Recent discoveries in the cycling, growing and aging of the p53 field

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Abstract: The P53 gene and it product p53 protein is the most studied tumor suppressor, which was considered as oncogene for two decades until 1990. More than 60 thousand papers on the topic of p53 has been abstracted in Pubmed. What yet could be discovered about its role in cell death, growth arrest and apoptosis, as well as a mediator of the therapeutic effect of anticancer drugs. Still during recent few years even more amazing discoveries have been done. Here we review such topics as suppression of epigenetic silencing of a large number of non-coding RNAs, role of p53 in suppression of the senescence phenotype, inhibition of oncogenic metabolism, protection of normal cells from chemotherapy and even tumor suppression without apoptosis and cell cycle arrest.

Not for the first time in the recent years, but the hero again remains p53. Importantly that it was not from one single discovery but instead from several different discoveries and most were unexpected. Gudkov and co-workers recently reported (also on line first) that p53, a tumor suppressor protein, recently renamed TP53, cooperated with DNA methylation to maintain the silencing of a large portion of the mouse genome. (Leonova KI, Brodsky L, Lipchick B, Pal M, Novototskaya L, Chenchik AA, Sen GC, Komarova EA, Gudkov AV. p53 cooperates with DNA methylation and a suicidal interferon response to maintain epigenetic silencing of repeats and noncoding RNAs. PNAS U S A. Epub 2012 Dec 10.) It was previously known that mammalian genomes contained various classes of interspersed and tandem repeat DNA sequences that were transcriptionally inactive. An essential unanswered question was why they are so many and why are they transcriptionally inactive?

The answer to this question was recently provided by the Gudkov team. The transcription of these sequences was determined to be blocked by p53 in conjunction with DNA methylation. In p53-deficient, but not in p53 wild-type mouse embryonic fibroblasts, treatment with a DNA demethylating agent caused massive transcription of short interspersed nuclear elements. These elements that were transcribed are near-centromeric satellite DNAs consisting of tandem repeats and multiple species of noncoding RNAs. Amazingly, the abundance of these transcripts exceeded the level of beta-actin mRNA by more than 150-fold. Accumulation of these transcripts, was accompanied by a strong, endogenous, apoptosis-inducing type I IFN response. This work was recently discussed in detail [1, 2]. This phenomenon, which Gudkov and co-workers named "TRAIN" (for "transcription of repeats activates interferon"), was observed in spontaneous tumors in two models of cancer-prone mice. The authors proposed that p53 and IFN cooperate to prevent accumulation of cells containing activated repeats and provide a plausible explanation for the deregulation of IFN function frequently observed in tumors. Therefore, p53 and IFN are key for genetic stability and therefore relevant to both tumorigenesis and aging.

This phenomenon may be linked to another discovery about the role of p53 and INF in long-lived and cancer-resistant rodents. Gurbunova et al [3] demonstrated that in the blind mole rat *Spalax*, a small subterranean rodent which is distinguished by its adaptations to life underground, there was a remarkable longevity (with a

maximum documented lifespan of 21 years), and resistance to spontaneous cancer induction. Spontaneous tumors have never been observed in these rodents. Cells obtained from blind mole rats proliferated for 7-20 population doublings, after which the cells began secreting IFN-beta, and the cultures underwent necrotic cell death. In another long-lived and cancer-resistant rat model, the release of IFN-beta was determined to result in the sequestration of p53 and Rb-rescued necrotic cell death. The precise link between two discoveries needs to be further elucidated. Noteworthy, IFN-beta is currently undergoing phase I clinical trials in various drug combinations [4].

Next we discuss a third phenomenon published in summer of 2012. It was shown that hypoxia, by inhibiting mTOR in human cells, prevented the development of senescent phenotype in non-dividing but not senescent cells [5]. mTOR is known to drive cell senescence in culture [6-9] and its inhibition extends the lifespan of mice [10-16].

As recently proposed, aging is not caused by accumulation of DNA damage but is driven by signaling pathways such as TOR [13-36]. Aging and age-related diseases are quasi-programs, an aimless continuation of developmental growth. The hyper-function theory was initiated by the hypothesis that active growth-promoting pathway must drive aging instead of growth, if the cell cycle is blocked [37, 38]. This increases cellular functions, leading to hyperfunction, age-related diseases and malfunctions. This theory, Recently named "the hyperfunction theory", this point of view is becoming increasingly accepted [17 ,39, 40].

Besides rapamycin and other rapalogs, mTOR is inhibited by p53 and hypoxia [5, 7]. Long-lived rats that live underground frequently experience hypoxia. Could hypoxia also contribute to their exceptional longevity? Also, it was known that fibroblasts from long-lived mutant mice exhibit lower mTOR activity after nutrient deprivation or oxidative stress [41].

Two recent papers demonstrated that rapamycin can increase life-span in p53- deficient mice, substituting p53 by rapamycin [42, 43]. This may be due to natural inhibition of mTOR by p53, as suggested recently, so rapamycin could potentially substitute for p53-dependent mTOR inhibition and extend lifespan [44]. p53 may not only initiate cell cycle arrest (a condition suitable for conversion to senescence driven by mTOR), but may also suppress this conversion from arrest to senescence by inhibiting mTOR [7]. The choice

between senescence and quiescence/apoptosis may be determined by inhibition of mTOR by p53 [5, 8, 45-50].

But the most unexpected discovery was the tumor suppression observed in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence [51, 52]. What could this result in? Most scientists remain skeptical. Could this missing tumor-suppression activity be gerosuppression by p53 as recently discussed [53]. But still this could be a very unique case in exceptional conditions and special mice.

There were numerous exciting reports increasing the diverse roles of p53 as a tumor suppressor [54-75] emphasizing its functions in apoptosis [76-81] and especially prevention of p53-mediated apoptosis by HIF-1 through a secreted neuronal tyrosinase [82] cell cycle arrest [83-86]. p53 has also been shown to be involved in the inhibition of invasiveness [87], and interact with other genes to suppress cancer [88], as well as suppress p63 to prevent induction of a pro-invasive secretome [89]. Moreover p53 has been shown to regulate telomere function [90] and p53 can suppress telomere-driven tetraploidization [91]. Interesting breakthroughs were in the identification of p53 as inhibitor of metabolism, [58, 92-94] its role in autophagy, [95, 96] it roles in induction of necrosis [97] and other diverse activities [98-110].

In fact, some of metabolic effects of p53 are associated with gerosuppression by p53 [53]. Noteworthy, rapamycin, like p53, may not only suppress oncogenic metabolism but also decrease lactate production by cancer cells [111, 112].

Given that the PI3K/mTOR pathway is activated in both aging [13] and cancer [113-125], aging and cancer share such characteristics as an increased metabolism, anabolic phenotype and other metabolic features [126]. By themselves, aerobic cancer cell and stromal metabolism become therapeutic targets [127]. Additional promising cancer-specific targets are gluta-minase [128] and PKM2 [126-134]. PKM2 expression is necessary for aerobic glycolysis and cell proliferation *in vivo* [129-134]. Pyruvate kinase M2 regulates glucose metabolism by functioning as a coactivator for hypoxia-inducible factor 1 in cancer cells [129-135]. Cancer cells universally express the M2 isoform of the glycolytic enzyme pyruvate kinase (PKM2). Although isoform selective inhibition of PKM2 with small molecules is feasible and support the hypothesis that inhibition of glucose metabolism in cancer cells is a viable strategy to treat human malignancy [125], the cancer-selectivity of PKM2 was recently doubted [136].

But here is a new twist: p53 may protect cells lacking p53 (all normal cells), thus in theory decreasing side effects, without decreasing the therapeutic effects against cancer cells lacking p53. Thus, it was shown that p53-mediated senescence impairs the apoptotic response to chemotherapy and clinical outcome in breast cancer [137]. But here is a silver edge of the cloud [138]. By inducing cytostatic levels of p53 and causing quiescence, we can protect normal cells from chemotherapy, without protection of cancer cells lacking p53. Protection of normal cells was called cyclotherapy [139-142]. Protection of normal cells by induction of p53 was further confirmed recently [143-147].

Finally, the role of p53 in somatic cell reprogramming was recently discussed in detail [148-153].

Conflict of Interest Statement

The authors of this manuscript have no conflict of interests to declare.

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