EXTENDED ABSTRACT

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PARP-1, from Dissipater to Kingmaker: Selective Induction of Conditional Synthetic Lethality in Cancer cells and the Development of Treatments based on Pharmacological Interference with DNA Repair Machinery

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Abstract:

Malfunctions of the control mechanisms responsible for detecting and/or repairing mutated genes promote transformation and cancer development. To make a virtue of necessity, cancer-related defects in DNA repair processes have become specific targets of novel treatments for certain cancers based on Theodosius Dobzhansky's concept of hybrid lethality whereby mutations in two genes are harmless when they occur singularly but lethal when they occur together. This concept originating from experimental biology is currently being exploited in clinical oncology. Synthetic lethal interactions were first detected exclusively in *BRCA1/2*-negative breast cancer cells exposed to inhibitors of poly(ADP-ribose)polymerase-1. *BRCA1/2*-encoded proteins play important roles in the recognition of double-stranded DNA breaks and their repair by homologous recombination. However, another synthetic lethal interaction was recently detected in human *BRCA1/2*-competent cancer cells, suggesting that synthetic lethality is not restricted to *BRCA*ness but can be also induced in neoplastic cells defective in other components of the DNA repair machinery, alternatively by transient inactivation of BRCA1/2 proteins. Targeted exploitation of characteristic deficiencies in DNA repair mechanisms in specific cancers may thus enable the development of efficient and selective cancer therapies.

Graphical abstract: