ROLE OF WERNER SYNDROME PROTEIN IN RESPONSE TO CISPLATIN-INDUCED DNA DAMAGE IN HEPATOCELLULAR CARCINOMA CELLS

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Purpose Werner syndrome protein (WRN) when mutated causes a genetic disorder of premature aging, Werner Syndrome. A number of studies have reported that defects in WRN function are responsible for not only progeria syndrome but also genomic instability through deregulation of DNA repair, replication, recombination, and telomere maintenance. Given the importance of WRN in repair process, we investigated the potential role of WRN in drug responsiveness by means of repair of cisplatin-induced DNA damage in human hepatocellular carcinoma cell lines (HCC).

Methods HCC and HeLa cells were determined endogenous expression level of WRN and the cytotoxicity to cisplatin. The quantification of cisplatin-induced DNA damage in WRN expressing or WRN-deficient cells was measured by γ-H2AX and single cell gel electrophoresis (comet assay). WRN translocation was examined by immunofluorescence microscopy. Protein interactions and co-localization of WRN and SIRT1 were detected by co-immunoprecipitation and immunofluorescence microscopy.

Results We found that cells expressed low levels of WRN respond favorably, whereas cells expressed high levels respond poorly to cisplatin. Forced expression of WRN protein displayed approximately 2-fold increase of cell viability compared to control in response to DNA damage. Detection of DNA damage by γ-H2AX protein level and comet assay revealed that WRN-deficient cells show sustained DNA damage probably due to insufficient DNA repair activity. Finally, we found that WRN interacts with human sirtuin1 (Sirt1) protein in the absence of genotoxic stress and this interaction becomes weaker in the presence of cisplatin.

Conclusion These results suggest that controlling the level of WRN expression is important in drug susceptibility and propose an antagonistic pleiotropy role of WRN in DNA damage response in cancer cells.