
Cancers (Basel) : 10(5) : pii: E135

Résumé

The p53 protein has been extensively studied for its capacity to prevent proliferation of cells with a damaged genome. Surprisingly, however, our recent analysis of mice expressing a hyperactive mutant p53 that lacks the C-terminal domain revealed that increased p53 activity may alter genome maintenance. We showed that p53 downregulates genes essential for telomere metabolism, DNA repair, and centromere structure and that a sustained p53 activity leads to phenotypic traits associated with dyskeratosis congenita and Fanconi anemia. This downregulation is largely conserved in human cells, which suggests that our findings could be relevant to better understand processes involved in bone marrow failure as well as aging and tumor suppression.

Essential role for centromeric factors following p53 loss and oncogenic transformation.

Genes & development : 463-480 : DOI : 10.1101/gad.290924.116

Résumé

In mammals, centromere definition involves the histone variant CENP-A (centromere protein A), deposited by its chaperone, HJURP (Holliday junction recognition protein). Alterations in this process impair chromosome segregation and genome stability, which are also compromised by p53 inactivation in cancer. Here we found that CENP-A and HJURP are transcriptionally up-regulated in p53-null human tumors. Using an established mouse embryonic fibroblast (MEF) model combining p53 inactivation with E1A or HRas-V12 oncogene expression, we reproduced a similar up-regulation of HJURP and CENP-A. We delineate functional CDE/CHR motifs within the Hjurp and Cenpa promoters and demonstrate their roles in p53-mediated repression. To assess the importance of HJURP up-regulation in transformed murine and human cells, we used a CRISPR/Cas9 approach. Remarkably, depletion of HJURP leads to distinct outcomes depending on their p53 status. Functional p53 elicits a cell cycle arrest response, whereas, in p53-null transformed cells, the absence of arrest enables the loss of HJURP to induce severe aneuploidy and, ultimately, apoptotic cell death. We thus tested the impact of HJURP depletion in pre-established allograft tumors in mice and revealed a major block of tumor progression in vivo. We discuss a model in which
an « epigenetic addiction » to the HJURP chaperone represents an Achilles’ heel in p53-deficient transformed cells.

Boris Bardot, Franck Toledo (2017 Feb 24)
**Targeting MDM4 Splicing in Cancers.**
*Genes*: DOI: E82

**Résumé**

MDM4, an essential negative regulator of the P53 tumor suppressor, is frequently overexpressed in cancer cells that harbor a wild-type P53. By a mechanism based on alternative splicing, the MDM4 gene generates two mutually exclusive isoforms: MDM4-FL, which encodes the full-length MDM4 protein, and a shorter splice variant called MDM4-S. Previous results suggested that the MDM4-S isoform could be an important driver of tumor development. In this short review, we discuss a recent set of data indicating that MDM4-S is more likely a passenger isoform during tumorigenesis and that targeting MDM4 splicing to prevent MDM4-FL protein expression appears as a promising strategy to reactivate p53 in cancer cells. The benefits and risks associated with this strategy are also discussed.

Eléonore Toufektchan, Sara Jaber, Franck Toledo (2017 Jan 26)
**[Dangerous liaisons: p53, dyskeratosis congenita and Fanconi anemia].**
*Medecine sciences* : M/S : 95-98 : DOI: 10.1051/medsci/20173301018

**Résumé**

Année de publication : 2016

Franck Toledo (2016 Aug 20)
**p53: A two-faced regulator of telomere metabolism? (comment on DOI 10.1002/bies.201600078).**
*BioEssays* : news and reviews in molecular, cellular and developmental biology : DOI: 10.1002/bies.201600149

**Résumé**

Sara Jaber, Eléonore Toufektchan, Vincent Lejour, Boris Bardot, Franck Toledo (2016 Apr 2)
**p53 downregulates the Fanconi anaemia DNA repair pathway.**
*Nature communications* : 11091 : DOI: 10.1038/ncomms11091

**Résumé**
Germline mutations affecting telomere maintenance or DNA repair may, respectively, cause dyskeratosis congenita or Fanconi anaemia, two clinically related bone marrow failure syndromes. Mice expressing p53(Δ31), a mutant p53 lacking the C terminus, model dyskeratosis congenita. Accordingly, the increased p53 activity in p53(Δ31/Δ31) fibroblasts correlated with a decreased expression of 4 genes implicated in telomere syndromes. Here we show that these cells exhibit decreased mRNA levels for additional genes contributing to telomere metabolism, but also, surprisingly, for 12 genes mutated in Fanconi anaemia. Furthermore, p53(Δ31/Δ31) fibroblasts exhibit a reduced capacity to repair DNA interstrand crosslinks, a typical feature of Fanconi anaemia cells. Importantly, the p53-dependent downregulation of Fanc genes is largely conserved in human cells. Defective DNA repair is known to activate p53, but our results indicate that, conversely, an increased p53 activity may attenuate the Fanconi anaemia DNA repair pathway, defining a positive regulatory feedback loop.

Résumé

Ribosome biogenesis dysfunction leads to p53-mediated apoptosis and goblet cell differentiation of mouse intestinal stem/progenitor cells.

Résumé

Ribosome biogenesis is an essential cellular process. Its impairment is associated with developmental defects and increased risk of cancer. The in vivo cellular responses to defective ribosome biogenesis and the underlying molecular mechanisms are still incompletely understood. In particular, the consequences of impaired ribosome biogenesis within the intestinal epithelium in mammals have not been investigated so far. Here we adopted a genetic approach to investigate the role of Notchless (NLE), an essential actor of ribosome biogenesis, in the adult mouse intestinal lineage. Nle deficiency led to defects in the synthesis of large ribosomal subunit in crypts cells and resulted in the rapid elimination of intestinal stem cells and progenitors through distinct types of cellular responses, including apoptosis, cell cycle arrest and biased differentiation toward the goblet cell lineage. Similar observations were made using the rRNA transcription inhibitor CX-5461 on intestinal organoids culture. Importantly, we found that p53 activation was responsible for most of the cellular responses observed, including differentiation toward the goblet cell lineage. Moreover, we identify the goblet cell-specific marker Muc2 as a direct transcriptional target.
of p53. Nle-deficient ISCs and progenitors disappearance persisted in the absence of p53, underlyng the existence of p53-independent cellular responses following defective ribosome biogenesis. Our data indicate that NLE is a crucial factor for intestinal homeostasis and provide new insights into how perturbations of ribosome biogenesis impact on cell fate decisions within the intestinal epithelium.


Mice engineered for an obligatory Mdm4 exon skipping express higher levels of the Mdm4-S isoform but exhibit increased p53 activity.

Oncogene : DOI : doi:10.1038/onc.2014.230

Résumé

Mdm4, a protein related to the ubiquitin-ligase Mdm2, is an essential inhibitor of tumor suppressor protein p53. In both human and mouse cells, the Mdm4 gene encodes two major transcripts: one encodes the full-length oncoprotein (designated below as Mdm4-FL), whereas the other, resulting from a variant splicing that skips exon 6, encodes the shorter isoform Mdm4-S. Importantly, increased Mdm4-S mRNA levels were observed in several human cancers, and correlated with poor survival. However, the role of Mdm4-S in cancer progression remains controversial, because the Mdm4-S protein appeared to be a potent p53 inhibitor when overexpressed, but the splice variant also leads to a decrease in Mdm4-FL expression. To unambiguously determine the physiological impact of the Mdm4-S splice variant, we generated a mouse model with a targeted deletion of the Mdm4 exon 6, thereby creating an obligatory exon skipping. The mutant allele (Mdm4(ΔE6)) prevented the expression of Mdm4-FL, but also led to increased Mdm4-S mRNA levels. Mice homozygous for this allele died during embryonic development, but were rescued by a concomitant p53 deficiency. Furthermore in a hypomorphic p53(ΔP/ΔP) context, the Mdm4(ΔE6) allele led to p53 activation and delayed the growth of oncogene-induced tumors. We next determined the effect of Mdm4(+/ΔE6) heterozygosity in a hypermorphic p53(+/Δ31) genetic background, recently shown to be extremely sensitive to Mdm4 activity. Mdm4(+/ΔE6) p53(+/Δ31) pups were born, but suffered from aplastic anemia and died before weaning, again indicating an increased p53 activity. Our results demonstrate that the main effect of a skipping of Mdm4 exon 6 is not the synthesis of the Mdm4-S protein, but rather a decrease in Mdm4-FL expression. These and other data suggest that increased Mdm4-S mRNA levels might correlate with more aggressive cancers without encoding significant amounts of a potential oncoprotein. Hypotheses that may account for this apparent paradox are discussed.

Année de publication : 2014

Mdm4 loss in mice expressing a p53 hypomorph alters tumor spectrum without improving survival.

Oncogene

Résumé

The p53 pathway is inactivated in most human cancers, and its reactivation in tumors appears as a promising therapeutic strategy. Overexpression of Mdm4, a p53 negative regulator, occurs in a significant fraction of human cancers. Mouse models were used to evaluate the therapeutic potential of strategies against Mdm4, and encouraging results were obtained for tumor cells in which Mdm4 overexpression prevents wild-type p53 to exert its tumor suppressive functions. However, missense mutations in the p53 gene occur in about half of human cancers, and 15% of such mutations lead to the expression of a mutant protein that retains partial activity. In this report, we used mouse models to address the therapeutic potential of strategies against Mdm4 in tumors expressing an hypomorphic p53 mutant. We found that, in an Rb(+/-) background promoting pituitary and thyroid tumors, decreased Mdm4 levels improved the survival of mice expressing wild-type p53, but not that of mice expressing p53(ΔP), a p53 hypomorph lacking the proline-rich domain. Importantly, however, most Rb(+/-) p53(ΔP/ΔP) mice developed pituitary adenomas, but these tumors were rare in Rb(+/-) p53(ΔP/ΔP) Mdm4(-/-) animals, because Mdm4 loss led to increased p21 levels, a suppressor of pituitary tumor growth. On the contrary, Rb(+/-) p53(ΔP/ΔP) and Rb(+/-) p53(ΔP/ΔP) Mdm4(-/-) mice developed anaplastic thyroid carcinomas at equal frequencies. Importantly, wild-type p53 represses the Plk1 gene, which encodes a promising therapeutic target in anaplastic thyroid carcinomas, and this repression is improved when Mdm4 levels are decreased. On the opposite, p53(ΔP) is a mediocre transcriptional repressor that is not improved by Mdm4 loss. In sum, depending on the tumor type, strategies against Mdm4 that work in cells expressing wild-type p53 may not work in cells expressing an hypomorphic p53. Furthermore, p53-mediated transcriptional repression should be considered when evaluating strategies to reactivate p53 in tumors.
Résumé

The clinical importance of tumor suppressor p53 makes it one of the most studied transcription factors. A comparison of mammalian p53 transcriptional repertoires may help identify fundamental principles in genome evolution and better understand cancer processes. Here we summarize mechanisms underlying the divergence of mammalian p53 transcriptional repertoires, with an emphasis on the rapid evolution of fuzzy tandem repeats containing p53 response elements.

Iva Simeonova, Sara Jaber, Irena Draskovic, Boris Bardot, Ming Fang, Rachida Bouarich-Bourimi, Vincent Lejour, Laure Charbonnier, Claire Soudais, Jean-Christophe Bourdon, Michel Huerre, Arturo Londono-Vallejo, Franck Toledo (2013 Feb 15)

Mutant mice lacking the p53 C-terminal domain model telomere syndromes. 
Cell reports : 2046-58 : DOI : 10.1016/j.celrep.2013.05.028

Résumé

Mutations in p53, although frequent in human cancers, have not been implicated in telomere-related syndromes. Here, we show that homozygous mutant mice expressing p53Δ31, a p53 lacking the C-terminal domain, exhibit increased p53 activity and suffer from aplastic anemia and pulmonary fibrosis, hallmarks of syndromes caused by short telomeres. Indeed, p53Δ31/Δ31 mice had short telomeres and other phenotypic traits associated with the telomere disease dyskeratosis congenita and its severe variant the Hoyeraal-Hreidarsson syndrome. Heterozygous p53+/Δ31 mice were only mildly affected, but decreased levels of Mdm4, a negative regulator of p53, led to a dramatic aggravation of their symptoms. Importantly, several genes involved in telomere metabolism were downregulated in p53Δ31/Δ31 cells, including Dyskerin, Rtel1, and Tinf2, which are mutated in dyskeratosis congenita, and Terf1, which is implicated in aplastic anemia. Together, these data reveal that a truncating mutation can activate p53 and that p53 plays a major role in the regulation of telomere metabolism.

Année de publication : 2012

Iva Simeonova, Vincent Lejour, Boris Bardot, Rachida Bouarich-Bourimi, Aurélie Morin, Ming Fang, Laure Charbonnier, Franck Toledo (2012 Nov 23)

Fuzzy tandem repeats containing p53 response elements may define species-specific p53 target genes. 
PLoS genetics : e1002731 : DOI : 10.1371/journal.pgen.1002731

Résumé

Evolutionary forces that shape regulatory networks remain poorly understood. In mammals, the Rb pathway is a classic example of species-specific gene regulation, as a germline
mutation in one Rb allele promotes retinoblastoma in humans, but not in mice. Here we show that p53 transactivates the Retinoblastoma-like 2 (Rbl2) gene to produce p130 in murine, but not human, cells. We found intronic fuzzy tandem repeats containing perfect p53 response elements to be important for this regulation. We next identified two other murine genes regulated by p53 via fuzzy tandem repeats: Ncoa1 and Klhl26. The repeats are poorly conserved in evolution, and the p53-dependent regulation of the murine genes is lost in humans. Our results indicate a role for the rapid evolution of tandem repeats in shaping differences in p53 regulatory networks between mammalian species.