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P53 GENE – A NEW TARGET OF ANTICANCER THERAPY

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The p53 gene is a tumour suppressor gene known as guardian of genome act as emergency break and it encodes a protein responsible for regulating the cell cycle, maintaining genomic stability, and preventing tumour formation. It plays a crucial role in responding to DNA damage by inducing cell cycle arrest, DNA repair, or apoptosis (programmed cell death) when necessary. Mutations in the p53 gene can lead to uncontrolled cell growth and contribute to cancer development.

P53 induces cell cycle arrest at the G1/S checkpoint, allowing for DNA repair or triggering apoptosis if damage is irreparable. p53 activates pro-apoptotic genes (e.g., BAX) and inhibits anti-apoptotic genes (e.g., BCL-2), promoting programmed cell death in damaged cells. p53 facilitates the expression of genes involved in DNA repair mechanisms. Approximately 50% of all human tumour have mutations in TP53, leading to the production of a dysfunctional protein that fails to regulate cell growth and survival.

Pharmacological implications that target molecular pathway to restore the normal functions and stabilize the gene. Nutlins are small molecules designed to mimic key amino acids in the p53 N-terminal region and bind to the MDM2 p53-binding pocket, disrupting the p53-MDM2 interaction and leading to p53 stabilization and activation. Nutlin-3 is an mdm2 antagonist that inhibits MDM2-p53 interaction and activates p53

Nutlin-3 has demonstrated potential in treating various cancers, particularly those with p53 pathway dysregulation, including leukaemia, sarcomas, breast cancer, lymphomas, and ovarian cancer. However, it is in phase 1 clinical trials.

A series of recent studies have strengthened the concept that selective, non-genotoxic p53 activation by Nutlin-3 might represent an alternative to the current cytotoxic chemotherapy, in particular for solid, paediatric tumours and for haematological malignancies, which retain a high percentage of p53(wild-type) status at diagnosis.