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 (17p13.1). 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.

Relevant results

Polymorphism R72P

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.

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)

3) Better stabilization of p53-R72 variant.

P53-R72 variant has significantly enhanced phosphorylation of residues Ser-6 and Ser-30. This produces a better stabilization of the protein.

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

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

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

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

Leukaemia

Treatment response from patients with R72/R72 genotype

↑ Risk of failure to imatinib therapy.

Better response to Thalidomide therapy.

Conclusions

- In vitro studies have demonstrated that p53-R72 has greater apoptotic potential, compared to p53-R72. Even though, further in vivo studies are required to determine whether other factors can influence differently p53 variants.
- Studies in leukaemic patients are more controversial. Larger studies are necessary to ascertain if p53 variants affect distinctly 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.