The Role of Mutations in BRCA1 BRCA2 and Other Factors Involved in Homologous Recombination in Cancer Development and Treatment PARP Inhibitors and Beyond

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Abstract:

Germline mutations in the breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2) lead to the predisposition of breast and ovarian cancer, along with being a high risk factor for various other cancers. Usually, BRCA1 or BRCA2 germline mutations are more likely to be present in patients who possess a strong family history of these diseases. BRCA1 and BRCA2 encode proteins that play a vital role in the repair of the most severe type of DNA damage, DNA double strand breaks. In recent years, BRCA1 and BRCA2 negative cancers have been successfully treated with PARP1 inhibitors, which are synthetically lethal with the BRCA deficiency. The synthetic lethality is based on targeting a DNA damage repair pathway while the alternative DNA damage repair pathway is already defective, subsequently causing increase of unrepaired DNA, genetic instability and apoptosis. BRCA1 and BRCA2 are essential for error-free DNA double strand break repair pathway known as homologous recombination. An enzyme known as poly (ADP-ribose) polymerase 1 (PARP1) is required for efficient repair of DNA single strand breaks. PARP inhibitors affect PARP1 enzymatic activity required for repair of DNA single strand breaks and trap it on DNA which increases the level of DNA damage. The unrepaired DNA single strand breaks and the trapped PARP1 cause increased levels of DNA double strand breaks during replication; since BRCA negative cancers are deficient in homologous recombination, they repair the DNA double strand breaks by error-prone non-homologous end joining pathway, which leads to accumulation of mutations, genome instability and ultimately apoptosis. The discovery of PARP inhibitors led to a paradigm shift in cancer therapy and gained plenty of success. Unfortunately, tumours often acquire resistance to PARP inhibitors. Due to this but also due to the big success of the PARP inhibitors there are efforts to make more inhibitors of other DNA repair proteins that can be used after the resistance to PARP inhibitors develops or in other genetic background. Therefore companies such as, AstraZeneca are developing novel DNA DDR inhibitors that target other factors involved in DNA damage repair, in various cancers to cause synthetic lethality successfully. This thesis summarises the molecular biology behind DNA double strand break repair and synthetic lethality of BRCA1/2 and PARP1 and researches some of the novel DDR inhibitors which are currently under clinical development and which display a bright future for cancer therapy involving synthetic lethality.