

Use your knowledge to identify an example where disruption of the cell cycle, mitosis, or DNA replication can result in disease. Please share this example (and your sources) with the class through a discussion post that describes the mutation in detail and its effects on the organism.

Upon infection due to intracellular pathogens, pyroptosis, a form of programmed cell death, is initiated by activating specific caspases: caspase-1/3/4/5 in humans. These caspases recruit several proinflammatory cytokines and the pore-forming protein gasdermin E (GSDME) encoded by the gene GSDME. GSDME expression is upregulated by **p53**, and activated by caspase-3 to form pores. Pore formation causes cell membrane to rupture, contributing to an inflammatory cascade, as more cytokines and various damage-associated molecular pattern (DAMP) molecules (e.g., HMGB-1) are released out of the cell. Due to pathological changes to GSDMD gene, the inflammatory response might not eradicate the pathogens or viruses; chronic form of inflammation follows associated with cancer, neurodegenerative and cardiovascular diseases.

DNA methylation is involved in gene regulation; hypermethylation or hypomethylation favor oncogenesis: abnormal methylation of promoter regions like hypermethylation of the GSDME promoter region ensues inactivation of GSDME gene and has been linked to cancer formation and tumor progression.

Are there any treatments for the disease? If so, please describe the therapeutic approach.

DNA methyltransferase inhibitors (DNMTs) reactivate the genes silenced by methylation and thus restore their function. DNMT inhibitors are classified into nucleoside and non-nucleoside inhibitors [1]:

- *Nucleoside inhibitors* include 5-azacitidine and 5-aza-2'-deoxycytidine (decitabine) which are derived from cytidine and require DNA integration. Azacytidine and decitabine have been effective for MDS and AML types of cancer. Decitabine has been reported as having fewer secondary effects and more active than azacytidine. More recently, RNA interference treatments (siRNA) have been more efficient in not only achieving demethylation but activating a battery of tumor suppressor genes (uPA, MMP2, CXCR4).
- *Non-nucleoside inhibitors* like curcumin and procaine, have various chemical properties and generally bind directly to DNMTs.

[1] C. Gros *et al.*, "DNA methylation inhibitors in cancer: Recent and future approaches," *Biochimie*, vol. 94, no. 11, pp. 2280–2296, Nov. 2012, doi: 10.1016/j.biochi.2012.07.025.