). Intriguingly, although MDMX shares with MDM2 the ability to bind p53 and also proficiently represses p53 transactivation, MDMX can stimulate neither the nuclear export of p53 nor its degradation, and actually appears to protect p53 from MDM2-mediated suppression (93). Negative regulation of p53 is crucial for organismal survival, as illustrated by the fact that *mdm2*$^{-/-}$ mice die early during embryonic development as a direct consequence of the failure to restrain p53-mediated apoptosis (142).

In physiological conditions, the half-life of p53 ranges from 6 to 20 min, an observation that has been (mis)interpreted for a long time as if p53 would be entirely dormant in unstressed cells (200). Recent studies, however, indicate that some activities of the p53 system contribute to the maintenance of

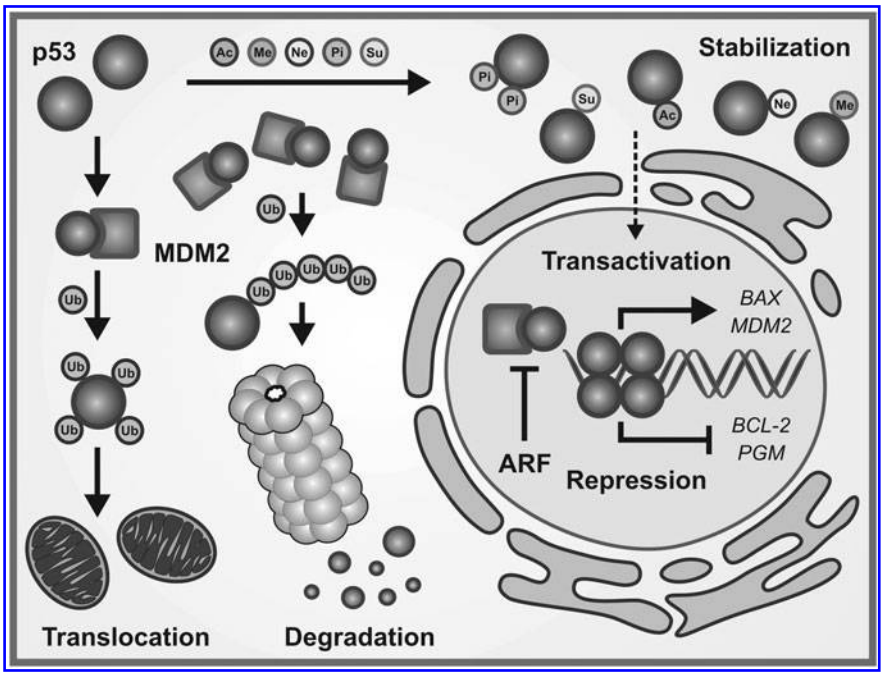

FIG. 3. The p53 system. In physiological conditions, the E3 ligase MDM2 negatively regulates p53 by polyubiquitination, which targets p53 to degradation by the proteasome. In response to several types of stress (*e.g.*, DNA damage), the p53 protein accumulates upon a number of post-translational modifications (including phosphorylation, methylation, acetylation, neddylation, and sumoylation) that reduce its affinity for MDM2. Alternatively, p53 is stabilized by MDM2-repressing mechanisms, such as that mediated by ARF in response to oncogenic stress. Of note, low levels of MDM2 promote p53 (poly)-monoubiquitination, which results in nuclear export and mitochondrial targeting. Deubiquitinated p53 rapidly oligomerizes (into dimers of dimers) and can be subjected to further post-translational modifications, which either increase its stability or stimulate site-specific DNA binding. In its tetrameric form, p53 binds to responsive elements on DNA to regulate (either repress or transactivate, depending on multiple parameters) gene transcription. Among p53 responsive genes whose promoter contains a p53 RE of the activator type is *MDM2* itself, mediating a negative feedback loop by which p53 self-restrains its own activity. Please consult the main text for further details. Ac, acetyl; Me, methyl; Ne, NEDD8; PGM, phosphoglycerate mutase; Pi, inorganic phosphate; Su, SUMO; Ub, ubiquitin.

intracellular homeostasis and regulate metabolism even in the absence of acute stress (178, 245), thereby exerting prosurvival functions (115) and regulating a number of physiological and pathological processes, including (but not limited to) aging, development, stem cell function, endurance, fecundity, and sun tanning (243, 245). Moreover, baseline activation of p53 has turned out to be critical for the management of weak insults that continuously arise under apparently normal conditions of growth and development, representing another facet of the oncosuppressive functions of p53 (see below) (243).

Although new roles for the p53 pathway are continuatively being uncovered, the primordial function of p53 is that of a stress-responsive transcription factor (60, 180). For many years, the precise relationship between the p53 system and cellular transformation has remained unclear, and a number of high-level scientific publications even pointed to *TP53* as a *bona fide* oncogene (53, 95, 112). Subsequently, it has become evident that increased levels of p53 were not a cause, but rather a consequence, of cellular transformation (19, 46), paving the way for the modern conception of p53 as an oncosuppressor protein. A huge number of studies have corroborated this notion through biochemical and epidemiological data, demonstrating that (i) stress-induced p53 exerts tumor suppression by transactivating proapoptotic and/or cell cycle-arresting genes (94, 154, 200, 242) and through transcription-independent mechanisms (161, 238), and that (ii) the p53 system is inactivated by genetic and/or epigenetic mechanisms in a high proportion of human cancers (70, 220, 221).

Thus, in response to a wide variety of stress stimuli (*e.g.*, DNA damage, oncogene activation, nutrient deprivation, hypoxia, and many others), the p53 protein can undergo multiple kinds of reversible post-translational modification, which are mediated by distinct upstream signal transduction mechanisms, yet all reduce the affinity of p53 for MDM2 and hence favor its stabilization (109, 200) (Fig. 3). These post-translational modifications include phosphorylation (which is highly prevalent for the N-terminal transactivation domain, containing the most famous Ser15 and Ser46 activation residues), methylation (which specifically targets the oligomerization domain of p53), acetylation, neddylation, and sumoylation (all of which may affect residues within either the oligomerization or the C-terminal domain) (109, 117). Alternatively, p53 can accumulate upon the activation of MDM2-repressing pathways, such as that mediated by ARF in response to oncogenic stress (see above) (91). Accumulating p53 rapidly assembles into tetramers (namely, dimers of dimers) and can be subjected to additional post-translational modifications, which further increase its stability or stimulate site-specific DNA binding (109, 200). Notably, p53 deacetylation by the histone deacetylase 2 has been shown to inhibit its DNA binding activity (79). With regard to this, it has been proposed (but not formally demonstrated) that the nature of the stress signal would be critical in determining the profile of p53 post-translational modifications, and hence would influence the precise transcriptional program that is activated by p53 (109, 179, 200).

Tetrameric p53 binds to p53 responsive elements (REs) to regulate the transcription of neighboring genes (Fig. 3). The transcriptional control operated by p53 is highly variable, ranging from a several hundred-fold transactivation (most often mediated by the local recruitment of general transcription proteins including TATA-binding protein-associated factors) to repression (which can be achieved through either direct or indirect mechanisms). A detailed analysis of these aspects of the p53 system (including the p53 consensus sequence and the factors that interact with DNA-bound p53 to regulate gene expression) goes largely beyond the scope of this article [for a recent and comprehensive review on these topics, please see ref. (200)]. Depending on a number of variables (*e.g.*, the profile of post-translational modifications imposed on the p53 protein, the activation status of other stress-responsive signal transduction pathways), p53 regulates the transcription of distinct sets of genes that can lead to highly diverse functional outcomes (200). Among these, the most common responses include a reversible cell cycle arrest (which is permissive for damage repair and cell survival), senescence and apoptotic cell death (both of which are terminal for the cell). Further, p53-mediated transactivation of specific target genes has been associated with the regulation of DNA repair (163, 217, 226, 227); positive and negative feedback loops in the p53 pathway (81); autophagy and autophagy-related signal transduction cascades (58, 59, 135); bioenergetic metabolism (12, 150); the cytoskeleton and the endosomal compartment (263); protein translation (2, 38, 195, 259); chaperone functions mediated by heat-shock proteins (4, 272); and the redox balance of the cell (48, 127, 209, 260).

In the following sections, we will discuss direct and indirect liaisons that bridge the p53 system to the vital and lethal functions of mitochondria.

Regulation of Energy Metabolism by p53

In normoxic conditions, eukaryotic cells generate the majority of ATP through mitochondrial respiration, whereas anaerobic glycolysis efficiently operates in a restricted number of settings (in particular when high amounts of ATP are rapidly demanded, see above) (182, 186, 241). The mutual regulation between aerobic respiration and anaerobic glycolysis is complex and involves multiple mechanisms, including substrate availability and product inhibition on several reactions from glycolysis and the TCA cycle, upregulation by Ca^{2+}, and phosphorylation-mediated allosteric (in)activation (241). This modulation is entirely subverted in tumor cells, which most often (if not always) exhibit an increased flow through glycolysis in spite of high oxygen tension (aerobic glycolysis), leading to enhanced lactate generation (18). This phenomenon is commonly known as the Warburg effect, in honor of the German physiologist and Nobel laureate who first described it (247, 248). The Warburg effect is sufficiently diffuse among distinct tumor types to be exploited for clinical imaging by means of a glucose derivative coupled to positron emission tomography (138). Still, as metabolic alterations were considered as a mere side-product of other tumorigenic events, their role in oncogenesis has been disregarded for many years. Recently, the importance of metabolic reprogramming in tumor cell biology has been fully re-evaluated, and metabolic alterations have been added to the established hallmarks of cancer (78, 108, 165). It is therefore no surprise that p53 plays a prominent role in the regulation of bioenergetic metabolism.

Inhibition of p53 reportedly leads to deficient mitochondrial biogenesis (87), decreased oxygen consumption (150),

and stimulated glycolysis, manifesting with increased lactate generation. Overall ATP levels do not change in the absence of the *TP53* gene (150, 228). However, $p53^{+/+}$ cells have been shown to produce ATP from glycolysis *versus* mitochondrial respiration in a proportion of 1:3, whereas their $p53^{-/-}$ counterparts do so at a ratio of 3:1 (150). The Warburg effect provides cancer cells with consistent advantages during oncogenesis, including the possibility to mobilize energy stores in a rather rapid fashion (which is required to sustain the massive biosynthesis of intracellular structures in highly proliferating cells) and a limited sensitivity to varying oxygen tension (as it is often experienced within the near-to-anoxic core of solid tumors) (9, 108).

Thus, p53 also exerts oncosuppressive functions by counteracting the Warburg effect. Several p53-responsive genes have been identified that (directly or indirectly) contribute to this tumor suppressive facet of p53 (13, 178, 243) (Fig. 4). Thus, p53 downregulates glycolysis by multiple mechanisms: (i) by directly inhibiting expression of the glucose transporter (GLUT)1 and GLUT4 (213); (ii) by reducing expression of GLUT3 *via* an indirect mechanism that reportedly involves a p53-dependent inhibition of the transcription factor NF-κB (98); (iii) by decreasing the levels of phosphoglycerate mutase (PGM) through post-translational modifications (100); and (iv) by transactivating TP53-induced glycolysis and apoptosis regulator (TIGAR) (12).

While reduced availability of intracellular glucose and decreased PGM enzymatic activity have obvious glycolysis-inhibiting effects, TIGAR suppresses the glycolytic flow *via* a more complex metabolic circuitry. TIGAR is homologous to the bisphosphatase domain of 6-phosphofructo-2-kinase, an enzyme that reversibly converts fructose-2,6-bisphosphate (F2,6BP) to fructose-6-phosphate (12). F2,6BP is at the same time a strong inhibitor of fructose-1,6-bisphosphatase (a rate-limiting enzyme in gluconeogenesis) and a potent allosteric activator of the glycolytic enzyme 6-phosphofructo-1-kinase (177). As in most instances TIGAR lowers F2,6BP levels, p53-mediated overexpression of TIGAR results in the block of glycolysis at the fructose-6-phosphate stage and in the redirection of glucose catabolism toward the oxidative branch of the pentose phosphate pathway (PPP) (12). Interestingly, the gene encoding glucose-6-phosphate dehydrogenase (G6PD), which catalyzes a rate-limiting step in the PPP (231), is also transactivated by p53 (131) (Fig. 4). Inhibition of glycolysis and stimulation of PPP by p53 has multiple outcomes including increased synthesis of nucleotides (which are required for DNA repair) and accumulation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which boosts antioxidant defenses (see below).

Apparently in contrast with these observations, p53 has also been shown to upregulate glycolytic enzymes, thereby *de facto* stimulating glycolysis (at least in some experimental settings) (178) (Fig. 4). Thus, although *PGM* is negatively regulated by p53 in fibroblasts (100), its p53-dependent transactivation has been shown to contribute to myoblastic differentiation (208). Similarly, p53 can transactivate the gene encoding hexokinase II (147), which catalyzes the rate-limiting step of glycolysis (*i.e.*, the conversion of glucose into G6P) while interacting with the PTPC, favoring the Warburg effect and exerting consistent antiapoptotic effects (67, 148, 183). p53 also induces the transcription of the genes coding for the muscular and brain isoforms of creatine kinase (*CKM* and *CKB*, respectively), which exert prosurvival functions by maintaining ATP levels at the expenses of phosphocreatine (7, 249). These apparently counterintuitive prosurvival activities of the p53 system presumably reflect a high degree of complexity that has not yet been entirely disentangled (244). Context- and tissue-dependent variations are likely to account for part of these phenomena. Moreover, accumulating evidence suggests that p53 responds to the low levels of constitutive stress (encountered by cells during everyday life) by exerting prosurvival effects, which can be viewed as another facet of its oncosuppressive functions (243, 245).

Still, the p53 system most often hinders glycolysis, which is paralleled by the ability of p53 to maintain mitochondrial homeostasis (15, 111, 118) and to drive mitochondrial respiration (150) (Fig. 4). These prorespiratory functions of p53 most likely derive from the transactivation of more than one single target gene, including (but are not limited to) genes encoding AIF (222), which can act as a caspase-independent cell death executioner (see above) (29, 159), but also is crucial for the assembly/stabilization of the respiratory chain (66, 194, 236); AIF-homologous mitochondrion-associated inducer of death (255), a mitochondrial flavoprotein that catalyzes the reduction of CYTC and other electron acceptors (143); CYTC oxidase (COX) subunit I (COX1) (176), the main subunit of the respiratory chain complex IV (241); synthesis of COX2 (SCO2), a key regulator of the COX complex (150); and p53R2, which has been shown to contribute to the maintenance of mtDNA copy number and to mitochondrial biogenesis (15) (Table 1).

The prominent prorespiratory activity of baseline levels of p53 has been underscored by genetic manipulations aimed at reducing expression of cytoplasmic polyadenylation element-binding protein (CPEB) (26). CPEB is a sequence-specific RNA-binding protein that stimulates polyadenylation-induced translation of multiple (including *TP53*) mRNAs (77). In murine and human cells subjected to RNA interference-mediated depletion of CPEB, the *TP53* mRNA exhibits an abnormally short poly(A) tail and a reduced translational efficiency, resulting in a ~50% decrease in p53 protein levels (26). Intriguingly, this is paralleled by reduced mitochondrial respiration, lowered ROS production, normal ATP levels, and enhanced rates of glycolysis, an ensemble of conditions that closely mimics the metabolic alterations usually displayed by malignant cells (26). The phenotype of cells that lack CPEB is recapitulated by the RNA interference-mediated downregulation of p53 (26), as well as by the disruption of *SCO2* (150).

Thus, several p53 activities, including the regulation of SCO2 and NF-κB, appear to function in the absence of acute stressors, suggesting that baseline levels of p53 constitutively operate to assure the maintenance of the aerobic functions of mitochondria in normal healthy cells.

Anti- and Pro-Oxidant Effects of p53

Although the main tumor suppressive functions of p53 (*i.e.*, senescence and cell death) are intimately connected to the induction of oxidative stress (132), recent evidence clearly indicates that baseline levels of p53 exert prominent antioxidant effects, thereby protecting cells from ROS, stimulating repair mechanisms and hence favoring survival (178, 244, 245).

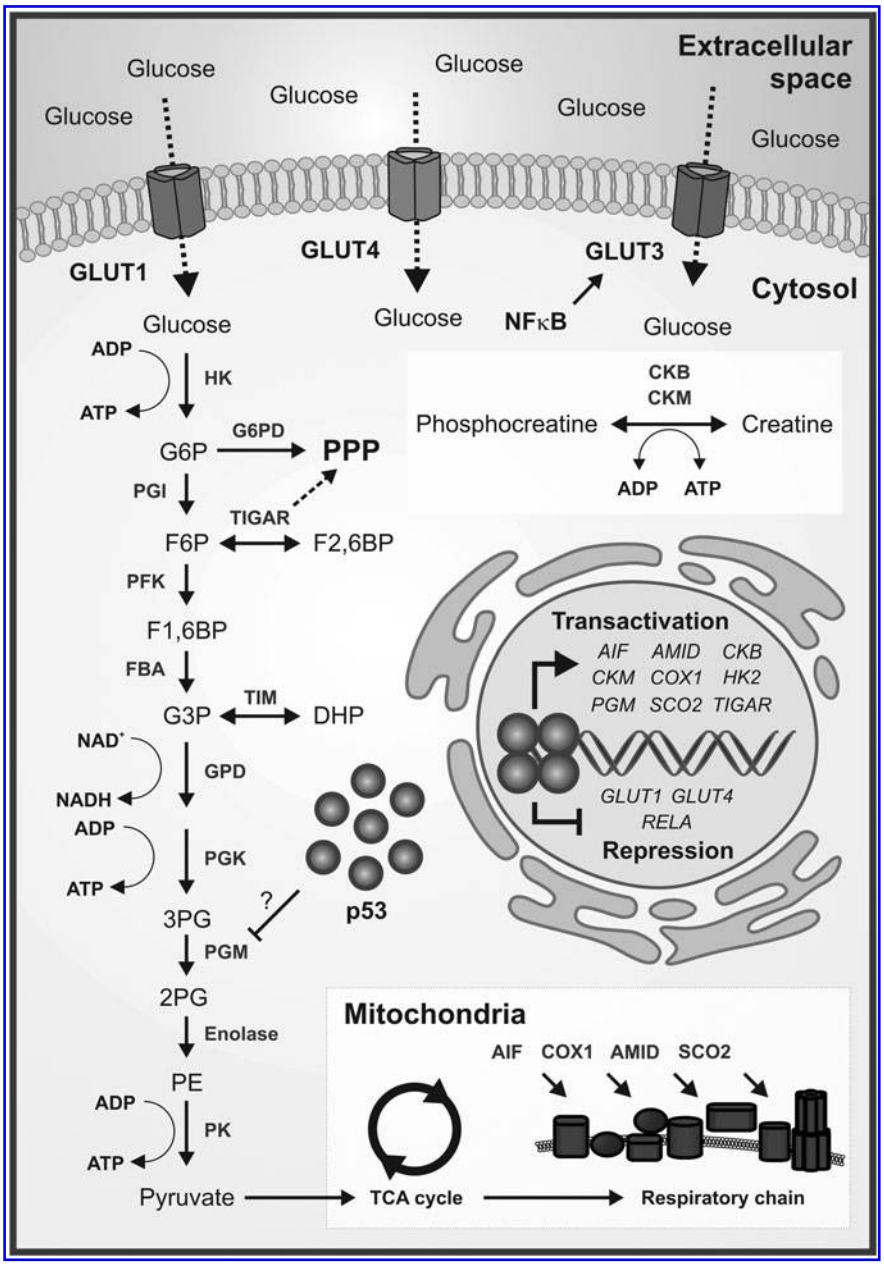

FIG. 4. Regulation of energy metabolism by p53. By controlling the transcription of multiple target genes, p53 limits the flux through glycolysis and stimulates oxidative phosphorylation, thereby opposing the Warburg effect, the most common metabolic alteration of cancer cells that consists in high glycolytic rates in spite of normal oxygen tension (aerobic glycolysis). However, some functions of p53 have also been shown to favor glycolysis, at least in selected circumstances. Please consult the main text for further details. 2PG, 2-phosphoglycerate; 3PG, 3-phosphoglycerate; AMID, AIF-homologous mitochondrion-associated inducer of death; COX, CYTC oxidase; CKB, creatine kinase (brain); CKM, creatine kinase (muscle); DHP, dihydroacetone phosphate; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose-6-phosphate; FBA, fructose bisphosphate aldolase; G3P, glyceraldehyde-3-phosphate; G6P, glucose-6-phosphate; G6PD, G6P dehydrogenase; GPD, glyceraldehyde phosphate dehydrogenase; GLUT, glucose transporter; HK, hexokinase; PE, phosphoenolpyruvate; PFK, 6-phosphofructo-2-kinase; PGI, phosphoglucose isomerase; PGK, phosphoglycerate kinase; PK, pyruvate kinase; PPP, pentose phosphate pathway; RELA, *v-rel* reticuloendotheliosis viral oncogene homolog A (NF-κB p65 subunit); SCO2, synthesis of COX2; TIGAR, TP53-induced glycolysis and apoptosis regulator; TIM, triosephosphate isomerase.

Collectively, the pro-oxidant functions mediated by p53 in response to acute stress may result from multiple mechanisms (Fig. 5). First, p53 can transactivate genes that encode *bona fide* pro-oxidant enzymes. These include tumor protein p53 inducible protein 3 (TP53I3, also known as p53-induced gene 3, PIG3) (61), a quinone oxidoreductase that has recently been implicated in the early cellular response to DNA damage (119, 193); proline dehydrogenase (oxidase) 1 (also known as PIG6), an enzyme that has been shown to be required for the p53-mediated proapoptotic activation of the Ca^{2+}/calmodulin-dependent phosphatase calcineurin (201); and ferredoxin reductase (127), a mitochondrial protein that contributes to p53-mediated apoptosis by promoting oxidative stress (it transfers electrons from NADPH to cytochrome P450 *via* ferredoxin) and whose expression levels may predict the response to 5-fluorouracil of metastatic colorectal cancer patients (88). Second, p53 can upregulate proteins that indirectly exert pro-oxidant functions, including the BCL-2 family members BAX and p53-upregulated modulator of apoptosis (PUMA), which cooperatively trigger apoptosis associated with ROS overgeneration (129); $p66^{SHC}$ (234), an adaptor protein intimately involved in the regulation of (mitochondrial) ROS production (181) and of mammalian lifespan (155); and SCO2, which indirectly facilitate the generation of ROS by promoting aerobic respiration (150). Third, p53 has been suggested to repress the transcription of antioxidant genes such as superoxide dismutase 2 (*SOD2*), one of the major cellular defenses against oxidative stress (51). Fourth, p53 reportedly can counteract the activity of the transcription factor nuclear factor-E2-related factor 2, which normally coordinates a prosurvival response to oxidative stress by transactivating multiple genes whose promoters contain an antioxidant response *cis*-elements (56). Intriguingly, at least in some cell types, including neurons, this indirect pro-oxidant

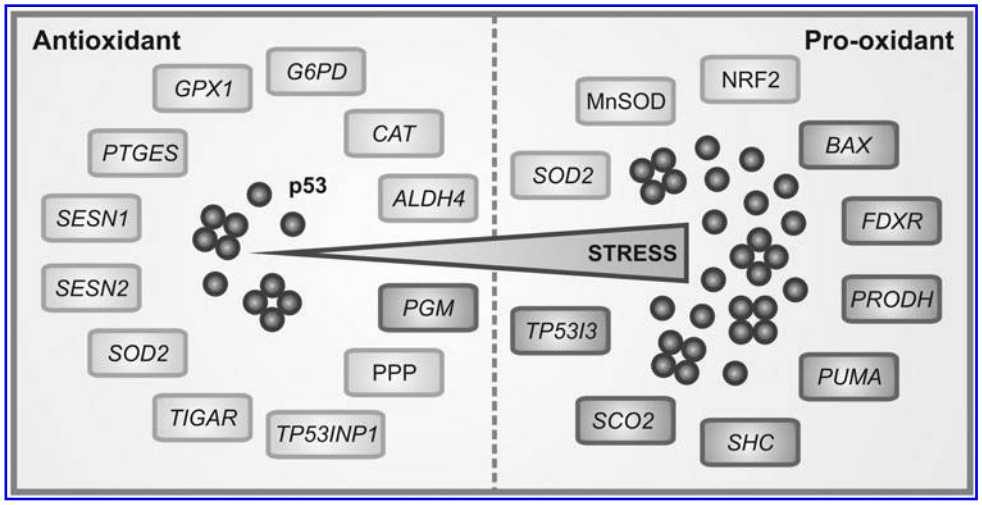

FIG. 5. Pro- and antioxidant functions of p53. In response to acute stress, p53 is known to upregulate several pro-oxidant proteins and to inhibit antioxidant defenses (either transcriptionally or in a transcription-independent fashion), thereby favoring oxidative stress. Conversely, in baseline conditions p53 appears to fulfill a cytoprotective role by stimulating a plethora of (direct and indirect) antioxidant systems. Although apparently counterintuitive, this dichotomy may simply reflect two facets of the oncosuppressive functions of p53. Light gray and dark gray boxes depict anti- and pro-oxidant factors, respectively. When the regulation by p53 occurs by transcriptional mechanisms, gene names are italicized. Please consult the main text for further details. ALDH4, aldehyde dehydrogenase 4; CAT, catalase; FDXR, ferredoxin reductase; GPX1, glutathione peroxidase 1; MnSOD, manganese SOD; NRF2, nuclear factor-E2-related factor 2; PRODH, proline dehydrogenase (oxidase) 1; PTGES, prostaglandin E synthase; PUMA, p53-upregulated modulator of apoptosis; SESN, sestrin; SOD2, superoxide dismutase 2; TP53I3, tumor protein p53 inducible protein 3; TP53INP1, tumor protein p53-inducible nuclear protein 1.

function of p53 appears to be suppressed by the product of the Polycomb group oncogene *BMI1* (33). Finally, p53 has been suggested to exert pro-oxidant functions by binding to (and hence inhibiting) the *SOD2* gene product (manganese SOD) at mitochondria (273).

Although the activation of p53 by stress has been shown to mediate pro-oxidant effects through multiple mechanisms, $p53^{-/-}$ mice exhibit augmented ROS levels, hinting at a physiological role for p53 as an antioxidant (209) (Fig. 5). Intriguingly, the absence of p53 *in vivo* apparently does not accelerate mutagenesis (presumably because of the function of a proficient DNA mismatch repair system) (25, 27). However, p53-null mice display increased oxidative damage to DNA, genetic instability (karyotypic abnormalities) (14, 76) and a strong propensity to develop tumors (mostly thymic lymphomas, by which they succumb by the age of 6 months) (49, 50). Remarkably, all these phenomena could be inhibited and/or delayed by supplementing the diet of $p53^{-/-}$ animals with the ROS-scavenger *N*-acetyl-cysteine (209), further corroborating the notion that the antioxidant role of p53 during everyday life represents an important component of its oncosuppressive activity.

Under physiological conditions (and sometimes also in response to stress), p53 can mediate antioxidant effects *via* at least two mechanisms (178, 245). First, functional p53 REs of the activator type are present in the promoter region of several antioxidant genes, including sestrin 1 and 2 [*SESN1* and *SESN2*, also known as *PA26* (239) and *HI95* (24), respectively], coding for components of the peroxiredoxin regeneration system that also participate in the regulation of autophagy (see below) (23, 70, 135); glutathione peroxidase 1 (*GPX1*), encoding an enzymatic scavenger of hydrogen peroxide or organic hydroperoxides (86, 225); aldehyde dehydrogenase 4 (*ALDH4*), whose product is a mitochondrial-matrix NAD^+-dependent enzyme that catalyzes the second step of proline degradation (260); *SOD2* (86); catalase (*CAT*), coding for a redox-active enzyme that has recently been shown to mediate (part of) the antioxidant effects of p53 *in vivo* (173); prostaglandin E synthase (*PTGES*, also known as *PIG12*) (191), encoding a microsomal glutathione-dependent enzyme participating in multiple inflammatory responses (92); and tumor protein p53-inducible nuclear protein 1 (*TP53INP1*), coding for a protein that possesses both p53-independent ROS regulatory and p53-dependent transcription regulatory functions (30) (Table 1). Second, the restraint imposed by p53 on glycolysis (see above) has indirect but consistent antioxidant consequences, which presumably originated by the need to control increased ROS generation by actively respiring mitochondria. Thus, p53-mediated transactivation of *TIGAR* and *G6PD* (12, 131) and repression of *PGM* (100) cooperatively inhibit the glycolytic flow and at the same time stimulate the PPP, thereby increasing the generation of NADPH, which is required for proficient ROS scavenging by reduced glutathione.

In near-to-physiological conditions p53 mostly mediates antioxidant effects, thereby preventing the accumulation of DNA damage and favoring repair mechanisms that may allow for cell survival. On the contrary, in response to acute stress, p53 exacerbates ROS generation and therefore promotes the elimination of irreparably damaged (and hence potentially tumorigenic) cells. This apparent discrepancy may reflect the opposing extremes of a continuous and complex spectrum of tumor suppressive functions mediated by p53 *via* redox reactions (178, 244, 245) (Fig. 5).

Mitochondria, Autophagy and p53

Autophagy is a highly conserved catabolic pathway that mediates the delivery of intracellular structures to lysosomes for bulk degradation (72). It constitutively operates at baseline levels to ensure the turnover of long-lived proteins and old or damaged (and hence potentially dangerous) organelles, thereby constituting a prominent antiaging and tumor suppressive mechanism (at least during the early steps of oncogenesis) (164, 165). Moreover, autophagy is upregulated

well above basal levels in response to a wide array of stressful conditions, including glucose deprivation, growth factor withdrawal, and hypoxia (122). Thus, autophagy constitutes a critical cytoprotective mechanism, as demonstrated by the fact that its pharmacological or genetic inhibition most often accelerates cell death (rather than preventing it) (17, 107), and may indeed facilitate the survival of cancer cells that experience metabolic and/or chemotherapeutic stress (165). In many instances (*e.g.*, when the autophagic pathway responds to nutrient deprivation and hence is aimed at generating novel metabolic substrates to meet the energy demand of the cell), autophagy occurs in a relative unselective fashion (72). Nevertheless, multiple intracellular structures can also be specifically tagged for autophagic degradation (262), including proteotoxins (196, 207, 250), peroxisomes (57), damaged endoplasmic reticulum (230), invading pathogens (121), and uncoupled mitochondria (a process that has been baptized "mitophagy") (169, 232, 270).

Both the lethal and vital functions of mitochondria are intimately linked to oncogenesis (71). Moreover, the defective elimination of damaged mitochondria (owing to either a specific defect in the molecular machinery for mitophagy or to a generalized impairment of the autophagic pathway) has been suggested to be permissive for tumor development (165). Thus, baseline levels of autophagy (and in particular of mitophagy) have been ascribed with *bona fide* oncosuppressive functions (71, 165), a notion that is strongly corroborated by the fact that multiple oncogenes code for autophagy-inhibitory factors, whereas several oncosuppressor proteins also stimulate the autophagic pathway (137, 165). Similar to its controversial role in the management of oxidative stress (see above), p53 regulates autophagy (and by extension mitophagy) in an ambiguous fashion, depending in its subcellular localization (135) (Fig. 6).

Multiple p53 target genes stimulate mitophagy, either in a direct fashion or (more often) indirectly, by inhibiting the signal transduction pathway converging on the negative regulator of autophagy mammalian target of rapamycin (mTOR). These genes code for the β1 and β2 subunits of AMP-activated protein kinase (AMPK) (58), an evolutionary conserved protein that responds to decreased ATP:AMP ratios, thereby acting a sensor of intracellular energy levels (59); tuberous sclerosis complex (TSC) protein 2 (TSC2) (58), which—in complex with TSC1—can transduce an anti-autophagic signal from AMPK to mTOR (89); SESN1 and 2, which function as upstream activators of AMPK (22, 136); damage-regulated autophagy modulator, a phylogenetically ancient lysosomal protein acting at the crossroad between p53-induced autophagy and cell death (43, 44); death-associated protein kinase 1 (144), an oncosuppressor with multiple proautophagic (264, 265) and proapoptotic (82) functions that is silenced in several malignancies due to promoter hypermethylation (74); and several proapoptotic members of the BCL-2 protein family including BAX (258), BAD (96), BNIP3 (271) and PUMA (258), all of which are thought to induce autophagy (at least in part) by displacing the essential autophagic modulator Beclin 1 from inhibitory interactions with their antiapoptotic counterparts BCL-2 and BCL-X_L (130).

Additional components of the stress-responsive p53 system have been attributed with proautophagic functions, including p73, a p53 family member that has been shown to promote autophagy in a damage-regulated autophagy modulator-independent manner (42), presumably by transactivating several AuTophaGy-related (*ATG*) genes (205); and ARF, which exists in two isoforms (198) that collectively stimulate autophagy by p53-dependent and p53-independent mechanisms (1, 189). Recently, the TP53INP1-related protein TP53INP2 (sharing 30% aa identity) has been indicated as an essential modulator of autophagy in mammalian cells (172), but it remains to be determined whether *TP53INP2* represents a *bona fide* p53 target gene. Of note, AMPK can respond to metabolic stress by directly phosphorylating p53, pointing to the existence of an intimate crosstalk between p53- and mTOR-mediated signaling pathways (59). Such a crosstalk might be part of a hitherto poorly defined autophagic switch (164). Altogether, these observations suggest that nuclear p53 mostly exerts proautophagic functions (Fig. 6).

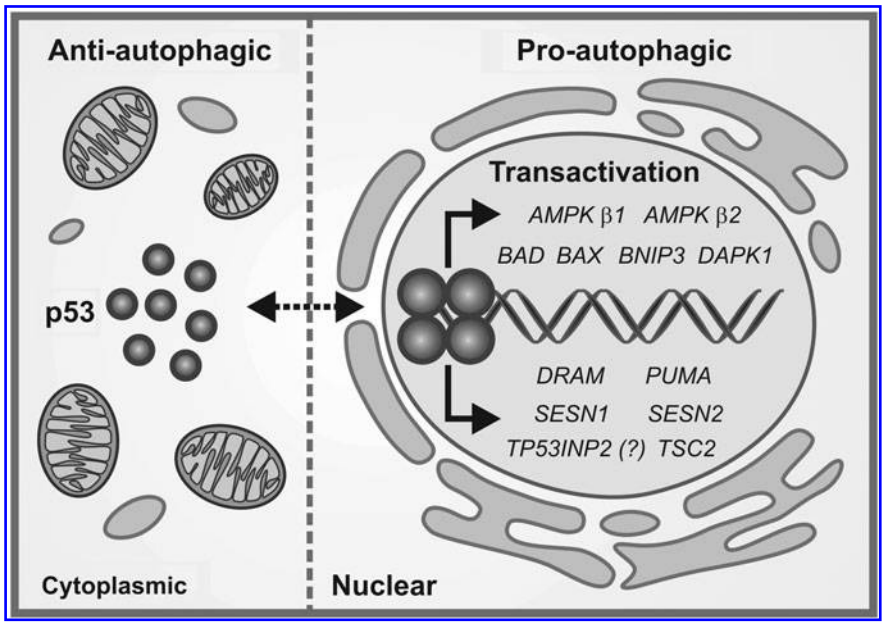

FIG. 6. p53, autophagy and mitochondria. p53 regulates autophagy (and hence mitophagy) in a controversial fashion, depending on its subcellular localization. Thus, while nuclear p53 transactivates a number of genes coding for proautophagic factors (among which the prominently promitophagic BH3-only protein BNIP3), cytoplasmic p53 exerts a tonic inhibition of autophagy *via* hitherto poorly characterized mechanisms. AMPK, AMP-modulated protein kinase; DAPK1, death-associated protein kinase 1; DRAM, damage-regulated autophagy modulator; TP53INP2, tumor protein p53-inducible nuclear protein 2; TSC, tuberous sclerosis complex.

Apparently in contrast with these observations, multiple cell types from evolutionarily distant model organisms have been found to react to pharmacological and/or genetic inactivation of p53 by activating autophagy (228). In line with this notion, several proautophagic stimuli, including nutrient deprivation and rapamycin-mediated inhibition of mTOR, have been shown to enhance the proteasomal degradation of p53 (228). These results pointed to the existence of a tonic inhibition of autophagy by p53 that is relieved under autophagy-stimulating conditions (228). In line with this hypothesis, $p53^{-/-}$ cancer cells are characterized by increased baseline levels of autophagy, which can be limited by the re-introduction of p53. Intriguingly, p53 inhibition triggers autophagy in a cell cycle-dependent fashion (229).

The autophagy-inhibitory effect of p53 persists in cytoplasts (228) and is not influenced by point mutations or short deletions targeting the p53 DBD, which render p53 transcriptionally inactive and/or unable to bind DNA and BCL-2 family members (see below) (167, 228). Moreover, autophagy inhibition by p53 correlates with its nuclear-to-cytosolic redistribution (167). In particular, the antiautophagic effect of p53 is exacerbated when its nuclear localization signal is deleted (leading to a purely cytoplasmic p53 localization), whereas it is abolished by the deletion of its nuclear export signal (resulting in the nuclear accumulation of p53) (167, 228). These results demonstrate that the cytoplasmic (extranuclear) pool of p53 inhibits autophagy by acting on hitherto unidentified molecular partners other than BCL-2-like proteins (Fig. 6).

p53 regulates autophagy in an apparently controversial manner, depending on its subcellular localization. Under physiological conditions and in response to mild stress, which might lead to partial (but incomplete) inhibition of MDM2, p53 is prominently localized in the cytoplasm [also owing to MDM2-mediated (poly)-monoubiquitination (123), see above], where it exerts antiautophagic functions. In response to acute stress, p53 undergoes post-translational modifications that allow for its stabilization and nuclear accumulation (see above), a process that might have a dual autophagy-stimulatory outcome. Indeed, although stress-activated p53 becomes able to transactivate multiple proautophagic genes, its nuclear accumulation is likely to be paralleled by a cytoplasmic depletion that also would promote autophagy. Further investigation is urgently required to elucidate this issue. However, if this model turned out to be true, the apparent discrepancy between the autophagy-inducing *versus* autophagy-inhibitory roles of nuclear *versus* cytoplasmic p53, respectively, would simply reflect a mechanism by which cells can achieve an all-or-nothing autophagic response to stress (and hence would constitute another facet of the autophagic switch) (164). Alternatively, since in several instances cytosolic p53 mediates a wave of mitochondrial dysfunction that largely precedes p53 target gene activation (55) (see below), autophagy inhibition by p53 might ensure that such a rapid proapoptotic reaction to stress would not be counteracted by the unwarranted activation of a prosurvival response mediated by mitophagy.

p53 and MMP

The proapoptotic function of p53 constitutes the best characterized facet of its oncosuppressive activities. Still, until recently, p53 was (mis)believed to promote MMP only by transactivating proapoptotic genes and/or by repressing genes that exert antiapoptotic effects. Now, it has become clear that the cytoplasmic pool of p53 mediates a direct apoptogenic effect at mitochondria by physically interacting with BCL-2 family members and hence stimulating MMP (36, 37, 161, 166, 237). Still, the physiological relevance of transcription-independent *versus* transcriptional p53 functions remains unclear. Recent results obtained in knock-in mice that express a transactivation-deficient variant of p53 (97) suggest indeed that p53-mediated tumor suppression would require p53 transcriptional functions (192).

Lethal proteins whose promoter contains a functional p53 RE of the activator type include proapoptotic members of the BCL-2 protein family such as BAD (96), BAK (184, 190), BAX (158, 184), BID (211), BOK (256), NOXA (also known as phorbol-12-myristate-13-acetate-induced protein 1) (174, 256), and PUMA (168), as well as other components of the mitochondrial apoptotic pathway like the cytosolic adaptor apoptotic peptidase activating factor 1 (162, 202), AIF (222), AIF-homologous mitochondrion-associated inducer of death (254, 255), p53-regulated apoptosis-inducing protein 1 (which physically localizes at mitochondria and directly mediates $\Delta\psi_m$ loss) (151, 175), oxidative stress-induced growth inhibitor 1 [a tumor suppressor protein also known as OKL38 or bone marrow stromal cell-derived growth inhibitor (246), which has recently been discovered to contribute to p53-dependent MMP in response to DNA damage (257)], and caspase-6 (133) (Table 2). Moreover, p53 has been shown to repress the transcription of genes coding for negative regulators of MMP such as BCL-2 (158), BCL-X_L (224), and MCL-1 (187), as well as for antiapoptotic proteins that operate downstream of mitochondria such as survivin (5, 85) (Fig. 7).

Extranuclear apoptogenic functions for p53 have first been suspected in the mid-1990s, when it was shown that p53-dependent apoptosis persist in the presence of transcriptional and translational inhibitors (28) and can be mediated by transactivation-deficient p53 mutants (83). These observations were reinforced by subsequent studies hinting at a direct role for p53 in the regulation of caspase activity (47, 73). Still, a direct mechanistic link between p53 and MMP was not elucidated until the year 2000, when Marchenko *et al*. first demonstrated that a fraction of stress-stabilized p53 translocates to mitochondria well before $\Delta\psi_m$ dissipation, CYTC release, and ignition of the caspase cascade (141) [and preceding p53 target gene activation (55)]. These observations have been confirmed by ectopic expression in p53-null cell lines of a mitochondrially targeted p53 variant, which has no residual transcriptional functions and is fully excluded from the nucleus, yet maintains the proapoptotic proficiency of its wild-type (WT) counterpart (156). A number of subsequent studies widened the spectrum of p53-activating stimuli that can trigger p53 mitochondrial translocation and transcription-independent MMP (8, 160, 210). Of note, the mitochondrial translocation of p53 occurs neither during p53-mediated cell cycle arrest nor during p53-independent instances of mitochondrial cell death (8, 141, 160, 210). The precise molecular mechanisms that underlie these observations are still elusive.

Several pathways may mediate the direct apoptogenic role of extranuclear p53 (166, 238) (Fig. 7). First, p53 has been shown to bind antiapoptotic members of the BCL-2 protein family, in particular BCL-2 and BCL-X_L (161, 233). In this

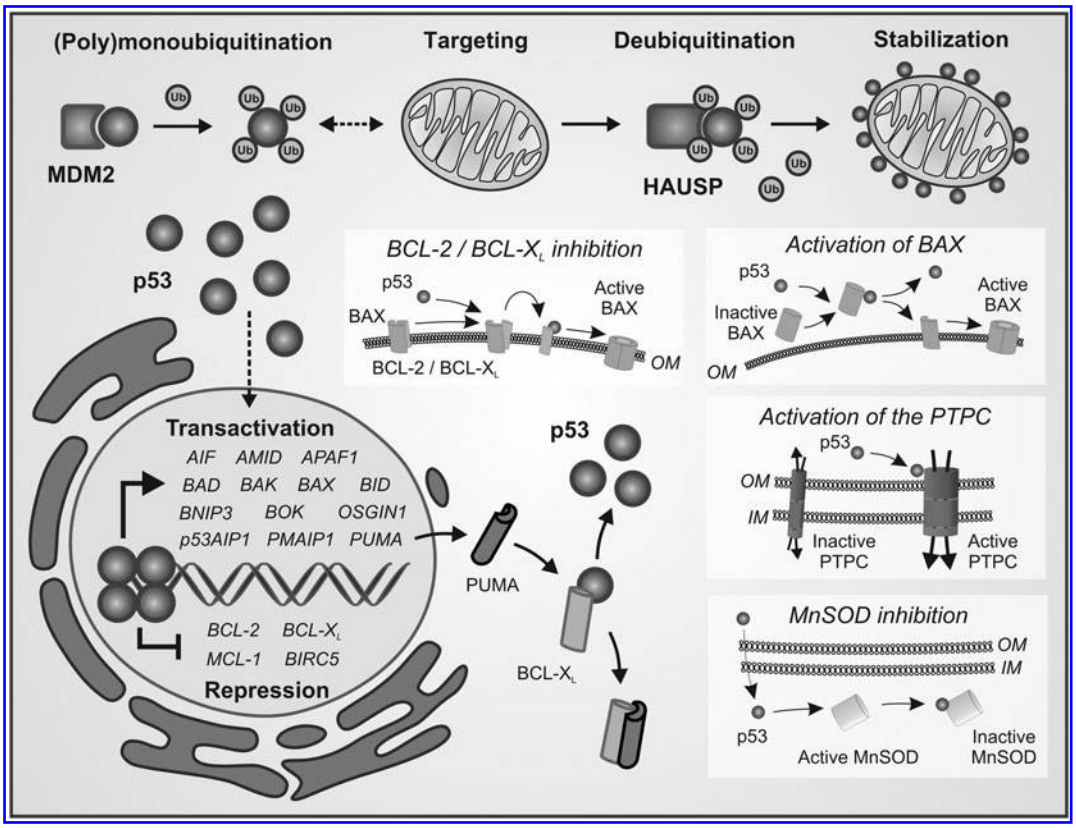

FIG. 7. p53 and MMP. p53 interacts with the molecular machinery for MMP and for intrinsic apoptosis at multiple (functional and subcellular) levels. First, nuclear p53 can upregulate several proapoptotic members of the BCL-2 protein family as well as multiple factors implicated in the postmitochondrial phase of intrinsic apoptosis. Second, nuclear p53 can repress the transcription of genes coding for antiapoptotic modulators. Third, mitochondrial p53 has been demonstrated to (i) interact with (and hence inhibit) antiapoptotic members of the BCL-2 protein family; (ii) physically stimulate proapoptotic BCL-2-like proteins and components of the PTPC; and (iii) block the antioxidant function of MnSOD. Of note, p53 translocates to mitochondria upon MDM2-mediated (poly)-monoubiquitination, and is locally deubiquitinated by HAUSP, which generates a mitochondrially restricted apoptotically proficient pool of the protein. Fourth, cytosolic p53 appears to be involved (together with BCL-X_L and PUMA) in the regulation of a proapoptotic pathway requiring both the transcriptional and mitochondrial functions of p53. Please refer to the main text fur further details. APAF1, apoptotic peptidase activating factor 1; BIRC5, baculoviral IAP repeat-containing 5 (survivin); HAUSP, herpesvirus-associated ubiquitin-specific protease; OSGIN1, oxidative stress-induced growth inhibitor 1; p53AIP1; p53-regulated apoptosis-inducing protein 1; PMAIP1, phorbol-12-myristate-13-acetate-induced protein 1.

scenario, p53 operates as a BH3-only protein of the depressor type (see above), thereby freeing proapoptotic BCL-2 family members such as BID and BAX from BCL-2/X_L-mediated inhibition (37). By protein modeling, structure/function mutagenesis and nuclear magnetic resonance spectroscopy, the region of interaction between BCL-2-like proteins and p53 has been localized to its DBD (185, 219), and it has been demonstrated that tumor-derived p53 mutants concomitantly lose their transcriptional functions and the ability to trigger MMP (233). Thus, tumor-associated mutations of the p53 DBD represent double hits, impairing both transcriptional and transcription-independent facets of the oncosuppressive activity of p53 (156). Second, p53 reportedly interacts with proapoptotic BCL-2-like proteins including mitochondrial BAK (120, 188), cytosolic BAX (37), BAD (96), and BID (218), as well as with PTPC components such as voltage-dependent anion channel (252). In doing so, p53 directly triggers MOMP or MPT, thereby exerting functions similar to those exhibited by activator BH3-only proteins (see above). Third, extranuclear p53 has been implicated in a cytosolic pathway for the regulation of MMP (36). In this setting, nuclear p53 has been suggested to mediate the rapid transactivation of *PUMA*, whose product in turn would liberate cytoplasmic p53 from BCL-X_L-mediated repression and hence unleash the proapoptotic potential of p53 (36). Of note, while the cytosolic p53 death pathway depends on BAX and PUMA (36, 37), the same does not hold true for its mitochondrial counterpart (252). Fourth, p53 has been shown to physically interact with manganese SOD at mitochondria (see above), eventually resulting in $\Delta\psi_m$ dissipation (273). Fifth, caspase-dependent proteolysis of p53 may generate fragments that translocate to mitochondria and induce MMP, thereby activating a feed-forward loop (emanating from active caspases) for the amplification of the apoptotic signal (212).

Also under physiological conditions a small pool of p53 can be found at mitochondria, where it reportedly contributes to mtDNA base excision repair, *via* hitherto unidentified mechanisms (34), as well as to mtDNA transcription and copy

number maintenance, by binding to (thereby regulating the activity of) the mitochondrial transcription factor A (253, 261). Although formal evidence in support of this hypothesis has not been provided yet, it is tempting to speculate that mitochondrial p53 might constitutively mediate homeostatic functions (as do its nuclear and cytoplasmic counterparts) for the management of everyday stress.

p53 does not contain a mitochondrial localization signal and its mitochondrial translocation does not result from post-translation acetylation and phosphorylation (171). Rather, it appears that MDM2-mediated (poly)-monoubiquitination is the major driving force for the mitochondrial relocalization of p53 (139, 140). Upon arrival at mitochondria, p53 is rapidly deubiquitinated by a local fraction of herpesvirus-associated ubiquitin-specific protease, generating a mitochondrially restricted apoptotically proficient pool of p53 (124, 139) (Fig. 7). The E3 ubiquitin ligase MSL2 has recently been shown to control the cytoplasmic localization of p53 (but not its stability) in an MDM2-independent fashion (110), but the possible involvement of MSL2 in p53 mitochondrial targeting has not yet been explored. An intriguing and yet unresolved issue regard the oligomerization state of mitochondrial p53 (238). The C-terminal oligomerization domain of p53 is not directly implicated in its interaction with BCL-2-like proteins (219), and mitochondrially targeted variants of p53 lacking the oligomerization domain have been shown to induce apoptosis as efficiently as WT p53 upon reintroduction into p53-null cells (141). In line with these observations and with the results of (some) cross-linking studies (84), the mitochondrial (but not the nuclear) functions of WT p53 have been found to be insensitive to dominant negative inhibition (84). In contrast, Murphy and colleagues reported that most mitochondrial p53 is clustered in dimers or higher-order multimers, and that mutations of the p53 oligomerization domain markedly affects its ability to stimulate the oligomerization of BAK (188). Future investigation will have to elucidate this controversy.

Concluding Remarks

Since >2 billion years ago, mitochondria have become irreplaceable for eukaryotic organisms. Mitochondria produce indeed the vast majority of a cell's ATP (thereby also representing the most prominent source of intracellular ROS), host (entirely or in part) a consistent number of metabolic circuitries, and modulate several signaling pathways that lead to cell death. Consistent with the central position occupied by mitochondria in both vital and lethal aspects of cell biology, mitochondrial dysfunctions constitute the etiological determinants (or at least contribute to the development) of a plethora of human diseases, including cancer. Thus, it is no surprise that p53 (which is inactivated in >50% of all human cancers) has been attributed with an ever-increasing number of functions that (directly or indirectly) mediate stress-induced oncosuppression at the mitochondrial level. In addition, recent research has focused on the baseline activity of p53 in unstressed cells, revealing hitherto unsuspected homeostatic circuitries by which the p53 system finely regulates mitochondrial energy production, limits oxidative damage, and suppresses autophagy. These homeostatic functions of p53 are likely to constitute yet another facet of its tumor suppressive role, suggesting that the complexity of the p53 system is far from being entirely understood. Although 30 years have passed since its discovery, p53 remains a blinding light (244).

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Address correspondence to:
Prof. Guido Kroemer
INSERM, U848
Institut Gustave Roussy
Pavillon de Recherche 1
F-94805 Villejuif (Paris)
France

E-mail: kroemer@orange.fr

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Abbreviations Used

5-FU = 5-fluorouracil
$\Delta\psi_m$ = mitochondrial transmembrane potential
aa = amino acids
AIF = apoptosis-inducing factor
ALDH4 = aldehyde dehydrogenase 4
AMID = AIF-homologous mitochondrion-associated inducer of death
AMPK = AMP-activated protein kinase
ANT = adenine nucleotide translocase
APAF1 = apoptotic peptidase activating factor 1
ATG = AuTophaGy-related
BDGI = bone marrow stromal cell-derived growth inhibitor
CAT = catalase
CKB = creatine kinase (brain)
CKM = creatine kinase (muscle)
COX = CYTC oxidase
CPEB = cytoplasmic polyadenylation element-binding protein
CYPD = cyclophilin D
CYTC = cytochrome *c*
DAPK1 = death-associated protein kinase 1
DBD = DNA-binding domain
DRAM = damage-regulated autophagy modulator
ENDOG = endonuclease G
$FADH_2$ = reduced flavine adenine dinucleotide
F2,6BP = fructose-2,6-bisphosphate
F6P = fructose-6-phosphate
FDXR = ferredoxin reductase
G6P = glucose-6-phosphate
G6PD = glucose-6-phosphate dehydrogenase
GLUT = glucose transporter
GPX = glutathione peroxidase
HAUSP = herpesvirus-associated ubiquitin-specific protease
HK2 = hexokinase II
IAP = inhibitor of apoptosis protein
IM = mitochondrial inner membrane
IMS = mitochondrial intermembrane space
MMP = mitochondrial membrane permeabilization
MnSOD = manganese superoxide dismutase
MOMP = mitochondrial outer membrane permeabilization
MPT = mitochondrial permeability transition
mtDNA = mitochondrial DNA
mTOR = mammalian target of rapamycin
NADH = reduced nicotinamide adenine dinucleotide
NADPH = reduced nicotinamide adenine dinucleotide phosphate
NO = nitric oxide
NRF2 = nuclear factor-E2-related factor 2
OM = mitochondrial outer membrane
OSGIN1 = oxidative stress induced growth inhibitor 1
p53AIP1 = p53-regulated apoptosis-inducing protein 1
PCD = programmed cell death
PDH = pyruvate dehydrogenase
PFK = 6-phosphofructo-2-kinase

Abbreviations Used (Cont.)

PGM = phosphoglycerate mutase
PIG = p53-induced gene
PMAIP1 = phorbol-12-myristate-13-acetate-induced protein 1
PPP = pentose phosphate pathway
PRODH = proline dehydrogenase (oxidase) 1
PTGES = prostaglandin E synthase
PTPC = permeability transition pore complex
PUMA = p53-upregulated modulator of apoptosis
RE = responsive element
ROS = reactive oxygen species
SCO2 = synthesis of COX2
SESN = sestrin
SOD = superoxide dismutase
TCA = tricarboxylic acid
TFAM = mitochondrial transcription factor A
TIGAR = TP53-induced glycolysis and apoptosis regulator
TP53I3 = tumor protein p53 inducible protein 3
TP53INP1 = tumor protein p53-inducible nuclear protein 1
TSC = tuberous sclerosis complex
VDAC = voltage-dependent anion channel
WT = wild type

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