Is DNA repair a potential target for effective therapies against malignant mesothelioma?

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JOURNAL:
Cancer Treat Rev 2020 Nov; 90:102101. doi: 10.1016/j.ctrv.2020.102101. Epub 2020 Aug 25.

BIBLIOGRAPHY:
PMID: 32892058, DOI: 10.1016/j.ctrv.2020.102101

INTRODUCTION

The bibliography review for the latter half of 2020 looks at DNA repair mechanisms as a new potential target for treating malignant pleural mesothelioma (MPM).

DNA damage can be induced by physical and chemical factors, but our bodies can activate repair mechanisms that can overcome and resolve this damage.
Studying and understanding how these mechanisms are activated is of vital importance for us to be able to develop new therapeutic strategies that are more targeted and effective.

This premise has led to an interest in investigating this topic for a disease whose prognosis remains poor to this day.

This bibliography review was recently published as an overview in a scientific journal, which can be accessed at the following link: https://pubmed.ncbi.nlm.nih.gov/32892058/

Is DNA repair a potential target for effective therapies against malignant mesothelioma?

Malignant pleural mesothelioma (MPM) is a rare malignancy mainly caused by asbestos exposure.

Germinal and acquired mutations in genes of DNA repair pathways, in particular of homologous recombination repair, are frequent in MPM.

As we know, germinal mutations are alterations that occur in the cells that give rise to a new life (germ cells); conversely, acquired mutations occur in any other cell of the body (somatic cells). It is important to remember that only germline mutations can be inherited.

There are many ways of repairing DNA damage, and homologous recombination in particular is considered one of the main mechanisms for repairing double-strand breaks. In practice, homologous recombination consists of exchanging the double-strand DNA strands, or segments with an identical or very similar sequence. This exchange allows one double-strand DNA segment to act as a template for repairing lost or damaged information in another double-strand DNA segment.
This mechanism repairs these alterations which may frequently occur in DNA replication cycles, and therefore constitutes an essential repair system for all proliferating cells.

The purpose of this review is to explore and report on the experimental data available, which suggest how an altered DNA repair system can affect the pathogenesis of MPM.

Studies about DNA molecule repair systems are particularly important.
In 2015, the Nobel Chemistry Prize was awarded to three scientists for their work on these repair mechanisms, namely Sweden's Tomas Lindahl, Turkish-born Aziz Sancar, and American Paul Modrich. They are very important methods and pathways for cells and are active 24 hours per day! DNA can be subjected to continuous stress from external sources, such as chemical or physical agents, or from the body itself, for example in the case of specific process errors such as DNA duplication. However, cells are equipped with specific systems to repair this damage to prevent dangerous consequences to the cell and the whole body.

Alterations in the DNA repair mechanisms may mean that there are genetic alterations that are in some way involved in this neoplasm.
Specifically, DNA repair defects appear to be a vulnerability or a limitation of MPM cells.

A potential therapeutic strategy for MPM in the future could be the use of targeted drugs to specifically target these DNA repair deficiencies.

Specifically, these findings may be useful in the future for developing innovative therapies. PARP inhibitors are an example of a therapeutic approach that leverages this hypothesis. These therapies act against tumor cells characterized by defects in the homologous repair process. PARP inhibitors block the action of Parp enzymes, which are molecules involved in the repair of single-strand DNA breaks.
These drugs make it impossible for the neoplastic cells to repair DNA damage, with the resulting increase in double-strand breaks. This results in a continuous loop system because all these alterations that have accumulated in the tumor cells cannot be corrected since the homologous repair system in these cells has been "deactivated", so to speak, by the drugs. This does not affect healthy cells, in which the mechanism is still active and which therefore survive.

This review confirms how vital it is to continue research to further understand the most deeply-seated mechanisms of MPM in order to find treatments that are more targeted and effective.