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To Die or To Senesce, Alternative Splicing is In Charge?

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Abstract

DNA damage responses are critical determinants of cancer development and age-associated pathogenesis. We have characterized the role of a damage induced alternative splicing variant of human tumor suppressor p53gene, p53beta in IR induced cellular senescence. Global splicing pattern is perturbed after IR which may provide novel therapeutic strategies for cancer treatment and age-related diseases.

Keywords: Alternative splicing; Senescence

Abbreviations: DDR: DNA Damage Response; AS: Alternative Splicing; SASP: Senescence Associated Secretory Phenotype.

Introduction

The integrity of human genome is constantly challenged by agents from a variety of sources (such as radiations, chemicals from the environment; intracellular oxygen radicals; telomere shortening etc.) [1]. Damaged DNA lesions activate cellular DNA damage response (DDR) pathways which alter global gene expression pattern by modulating chromatin structure, transcription and translation programs, and result in temporary cell cycle arrest for repair or apoptosis and/or senesce. Recently, accumulating data suggest that DDR also impacts alternative splicing (AS) program, a highly regulated process evolved in eukaryotes to diversify their transcriptomes and proteomes [2,3]. This observation raises a number of important questions: how is damage signal transduced to trigger AS events? Are alternatively spliced transcripts functionally involved in DDR? Is AS the determinant of cell fate (to arrest, die or to senesce) after stress? Our recent findings tentatively addressed some of the above questions in the context of a specific splice variant of tumor suppressor p53, i.e. p53β in DNA damage induced cellular senescence [4].

Discussion

Different from what have been described by Muñoz et al. [5] that upon UV irradiation, human cell produces a proapoptotic splice variant of BCL-X for p53 independent apoptosis, we have observed that p53β, one of the 12 splice variants of p53 gene is induced by ionizing irradiation, H_2O_2 and other genotoxic drugs such as MMS[4] and participates in cellular senescence caused by damage.p53βvariant is generated by retention of a cryptic exon inside intron9 of p53 gene via alternative splicing

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[6]. The retained intron contains a premature stop codon which leads to a replacement of the entire p53 C-terminal oligomerization domain with a short 10 a tail in p53β protein. Like full length p53, p53β protein maintains the DNA binding domain and still functions as a transcription factor. However, p53β when over expressed, triggers cellular senescence instead of apoptosis seen in full length p53 over expressing cells (unpublished data).

Over expressed p53β activates/represses known p53 target genes in both p53 dependent and independent manners. On the other hand, selective knockout of p53β by CRIPSR-Cas9 system significantly reduces IR-induced senescence markers (such as senescence associated β-galactosidase activity, senescence associated secretory phenotype (SASP), etc.). Cells lacking p53β expression fail to transcriptionally repress negative regulators of aging such as BCL2, SIRT1 etc. but have apoptotic genes unaffected post IR. Interestingly, both BCL2 and SIRT1 epigenetically regulate downstream target gene expression.

Therefore, transient induction of p53β after IR may rapidly spread the instruction inside cells to enter senescence through epigenetic alterations. Recent clinical data demonstrated that high p53β mRNA level in patients with breast cancer or clear renal cell carcinoma is associated with better overall survival [7,8]. Suggesting that the cellular senescence phenotype triggered by p53β may benefit cancer treatment and this p53 splice variant can be a prognostic marker for these patients. Unfortunately, so far, no definitive data have yet provided mechanistic insights of how p53β initiates damage induced senescence program and how full length p53 interplays with p53β in this aspect if any.

Conclusion

In addition to the change of p53 gene splicing, IR altered the splicing pattern of over 100 genes. It is still unclear whether and how any of those damage regulated splicing events contributes to cell fate determination in response to genotoxic insults. Carefully designed RNA seq experiments on damaged tissues and/or cells are needed to identify and confirm novel alternative splice events for further characterization. To die or to senesce is important decision made by cells after stress. Understanding how stress induced splice variants fine tune their relevant network for cellular senescence or apoptosis may reveal potential therapeutic targets and trajectories for aging associated diseases and side effects caused by therapy induced senescence.

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