No discussion of cancer biology is complete without mention of tumor suppressor p53 and its stress-activated protection of the genome. A plethora of regulatory signaling impinges on p53 to either limit p53 protein levels, in the absence of stress signaling, or to rapidly induce protein levels and mediate cell cycle arrest or cell death in the face of threats to genome integrity [1,2]. Although reports of p53 regulation and functions in cellular surveillance add up to an astounding number, recent discoveries that illustrate functions of p53 in cellular metabolism reveal that much is left to learn [3,4]. The ability of the p53-null mouse to survive to adulthood with few apparent challenges to normal development casts a shadow over likely roles for p53 in normal, cellular homeostasis [5]. Early development of specific tumors, the profile of which is dependent on strain, is the most striking embodiment of p53-mediated regulation in lipid metabolism is especially appropriate, as the liver is a key player in lipid intake, synthesis, processing and secretion [10]. At first glance, the liver would not seem a likely site where p53 would have a major functional role. Unlike many other tissues, the liver is non-responsive to whole-body irradiation, showing no p53 activation or induction of protective apoptotic pathways [11]. Specific mutations in the gene encoding p53 occur in HCC, but often arise relatively late during tumorigenesis or are secondarily induced as a result of environmental insults, such as adducts formed in the presence of aflatoxin poisoning [12,13]. However, dysfunction in p53, due to inactivation by proteins produced in hepatitis B or C infection, is likely causal in virus-associated HCC [14]. More recent studies of genome wide expression patterns in human and mouse HCC suggest a signature of pathways associated with tumor development, among which p53 regulation and intersection are significant [15].

Goldstein et al. use a variety of platforms to assess hepatic functions for p53, not only in human hepatic tumor-derived, cultured cell lines but also in donor liver primary hepatocytes, mouse hepatocytes and embryonic fibroblasts. In an unbiased approach, microarray analysis of gene expression was carried out in human hepatoblastoma-derived HepG2 cells, engineered by retroviral introduction of shRNA targeting p53 or control shRNA, and further altered in p53 expression levels by exposure to the inhibitor Nutlin. The specific mechanism of Nutlin-mediated stability of p53, due to disruption of Mdm2-p53 interaction without exposure to DNA damaging agents or induction of genotoxic stress [16], may have been critical in linking p53 to hepatic genes active in lipid metabolism; robust activation of early response genes, active in damage control or cell death, could potentially obscure expression of other p53-regulated genes. Over 300 genes were significantly activated in this study, of which 5% were associated with lipid metabolism.

The group of genes, classified as lipid metabolic pathway genes, covers multiple aspects of lipid metabolism, including regulators of intracellular ceramide and fatty acids, systemic lipid absorption and lipoprotein metabolism. The authors performed detailed, in-depth analyses to show that p53 directly regulates specific genes from the larger number in this category:
(1) phospholipid transfer protein (PLTP), which is secreted by the liver as an HDL-bound protein and is associated with atherogenesis [17,18]. (2) Carboxyl ester lipase (CEL), an enzyme that hydrolyzes dietary triglycerides and ceramide, and promotes uptake of HDL-associated cholesteryl esters in the liver [19]. (3) Adenosine triphosphate-binding cassette, subfamily A, member 12 (ABCA12), a member of the large ABC superfamily of ATP-dependent trans-membrane proteins, which functions in active transport of lipids across the cell membrane [20]. p53-mediated regulation of apolipoprotein levels in non-hepatic, cultured cells was previously reported in DNA damage-induced transcription of ApoB, which encodes the primary apolipoprotein responsible for cholesterol transport to tissues, and Apobec1, a cytidine deaminase that edits Apob and Nf1 mRNA [21].

Previous links between p53, oxidative stress and metabolic regulation, as reviewed in depth by Vousden and colleagues [3,4], broaden the functions of p53 in tumor suppression. The metabolic demands of tumor growth and malignant progression may induce a switch to glycolysis, which p53 opposes by repressing glycolytic gene expression, activating TIGAR to slow glycolysis and preventing reactive oxidant accumulation [22]. Importantly, as shown in the current study of lipid metabolism genes, many of these functions of p53 in metabolic control occur during normal cellular growth and homeostasis, as well as in response to stress induction.

With this report of p53-mediated control of specific genes in lipid metabolism, functions of p53 are further extended from tumor suppression to lipid-transfer control, cardiometabolic diseases and atherogenesis [23]. Taken together with indirect regulation of inflammation, by virtue of p53-mediated suppression of NF-kB activation [24], these p53-regulated pathways may add to the complex picture of p53 functions in aging [25]. Premature signs of aging are also reported for TA-p53 deleted mice [26], emphasizing that, while downstream targets of p53 are numerous, upstream regulation of p53 is complex, influenced by a large variety of homeostatic and stress-induced controls, and likely involves interactions among its family members and isoforms. These variables must be considered and further defined to fully assess or interpret the impact of p53 dysfunction, and to develop effective treatments of cancers, cardiometabolic diseases and likely others, yet to be discovered under the regulatory influence of p53.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References