SciForschen
Open HUB for Scientific Research

ISSN 2381-3318

International Journal of Cancer Research and Molecular Mechanisms

Review Article | Volume: 3.1 | Open Access

Physiologically Aberrant Homologous Recombination Coupled to Synthetic Lethality and especially Viability Pathways in Carcinogenesis within Contextually Active DNA Synthesis and Cell Cycling

Lawrence M Agius*

Former Member, Department of Pathology, Mater Dei Hospital, University of Malta Medical School, Msida, Republic of Malta

***Corresponding author:** Lawrence M Agius, Former Member of Mater Dei Hospital, 27 Ballarat, Guzeppe Caruana Street, Tal-Virtu, Rabat, Rbt09, Republic of Malta, Tel: 356-21451752; **E-mail:** lawrence.agius@um.edu.mt

Received date: 15 Mar 2017; **Accepted date:** 11 Apr 2017; **Published date:** 18 Apr 2017.

Citation: Agius LM (2017) Physiologically Aberrant Homologous Recombination Coupled to Synthetic Lethality and especially Viability Pathways in Carcinogenesis within Contextually Active DNA Synthesis and Cell Cycling. Int J Cancer Res Mol Mech 3(1): doi http://dx.doi.org/10.16966/2381-3318.133

Abstract

It is proposed that synthetic lethality, whereby the cell life-span is terminated by the appearance of a second modulated gene deletion/mutation, is a governing series of mechanisms that operates to induce, in alternative ways, the emergence of a series of potential carcinogenetic pathways implicating processes of aberrant homologous recombination repair. The stalling of replication forks is symptomatic of mechanistic pathways that significantly induce the creation and progression of double strand breaks inherent to physiologic meiotic pathways. It is further to the disruption of pathways of double strand break repair that the DNA synthesis and cell cycling events further establish the importance of aberrant genetic diversity in tumorigenesis and progression. Synthetic viability, in contrast to synthetic lethality, may potentially aid in the understanding of several steps in the malignant transformation process. It would appear necessary to associate synthetic viability with an essential contrasting process of synthetic lethality, although up to date synthetic viability has been insufficiently emphasized in the discussions regarding the mechanics of carcinogenesis.

The contextual genetic environment in carcinogenesis has been insufficiently characterized and would include the dynamics of an overwhelming contrast of individual gene action with the underlying mechanisms in tumorigenesis of compound events that include proliferation, invasion and spread of individual and grouped malignant cells. It is to be noted that the dimensions of involvement in carcinogenesis transcend implicated actions of individual oncogenes or of suppressor genes in the orchestration of events. In terms of ongoing events in malignant transformation, synthetic viability may be better understood in comparison and in contrast to its opposite model dysfunctionality induced by synthetic lethality of tumor cells once generated.

Keywords: Homologous recombination; Synthetic lethality; Carcinogenesis; DNA synthesis; Cell cycling

Introduction

Increased stemness and cancer cell plasticity have proved important mechanisms of anticancer drug resistance [1]. Synthetic lethality of specific groups of tumor cells is a promising approach mode to selective tumor cell targeting without the involvement of normal cell-induced death pathways. NOTCH signaling is linked to Olaparib (a PARP (Poly ADP Ribose Polymerase) inhibitor) resistance and commonly contributes to PARP inhibitor resistance; transcription factor dynamics effectively identify targets for intervention in chemotherapy-resistant cancers [2]. Combined sigma-2 receptor ligands and PARP inhibitors may synergistically trigger tumor cell death in certain breast cancer cells [3]. PARP inhibitors target poly (ADP-ribose) polymerase to potentiate synthetic lethality, particularly in patients with germ-line mutations in either BRCA1 or BRCA2 [4].

In such context, the combinatorial presence of two-gene mutation, deletion or suppression, as by chemical compounds or small interfering RNAs, constitutes a vital mode of potential control of double-strand break repair in activating tumor cell death pathways. PARP inhibitors inhibit single-stranded DNA repair and induce synthetic lethality in cells with deficient homologous recombination, as in ovarian cancers showing mutation of BRCA1 or 2 [5]. Cell-cycle checkpoints and DNA repair pathways function to maintain genome stability and RAD54B constitutes an ideal target for synthetic lethality with targeting specific genes associated with carcinogenesis [6]. Resection-dependent canonical non-homologous end joining is significantly associated with deletions and translocations in checkpoint G1 phase, with consequent initiating events in tumorigenesis [7]. Activation of reactive oxygen species generation in particular is important in the inhibition of colon cancers [8].

Synthetic Lethality

PARP inhibition acting within a BRCA-deficient context allows for the emergence of synthetic lethality and is particularly applicable in germline BRCA mutations.

Such germline deficiency of BRCA1 and BRCA2 genes and proteins allows for the potential application of such agents as hypoxia, combinatorial chemotherapeutics and the suppression of DNA helicases within the given contexts of defective homologous recombination pathways and also of upstream defects in the Fanconi Anemia pathway. Many efforts have shown the viability of both natural and artificial genetic code variations rather than the development of devastating global proteome modification [9]. Epigenetic regulatory gene mutations and synthetic lethality of cancer cells with loss-of-function mutations are being investigated in many clinical trials [10]. Some 50% of high-grade serous ovarian carcinomas have defective BRCA 1/2 genes involved in homologous recombination [11].

BRCA Mutants

Within-pathway and inter-pathway defects of BRCA and other genes such as other components in the homologous recombination pathways permit the utilization of two gene defects on the same chromosome, in particular, to operate in synchronous fashion and activate tumor cell apoptosis or other forms of cell death. Superoxide dismutase1 operates also as a nuclear transcription factor, as RNA binding protein, as a synthetic lethal interactor and as a signal modulator in glucose metabolism, in distinctly different context of its antioxidant enzyme action [12].

It is further to such potential approaches that clinical trials with inhibitors of PARP (poly (ADP-ribose) polymerase), especially Olaparib, are utilized in the context of BRCA1 and BRCA2 deficits to induce selective targeting of proliferating and progressing carcinogenetic cells. Beta lactase stimulate apoptosis through the mitochondrial pathway and may induce anticancer effect in acute lymphocytic leukaemia cells [13]. Synthetic lethality develops between interacting poly(ADP-ribose) glycohydrolase and BRCA1, BRCA2, PALB2, FAM175A (ABRAXAS) and BARD1 [14]. A prospective targeting of PTEN-deficient tutors is based upon altered glutamine metabolism, DNA replication and DNA damage response [15]. In addition, the retinoblastoma tumor suppressor also binds to DNA double-strand breaks and this depends on E2F1 and ATM kinase and promotes repair via homologous recombination, thus leading to uncontrolled cell proliferation [16].

It is within the spectral utilization of biomarkers such as RAD51 that interfering microRNAs appear to evolve as an induced potential for defective homologous recombination pathways. RAD51D-deficiency shifts double strand break repair toward highly deleterious single-strand annealing and end-joining processes with loss of significant chromosomal segments [17].

Homologous Recombination

Homologous recombination is essentially an error-free repair mechanism that operates within the processes of meiosis; it allows for the repair of double-strand breaks inherent to the meiosis phases I and II that allow repair through sister chromatid pairing. Genetic crossover between homologous chromosomes is involved in meiosis-implicated processes in the creation of diversity in gene constitution. In phase II of meiosis the sister chromatids segregate individually within separate daughter gametes by utilizing the mechanisms involving created unique paternal and maternal genetic determinants in developing genetic diversity.

Hence, meiosis is integrally complexed as a system utilization of homologous recombination in the setting mechanics of genetic crossover that is inherently beneficial in inducing genetic diversity. Such contextual conditioning of meiosis is reflected in the essential functions and dysfunctions of impaired homologous recombination in the formulated emergence of carcinogenetic pathways. Thiazolidinones induce antimicrobial, anti-inflammatory, anti-oxidant and anticancer effects as in glioblastoma [18].

The levels of several enzymes involved in removal of exocyclic adducts from DNA are altered during carcinogenesis [19]. No targeted agents are effective in KRAS-mutant cancer due to activated compensatory pathways resulting from augmented homologous recombination repair signaling; there is increased recruitment of RAD51 to radiation-indued DNA double-strand breaks [20]. Depletion of USP39, a deubiquitinase, causes significantly reduced efficiency in pre-mRNA, and is a critical gene for viability of KRAS-dependent cancer cells [21].

Genetic Diversity

Essential genes are required for viability of the organisms [22]. Mechanistic pathways in inducing genetic diversity during meiosis are hence a core phenomenon in carcinogenetic pathways in a manner that dictates steps in creating tumor formulated genetic pathways within the context of defective double-strand break repair. Double strand breaks are highly cytotoxic DNA lesions and their accurate repair by non-homologous end-joining or homologous recombination determines genomic integrity and is strongly affected by the local chromatin environment [23].

An error-free mechanism such as homologous recombination, in contrast to end-joining strand joining, allows for the prevention of created genetic mutations (double strand breaks) that in turn are required for carcinogenesis to be induced.

Hereditary Breast/Ovarian Tumors

The hereditary breast and ovarian tumors are linked in many patients to a defective homologous recombination series of pathways implicating many of their component mechanistic components either individually or in combination. BRCA1 and BRCA2 mutations are predominantly involved in such a phenomenon. PARP inhibitors induce significant tumor responses in cancer patients carrying germline BRCA1/2 mutations and may be useful also in the treatment of castration-resistant prostate cancer [24]. Aberrant expression of casein kinase 2 is implicated in prostate carcinogenesis and its suppression represses androgen-dependent prostate cancer cells by attenuating the androgen receptor signalling pathway [25].

BRCA2 in particular, but also BRCA1, are implicated in other organ systems of carcinogenesis that include pancreas and prostate, and also lymphomas and leukemias and thymic tumors, as evidenced in animal transgenic models.

Such contexts of carcinogenesis appear linked to other functions and dysfunctions of BRCA genes and proteins in the processes of cell proliferation. Cyclin-dependent kinase mutations have been described in many tumors and have been suggested as a cause of defective DNA repair in ovarian cancer [26].

Cell Proliferation

Proliferation-based creation of double-strand breaks is a significant mechanistic setting for the role of normal homologous recombination pathways in repairing double-strand breaks and in the prevention of carcinogenesis. This double strand DNA break repair by homologous recombination protects genomic stability and involves the formation of the RAD51 nucleofilament, which in turn facilitates the search for a homologous sequence and invasion of the template DNA strand [27]. Regulation of end-processing is critical for accurate DNA repair involving a switch between homologous recombination and non-homologous end joining [28]. Added to this is the under-estimated role of p53 mutations in the hereditary induction of tumorigenesis pathways by BRCA gene defects.

Synthetic viability involves a combination of altered genes that can rescue the lethal effects of a single gene alteration and may account for drug resistance of tumor cells; parameters may include copy number change, whole-exome mutation, expression profile [29]. Such a phenomenon may also account in part for the organ-site selectivity of tumors in hereditary breast and ovarian cancer patients that are BRCA mutant carriers.

Cancer Phenotypes

The basal-like breast cancers in BRCA1 mutant carriers and the luminal breast cancer BRCA2 mutant carriers are classic distinctions that evolve within the progression of homologous recombination dysfunction. It is significant to apply the potential roles of synthetic lethality and of synthetic viability pathways in terms also of dosage phenomena in these pathways and to understand individual molecular components involved in repair of double strand breaks. The construction of transcriptional regulatory

networks may help understand underlying regulatory mechanisms in carcinogenesis [30]. Double strand breaks are significant in inducing stalled replication forks involving, in particular, the G1-S checkpoint in the case of mutated BRCA1 and of the G2-M checkpoint in mutated BRCA2 patients.

Lesion tolerance pathways allow cells to bypass replication-blocking lesions in their genome with the creation of daughter strand gaps opposite replication-blocking lesions; most gaps are then repaired by Homology Directed Gap Repair utilising RecA [31].

Hence, specific dynamics of activation of cell-cycle checkpoints, such as the progression of cell cycling by p21, are essential contextual parameters in the dysfunctional or failed repair by aberrant homologous recombination pathways. High grade serous ovarian carcinoma is molecularly heterogeneous but 50% of them show genetic features of homologous recombination deficiency [32].

BRCA Mutant Carriers

Nuclear localization domains and the DNA binding domain of BRCA1 and BRCA2 proteins underlie dynamics of progression in mutated BRCA carriers and allow for the C-terminal domain in particular to affect also oligomer fold domains to involve aberrant functionality of the homologous recombination processes. The E3 ubiquitin ligase domain of BRCA1 is not implicated in degradation pathways but allows for the interactions of the BRCA1-BALD1 heterodimer complex domain and implicates BALD1 as a significant high-penetrance gene in breast carcinogenesis.

DNA Synthesis and Cell Cycling

Both DNA synthesis, as seen in the subtype homologous recombination mechanism of synthesis-linked end-annealing, and cell proliferation pathways are central characteristics of potential breast carcinogenesis as dictated particularly by the BRCA1 and BRCA2 aberrant pathways. The roles particularly of BRCA1 in gene transcription and cell cycle progression are therefore significant in carcinogenesis within a setting of further aberrant roles of a dysfunctional homologous recombination series of mechanisms.

Homologous recombination may actually occur not only in S/G2 cells where intact sister chromatids are available as donor templates but may implicate also double strand break repair within actively transcribed regions [33].

It would appear that synthetic lethality is significant not only from a therapeutic point of view but also in the creation of aberrant pathways leading to aberrant homologous recombination repair pathways. Within such context, the application of PARP inhibitors and for anti-cancer agents such as radiation and platinum may sensitize cells to undergo cell death pathways, within the further conditioning settings of hypoxia and defects in BRCA1 and BRCA2 mutant carriers.

d,l-Sulforaphane may induce apoptosis in glioblastoma cells via reactive oxygen species-dependent in activation of STAT-3 phosphorylation in a dose- and time-dependent manner [34]. Families of tumor suppressor genes implicated in homologous recombination or mismatch repair may be related to genomic repair and promote carcinogenesis when defective; the hypoxia pathway may be associated with aggressive tumorigenesis and involve tumor-suppressor genes [35].

Concluding Remarks

The coordinating roles of component proteins involved in homologous recombination are core physiologic mechanisms in dealing with double-strand breaks that accompany the genesis not only of tumorigenesis, but also processes that accompany physiologically the genetic crossover in meiosis and thus allow for genetic diversity. During epithelial-mesenchymal transition-mesenchymal epithelial transition, DNA repair involving non-homologous end joining and homologous recombination is critical in reactivation of dormant tumor cells [36].

The implications of mechanistic DNA synthesis and of cell cycle progression come to play essential roles in determining the effective or aberrant homologous recombination repair processes in safeguarding the genome from error-induced mutagenesis and subsequent potential carcinogenesis.

Breast cancer associated (BRCA) genes are critically implicated in DNA repair, and their germline mutations are common in ovarian carcinoma [37]. Many common variants of DNA repair genes may induce small effect sizes that do not impact stringent significance testing criteria [38].

DNA Repair proteins may be involved in more than one repair pathways; opening the possibility of combined targeting of different repair mechanisms like for example non-homologous end joining and base excision repair [39]. Synthetic viability outcomes in synthesis pathways are probably an underestimated system of pathways that may potentially contribute to aggressive cancer phenotypes and may model parameters inherent to dynamic DNA synthesis and cell cycling.

References

1. Yakisich JS, Azad N, Kaushik V, O'Doherty GA, Iyer AK (2017) Nigericin decreases the viability of multi-drug-resistant cancer cells and lung tumorspheres and potentiates the effects of cardiac glycosides. Tumour Biol 39.
2. Decker JT, Hobson EC, Zhang Y, Shin S, Thomas AL, et al. (2017) Systems analysis of dynamic transcription factor activity identifies targets for treatment in olaparib resistant cancer cells. Biotechnol Bioeng.
3. McDonald ES, Mankoff J, Makvandi M, Chu W, Chu Y, et al. (2017) Sigma-2 ligands and PARP inhibitors synergistically trigger cell death in breast cancer cells. Biochem Biophys Res Commun 486: 788-795.
4. Lord CJ, Ashworth A (2017) PARP inhibitors: Synthetic lethality in the clinic Science 355: 1152-1158.
5. Kanjanapan Y, Lheureux S, Oza AM (2017) Niraparib for the treatment of ovarian cancer. Expert Opin Pharmacother 18: 631-640.
6. McAndrew EN, McManus KJ (2017) The enigmatic oncogene and tutor suppressor-like properties of RAD54B: insights into genome instability and cancer. Genes Chromosomes Cancer.
7. Biers R, Steinlage M, Barton O, Juhasz S, Kunzel J, et al. (2017) DNA double-strand break resection occurs during non-homologous end joining in G1 but is distinct from resection during homologous recombination. Mol Cell 65: 671-684.
8. Zhang J, Feng Z, Wang C, Zhou H, Liu W, et al. (2017) Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. Am J Cancer Res 7: 275-288.
9. Lin X, Yu AC, Chan TF (2017) Efforts and challenges in engineering the genetic code. Life (Basel) 7: 2-12.
10. Pfister SX, Ashworth A (2017) Marked for death: targeting epigenetic changes in cancer. Nat Rev Drug Discov 16: 241-263.
11. Mathur D, Stratikopoulos E, Ozturk S, Steinbach N, Pegno S (2017) PTEN regulates glutamine flux to pyrimidine synthesis and sensitivity to dihydroorotate dehydrogenase inhibition. Cancer Discov 7: 380-390.
12. Chung WH (2017) Unraveling new functions superoxide dismutase using yeast model system: beyond its conventional role in superoxide radical scavenging. J Microbiol.

13. Pirahmadi N, Zarghi A, Salimi A, Areni H, Pourahmad J (2017) Beta-lactam structured, 4-(4-(Methylsulfonyl)phenyl)-1-pentyl-3-phenoxyazetidin-2-one: selectively targets cancerous B lymphocyte mitochondria. Anticancer agents Med Chem.

14. Gravelly P, Grant E, Smith KM, James DI, Bryant HE (2017) Specific killing of DNA damage-response deficient cells with inhibitors of poly(ADP-ribose) glycohydrolase. DNA Repair (Amst) 52: 81-91.

15. George E, Kim H, Kepler C, Wenz B, Makvandi M, et al. (2017) A patient-derived-xenograft platform to study BRCA-deficient ovarian cancers. JCI Insight 2: e89760.

16. Velez-Cruz R, Manickavinayaham S, Biswas AK, Clary RW, Premkumar T, et al. (2016) RB localizes to DNA double-strand breaks and promotes DNA end resection and homologous recombination through the recruitment of BRG1. Genes Dev 30: 2500-2512.

17. Kalimutho M, Bain AL, Mukherjee B, Nag P, Nanayakkara DM, et al. (2017) Enhanced dependency of KRAS-mutant colorectal cancer cells on RAD51-dependent homologous recombination repair identified from genetic interactions in *Saccharomyces cerevisiae*. Mol Oncol.

18. da Silveira EF, Azambuja JH, de Carvalho TR, Kunzler A, da Silva DS, et al. (2017) Synthetic 2-aryl-3-((pieridin-1-yl)ethyl)thiazolidin-4-ones exhibit selective in vitro antitumoral activity and inhibit cancer cell growth in a preclinical model of glioblastoma multiforme. Chem Biol Interact 266: 1-9.

19. Reh WA, Naim RS, Lowery MP, Vasquez KM (2016) The homologous recombination protein RAD51D protects the genome from large deletions. Nucleic Acids Res.

20. Tudek B, Zdzalik-Bielecka D, Tudek A, Kosicki K, Fabisiewicz A, et al. (2016) Lipid per oxidation in face of DNA damage, DNA repair and other cellular processes. Free Radic Biol Med S0891-5849: 31079-31086.

21. Fraile JM, Manchado E, Lujambio A, Quesada V, Campos-Iglesias D, et al. (2017) USP39 deubiquitinase is essential for KRAS on-cogene-driven cancer. J Biol Chem 292: 4164-4175.

22. Yu Y, Yang L, Liu Z, Zhu C (2017) Gene essentiality prediction based on fractal features and machine learning. Mol Biosyst 13: 577-584.

23. Hansen RK, Mund A, Poulsen SL, Sandoval M, Klement K, et al. (2016) SCAI promotes DNA double-strand break repair in distinct chromosomal contexts. Nat Cell Biol 18: 1357-1366.

24. Castro E, Mateo J, Olmos D, de Bono JS (2016) Targeting DNA repair: the role of PARP inhibition in the treatment of castration-resistant prostate cancer. Cancer J 22: 353-356.

25. Deng C, Chen J, Guo S, Wang Y, Zhou Q, et al. (2017) CX4945 suppresses the growth of castration-resistant prostate cancer cells by reducing AR-V7 expression. World J Urol.

26. Chila R, Guffanti F, Damia G (2016) Role and therapeutic potential of CDK12 in human cancers. Cancer Treat Rev 50: 83-88.

27. Browning CL, Qin Q, Kelly DF, Prakash R, Vanoli F, et al. (2016) Prolonged particulate hexavalent chromium exposure suppresses homologous recombination repair in human lung cells. Toxicol Sci 153: 70-78.

28. Palermo V, Rinalducci S, Sanchez M, Grillini F, Sommers JA, et al. (2016) CDK1phosphorylates WRN at collapsed replication forks. Nat Commun 7: 12889.

29. Gu Y, Wang R, Han Y, Zhou W, Zhao Z, et al. (2017) A landscape of synthetic viable interactions in cancer. Brief Bioinform.

30. Xu G, Li K, Zhang N, Zhu B, Feng G (2016) Screening driving transcription factors in the processing of gastric cancer. Gastroenterol Res Pract.

31. Fuchs RP (2016) Tolerance of lesions in *E. coli*: Chronological competition between Translesion Synthesis and Damage Avoidance. DNA Repair (Amst) 44: 51-58.

32. Mittempergher L (2016) Genomic Characterization of High-Grade Serous Ovarian Cancer: Dissecting Its Molecular Heterogeneity as a Road Towards Effective Therapeutic Strategies. Curr Oncol Rep 18: 44.

33. Wei L, Levine AS, Lan L (2016) Transcription-coupled homologous recombination after oxidative damage. DNA Repair (Amst) 44: 76-80.

34. Miao Z, Yu F, Ren Y, Yang J (2017) d,l-Sulforaphane Induces ROS-Dependent Apoptosis in Human Gliomablastoma Cells by Inactivating STAT3 Signaling Pathway. Int J Mol Sci 18: E72.

35. Henegan JC Jr, Gomez CR (2016) Heritable Cancer Syndromes Related to the Hypoxia Pathway. Front Oncol 6: 68.

36. Dai Y, Wang L, Tang J, Cao P, Luo Z, et al. (2016) Activation of anaphase-promoting complex by p53 induces a state of dormancy in cancer cells against chemotherapeutic stress. Oncotarget 7: 25478-25492.

37. Unni SK, Schauerhamer MB, Deka R, Tyczynski JE, Fernandes AW, et al. (2016) BRCA testing, treatment patterns and survival in platinum-sensitive recurrent ovarian cancer - an observational cohort study. J Ovarian Res 9: 18.

38. Scarbrough PM, Weber RP, Iversen ES, Brhane Y, Amos CI, et al. (2016) A Cross-Cancer Genetic Association Analysis of the DNA Repair and DNA Damage Signaling Pathways for Lung, Ovary, Prostate, Breast, and Colorectal Cancer. Cancer Epidemiol Biomarkers Prev 25: 193-200.

39. Nikitaki Z, Michalopoulos I, Georgakilas AG (2015) Molecular inhibitors of DNA repair: searching for the ultimate tumor killing weapon. Future Med Chem 7: 1543-1558.