Polymorphisms in p53 and Cancer Therapy:

How Does the p53-R72P Polymorphism Affect the Treatment Outcome?

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Introduction

Cellular tumour antigen p53, also called p53, is codified by the gene *TP53*, located in the chromosome 17 (17p 13.1). This protein acts as a tumour suppressor in human cells due to its ability to induce apoptosis after DNA damage or in stressful cellular conditions. Its suppression is considered a universal hallmark of human cancers.

Some anti-cancer drugs promote apoptosis of tumour cells using the p53 pathway, generally, by inducing DNA damage. This is the reason why mutations and polymorphisms that affect this protein can also influence the response to chemotherapeutic agents.

The objective of this review is to provide information about how polymorphisms in protein p53 can influence the response to cancer treatment. Specifically, the study will focus on the p53-R72P polymorphism.

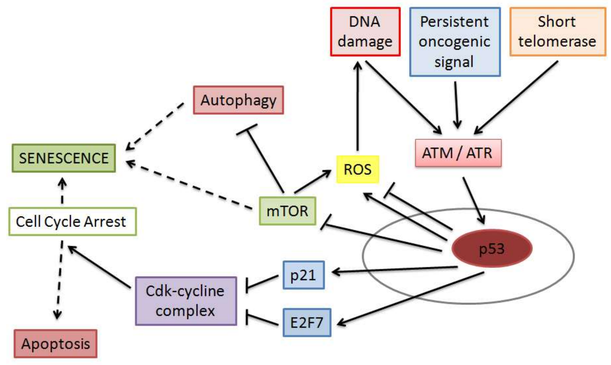

Figure 1. Regulation of the cell cycle by p53 (1).

Materials and Methods

Scientific literature search on **PubMed database** and selected by relevance, journal and publication date. Reviews and research papers were consulted.

Key words: *p53 pathway* + *polymorphism R72P* + *apoptosis* + *treatment* or other similar combinations.

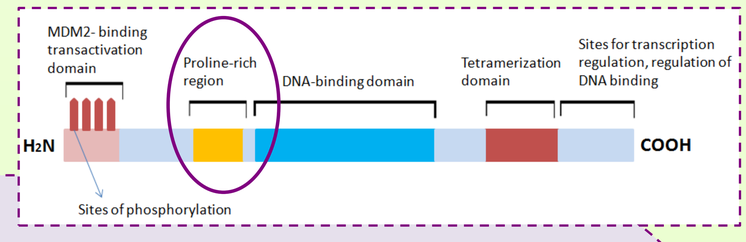

Figure 2. Structure of p53 protein and localization of the proline-rich domain (1).

Relevant results

Polymorphism R72P

- Codon 72, in human populations, has either the sequence CCC, which encodes proline (p53-P72), or CGC, which encodes arginine (p53-R72).
- Comparative sequence analysis suggested that p53-P72 is the ancestral variant, although there are populations which present a high rate of p53-R72 variant.
- Codon 72 is located in the exon 4 of the *TP53* gene, which encodes the proline-rich domain.
- The proline-rich domain is not as conserved as the DNA-binding domain and it is supposed to be necessary for the full apoptotic response mediated by p53.

P53-R72 ↑ apoptotic potential *in vitro*

In vitro studies agree in the fact that p53-R72 variant has a greater apoptosis potential, compared with p53-P72 variant. However, there are different possible explanations for this effect.

1) Enhanced transactivation of *PIGPC1* by p53-R72.

The expression of p53-target genes have been studied depending on the p53 variant and results show controversy.

The only gene that seems to be clearly affected by p53 variants is *PIGPC1* (or *PERP*), which is better transactivated by p53-R72 and is related to apoptosis induction.

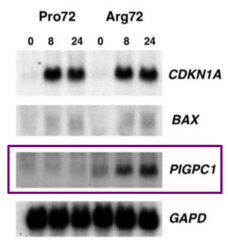

Figure 3. Western-blot analysis. *Adapted from (2).*

2) Greater apoptosis induction in a transcriptional-independent manner by p53-R72.

P53-R72 variant has a better mitochondrial localization, therefore it can activate more efficiently apoptosis (by direct induction of cytochrome c release). This happens due to a better interaction with

- CRM1 (nuclear export protein)
- GRP75 and Hsp60 (mitochondrial import proteins)
- MDM2 (ubiquitin ligase)

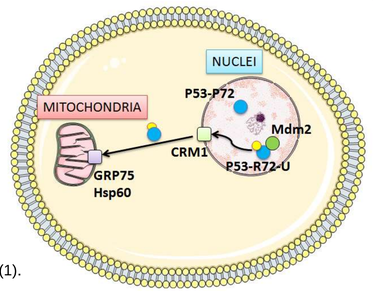

Figure 4. Mitochondrial addressing of p53 variants (1).

3) Better stabilization of p53-R72 variant.

P53-R72 variant has significantly enhanced phosphorylation of residues Ser-6 and Ser-20. This produces a better stabilization of the protein.

In addition, p53-R72 is less ubiquitinated by MDM2 and escapes better from the degradation at proteasome.

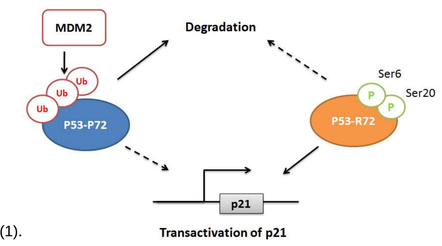

Figure 5. Phosphorylation and degradation patterns of p53 variants (1).

4) p53-R72 has higher affinity to ASPP protein family.

ASPP family have higher affinity to p53-P72 variant, especially iASPP which is an inhibitory protein. P53-R72 is able to escape the binding and inhibition by iASPP.

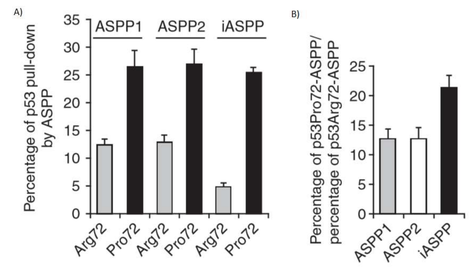

Figure 6. Quantifying of inhibition by ASPP protein family. *Adapted from (3).*

Despite this, studies in human populations are more controversial. It is the case of leukaemia.

Leukaemia → Treatment response from patients with **R72/R72 genotype**

- Better response to Thalidomide therapy.
- ↑ Risk of failure to Imatinib therapy.

Studies reveal that R72/R72 genotype is not always associated with a better response to the treatment as it could be expected. This suggests that the response to different anti-cancer drugs could be affected by the p53-R72P polymorphism differently.

Conclusions

- *In vitro* studies have demonstrated that p53-R72 has greater apoptotic potential, compared to p53-P72. Even though, further *in vivo* studies are required to determine whether other factors can influence differently p53 variants.
- Studies in leukemic patients are more controversial. Larger studies are necessary to ascertain if p53 variants affect distinctively the response to different anti-cancer drugs.
- Further investigation in this field would provide the possibility to adapt cancer treatment to the genetic characteristics of each individual in order to get the best possible treatment outcome.

References

(1) Images have been created for the purpose of the poster.

(2) Dumont P, Leu J, Della Pietra A, George D and Murphy M. (2003). The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nature Genetics*, Vol. 33; 357-65.

(3) Bergamaschi D, Samuels Y, Sullivan A, et al. (2006). iASPP preferentially binds p53 proline-rich region and modulates apoptotic function of codon 72-polymorphic p53. *Nature Genetics*, Vol. 38; 1133-41.