Review

Co-targeting c-Met and DNA double-strand breaks (DSBs): Therapeutic strategies in BRCA-mutated gastric carcinomas

Chrysovalantou Mihailidou a,1, Michalis V. Karamouzis a,*,1, Dimitrios Schizas b, Athanasios G. Papavassiliou a,***

a Molecular Oncology Unit, Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece
b First Department of Surgery, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece

A R T I C L E  I N F O

Article history:
Received 31 July 2017
Accepted 4 September 2017
Available online 7 September 2017

Keywords:
Gastric cancer
Hepatocyte growth factor receptor c-MET
BRCA proteins
HR

A B S T R A C T

Gastric cancer (GC) is a threatening malignancy characterized by heterogeneity. Current therapies use DNA damaging agents, for example, chemotherapeutic agents and ionizing radiation (IR). However, a significant portion of GC patients develops therapeutic resistance to DNA damage response (DDR) - inducing agents. An important mechanism is the stimulation of the c-MET RTK, which is a tyrosine kinase receptor and its ligand hepatocyte growth factor (HGF), which facilitates cell survival by boosting DNA damage repair pathways and via escaping cell cycle arrest. A small subgroup of GC diagnosed patients has defects in BRCA1 and BRCA2 as mediators of DNA repair proteins. BRCA1/2 related-tumors acquire resistance to chemotherapy through the DSBs (DNA double strand breaks) repair pathways. However, BRCA2-deficient cells, are vulnerable to PARP [poly (ADP-ribose) polymerase] inhibitors as the replication forks collapse and the DNA-induced damage is not reversed. Herein, we pose that taking into consideration the defective DDR machinery can trigger GC cell sensitization to therapies via inhibition of DNA repair response. Inhibition of DNA damage response axis may designate cancer cells with BRCAAness (BRCA-mutant cells) more vulnerable to DNA-damaging mediators, such as c-Met inhibitors.

http://dx.doi.org/10.1016/j.biochi.2017.09.001
0300-9084/© 2017 Elsevier B.V. and Société Française de Biochimie et Biologie Moléculaire (SFBBM). All rights reserved.
1. Introduction

Gastric cancer (GC) is a tremendously complex heterogeneous disease with an expanding amount of “driver” mutations having been documented in almost 40% of diagnosed GC [1]. HGF and its receptor c-Met, have a fundamental responsibility in the progression of GC, while its’ expression is related to dismal prospects [2]. Gastric tumors are exhibiting constitutive activation of HER family members intercede resistance to MET targeted therapy in gastric carcinoma cells [3]. Therapeutic agents targeting HGF/MET pathway, such as, milatuzumab and onartuzumab, have been industrialized and evaluated in advanced GC patients [4–6].

The ACRG (Asian Cancer Research Group) had identified four molecular subtypes referred on established genetic characteristics of GCs: MSI (microsatellite instable), MSS (microsatellite stable)/EMT (epithelial-mesenchymal transition), microsatellite stable/tumor protein 53 (TP53)++, and microsatellite stable/tumor protein 53 (TP53)−, subtypes [7]. Also, the TCGA (The Cancer Genome Atlas) network had created a four subtype molecular classification system for GC referred on the underlying genetic profiling of each subtype: Epstein-Barr virus (EBV)−positive, genomically stable, chromosomal instability (CIN), microsatellite-instability (MSI) [8]. Reports have been stated that approximately 8% of GC cases are associated with CIN and MSI, indicating to inadequate DNA mismatch repair [7,8]. Interestingly, tumor cells with abnormalities in DDR apparatus, become obsessed to maintain intact repair pathways through the NHEJ (non-homologous end joining) pathway. NHEJ helps cancer cells to sustain their growth and simultaneously represents a resistance mechanism to DNA-damaging cytotoxic treatments, for example, radiochemotherapy. The up-regulated DNA damage signaling and DNA repair pathways that cancer cells are addicted, may also symbolize cancer’s “Achilles heel” [9]. Inhibition of DNA repair pathways might probably promote a tumor-selective anti-cancer effect by inhibiting the DNA damage repair via utilizing the theory of synthetic lethality. PARP (Poly(ADP-Ribose) polymerase) proteins bind to DNA breaks and recruit DNA repair proteins to the locus of damage. PARP inhibitors promote DSBs, the most harmful structure of DNA damage, exhibiting defective DNA repair mediated by homologous recombination (HR) repair [10]. The BRCA1 and BRCA2 genes that generate tumor suppressor proteins are crucial to minimize genetic alterations and instability for HR [11,12]. Inherited mutations of BRCA genes are linked to high risk for GC [11]. BRCA defective tumors have a tendency to be sensitive to PARP inhibitors [11]. The interaction between PARP and BRCA is an important synthetic lethal method that could be utilized in this subset of GCs [1].

Accumulating evidence suggests that MET signaling is linked to DSBS damage response pathways [13]. Depended on these data, we may identify aberrant MET function conferring acquired resistance to DNA damaging agents (DDAs). This paper demonstrates a synopsis of the c-MET signaling, including its’ task in the progression of GC, and at the same time provides a foundational rationale for targeting this pathway. Furthermore, we discuss the implications of the so far presented clinical data regarding targeting DSBR repair pathways in the management of GC. Additionally, we highlight the significance of linking c-Met and DSBR repair inhibitors with the intention of achieving synergistic therapeutic effects in certain GC patients with BRCAerness.

2. The MET/HGF pathway - an overview

2.1. c-MET/HGF - structure and function

c-MET was initially discovered by the early ‘80s, in an established osteogenic sarcoma cell line treated with the carcinogen compound MNNG (N-methyl-N’-nitroN-nitrosoguanidine), by a chromosomal reorganization that combines two genetic loci, the sequence from the translocated promotor region (TRP) locus on chromosome 1 to a sequence from MET on chromosome 7 with the TRP locus on chromosome 1. Subsequent studies showed that the encoded protein was a receptor tyrosine kinase (RTK), c-MET transcription is induced by HGF and multiple growth factors, producing an oncogenic protein, the c-MET tyrosine kinase [14,15] [Fig. 1A]. Two different experimental approaches characterized the ligand for c-MET; as a mitogen (stimulation of cell growth) factor for hepatocytes and as a motility factor for epithelial cells, while this factor was afterward revealed to be HGF, otherwise called scatter factor (SF) [15,16].

Binding of HGF/SF to its cognate receptor c-MET undergoes tyrosine residue phosphorylation and homodimerization, allowing the recruitment of multiple adaptor proteins and triggering downstream stimulation of the phosphoinositide 3-kinase (PI3K)/AKT, RAS/mitogen-activated protein kinase (MAPK), activation of transcription proteins (STAT), and nuclear factor-kB [17] [Fig. 1B]. In hepatocytes and placental trophoblast cells, c-HGF and MET offer crucial signals for cell growth, cell survival and cell proliferation for the period of development. Accordingly, Hgf or MET knock out embryos died due to severe developmental defects in the placenta and liver [14]. Nevertheless, abnormalities of the c-MET pathway indicate a central role in cell growth, cell proliferation, apoptosis, metastasis and angiogenesis [17,18] [Fig. 1B].

2.2. The impact of HGF/c-MET axis in GC

The significance of c-MET in GC was first identified in GTL-16 gastric carcinoma cells with well-documented c-MET gene [19]. TPR-MET RNA overexpression was identified in precancerous GC lesions [20]. In retrospective studies, elevated expression of c-MET has been reported in about 40% of detecting GC cases and amplification of c-MET gene was reported in 12% of patients. c-Met expression in tumors is associated with the stage of invasion and metastasis and dismal prognosis. Moreover, Hs746T, MKN45, NUGC4 and SNU5 gastric cancer cell lines, have MET amplification and were used in preclinical reports of MET inhibition [21,22]. Reports have been also indicated that SOBP-MET (T07) and LACE1-MET (T20) genes are amplified in GC identified patients [23]. In GC, c-MET gene mutations are rare. The first one reported was in the MET juxtamembrane domain (P1009S) in primary GC [24]. Moreover, after genetic analysis of the cytoplasmic domains of c-MET in Hs746T gastric cancer cell line an exon 14 mutation of c-MET was detected, triggering deletion of the juxtamembrane domain [25]. Therefore, accumulated data have demonstrated a key function of...
c-MET and a reasoning for the development of c-MET inhibitors in GC.

2.3. The development of c-MET axis inhibitors in GC

Several agents targeting c-MET have been categorized, developed and clinically tested in GC patients [Fig. 1B, Table 1]. Monoclonal antibody rilotumumab showed clinical benefit in conditions of survival and response in randomized phase I/II clinical trials. Moreover, rilotumumab plus chemotherapy resulted in a prolonged progression-free survival (PFS) when assessed with chemotherapy only, particularly in diagnosing patients characterized by overexpression of c-MET [5].

In the same vein, a phase III study examining chemotherapy in the presence or absence onartuzumab in patients with metastatic ErbB2-negative and c-MET-positive GC has been terminated due to efficacy problems in the onartuzumab arm [28]. Onartuzumab treatment to first-line mFOLFOX6 did not significantly improve clinical benefits in patients with MET-positive gastrointestinal adenocarcinoma [29]. Additionally, no clear anti-cancer activity was found by the use of selective small molecule c-MET RTK inhibitors, excluded of tumors overexpressing c-MET [30].
randomized phase II study showed that foretinib, an oral multi-
kinase inhibitor targeting c-Met, AXL, TIE-2, RON and VEGFR2 re-
ceptors, can decrease phospho-Met (pMet)/total Met tumor ratio
[31]. However, these findings showed that foretinib lack effective-
ness in a non-selected population of patients with advanced GC
[31,32]. In a randomized phase II trial the action of a non-ATP small-
molecule c-Met inhibitor Tivantinib displayed modest efficacy in
advanced GC patients [33]. Crizotinib is also a potent small mole-
cule c-Met inhibitor modulating c-Met, AKT and ERK signaling axis.
Crizotinib has shown promising antineoplastic actions in c-Met-
amplified GC patients [34]. Application with AMG 337 influenced
the survival of SN5U and Hs746T GC cell lines and demonstrated a
dose-dependent antitumor effectiveness in GC xenograft models
with c-Met gene amplification [22]. Additional tyrosine kinase inhibi-
tors, caboazantinib and golovatinib, which block the autophos-
phorylation of c-Met are being tested [35] [Table 1].

Finally, recent in vitro and in vivo studies investigated selective
c-Met inhibitors. Combination treatment with PF-04217903; a c-
Met inhibitor and PF-04880594; an Raf inhibitor, inhibited phos-
phorylation of ERK and reduced cell growth, suggesting that the
combined application of a c-Met tyrosine kinase inhibitor with a
MEK inhibitor or a B-Raf inhibitor might be more successful in
response to a tumor-resistant tumors that utilize stimulated B-Raf to
evade the inhibition of c-Met signaling in G161 cells [36]. Also, a small-
molecule kinase inhibitor, T-1840383, that targets VEGFRs and c-
Met by inhibiting HGF-stimulated c-Met phosphorylation and
activation of VEGFR has illustrated anticancer action in a peritoneal
dissemination gastric tumor model [37]. Yhuh3813 [38] and KRC-
00715 [39] inhibitors can also reduce c-Met activity and the
downstream signaling pathways, suggesting a potential therapeu-
tic activity in c-Met overexpressing GCs. Strong data establishes
that HGF/c-Met inhibitors might need, not only an evaluation of
HGF/c-MET positivity in tumors but also a deeper understanding of
how and to what level gastric carcinomas are HGF/c-MET linked
with ligand-dependent/or independent signaling axis [22].

3. DNA damage signaling on phenotypes of gastric cancer

3.1. DNA damage response (DDR) processes and consequential
repair pathways

Once the DDR machinery detects DNA damage lesions, it re-
cruits a complicated and entangled network to guarantee that the
transcription and translation actions are paused by preventing
progression from one stage of the cell cycle to the next stage, either
allowing time to the cell to fix the damage or promote cell apoptosis
[40,41]. The major mediators in DDR pathways are members of the
protein kinase PI3K (phosphatidylinositol 3-kinase) family, in-
cluding Rad 3-related (ATR), ataxia-telangiectasia mutated (ATM)
and DNA-dependent protein kinase (DNA-PK). When DNA damage
lesions are detected by a sensor protein, these mediators are
recruited to the site of the damage and simultaneously phosphor-
ylation of downstream proteins, that are involved in the DDR, is
occurred [40]. In addition to these mediators, poly (ADP-ribose)
polymerases (PARPs), are well-documented elements with impor-
tant roles in DDR [42]. PARP-1 and PARP-2 have been proposed to
play a crucial role in single-strand DNA-binding protein [ssDNA-
binding protein (SSB)] by its’ rapid binding to SSB and subsequent
rounds of SSB detection and signaling [43–45]. PARP-3 has newly
been acknowledged to also have a task in facilitating NHEJ [46].
The development of several PARP inhibitors (PARPi) is considered to
have a promising role in cancer therapeutic strategy, as they are
appearing to cause the most lethal structure of DNA damage, the
DSBs [43]. The failure of DSB repair can promote chromosomal
aberrations (genomic instability) and increased tumorigenesis.
Homologous recombination (HR) and nonhomologous end joining
(NHEJ) are the most crucial DSB repair pathways in yeast and higher
eukaryotes [47,48]. DSBs are repaired by NHEJ in the G1 phase,
whereas HR occurs during the end of S and G2 phases of the cell
cycle [Fig. 2].

3.2. DSB repair pathways - associated BRCA genes in GC

BRCA1 and BRCA2 are breast cancer susceptibility proteins, both
mandatory components of HR, although they have different roles in
the assembly of HR. BRCA1 participates in the early embryonic
development, interacts with proteins that have a key role in cell
cycle progression (cell cycle checkpoints) during the end of S and
G2 phases. As a consequence BRCA1 promotes apoptosis in
response to DNA lesions and initiates HR. The main function of
BRCA2 is to interact with BRCA1 upon DNA damage [49,50]. BRCA1
or BRCA2 gene mutations might result in HR silencing. BRCA defi-
ciency leads to genome translocations and aberrant rearrange-
ments, that can develop cancer in normal healthy tissues [51].
Multiple studies suggest a connection between BRCA1/2 mutations
and GC [1,30]. The mutation of the BRCA2 gene, rather than BRCA1
gene, has a greater impact on the risk of developing GC as well as in
the survival of patients. BRCA1/2 abnormalities have been demon-
strated to increase the risk of developing gastric cancer by as much
as six fold increase among first-degree relatives of BRCA1/2 ab-
normalities carriers. The risk is reported to be fourfold higher in
BRCA1 abnormalities carriers and at least twofold higher in BRCA2
abnormalities carriers [11]. However, it has also been proposed that
while there are apparent correlations among ovarian, prostate,
breast, pancreatic and gastric malignancies, it is likely that such associations may be caused by additional factors than having a BRCA1 or BRCA2 gene mutation [10,52].

3.3. DSB repair pathways - associated resistance of GC

The NHEJ mechanism is regulated by the DNA-PK complex consisting of DNA-PKcs, a catalytic subunit, and its heterodimer Ku regulatory subunits [p86 (Ku 80) and p70 (Ku 70)] [Fig. 2]. The DNA-PK complex attaches to DNA ends and functions as a scaffold for additional DNA repair proteins. Activation of DSB repair enzymes contributes to chemotherapy and radiotherapy resistance. Protein levels of Ku and DNAPKcs have been reported to be increased in GC cell lines [53]. Additionally, the level of γH2AX foci, a sensor of DSB repair, remain elevated in gastric cancer cell line N87, treated with radiation [53]. Higher levels of Ku have been established with elevated DNA binding potential and increasing radiosensitization in cancer cells, demonstrating advanced repair [54]. Additionally, it has been documented that over-activation of DSB repair pathways is associated with chemoresistance in GC [55].

3.4. DSB repair pathways - related BRCA as a target

Mutations in X-ray cross complementing group 1 (XRCC1) and in BRCA1 seem to have a positive impact on taxane and cisplatin therapy in GC patients [56]. XRCC1 takes part in the single nucleotide excision repair and it is also a player in the process of the A-NHEJ [57]. It has been also found that in BRCA1 positive carcinomas, the protein XRCC1 has been often deregulated, suggesting that the A-NHEJ pathway may be stimulated in these cells [56]. Moreover, PARP1 gene expression and activation are found in deficient cancer cell lines, which is another hint that components of the A-NHEJ pathway are overactive in BRCA associated tumors [57]. A recent study has shown that BRCA1-deficient cancers were highly sensitive to the inhibition of A-NHEJ [58]. It was also demonstrated that polymerase theta (Polθ) is capable to extend the 3’ ssDNA mediating a combine of template-dependent/independent activities. (This figure is modified from Blakis et al. 2015) [40].
treatment has raised as a potential novel treatment approach in the era of precision cancer therapy [59]. PARP inhibitors have been evaluated in many carcinomas with promising results [60,61]. The success of their use in patients with ovarian cancer has generated great expectations [62]. Although the occurrence of BRCA mutations in GC is small, it has been found that the employ of PARP inhibitors in GC cell lines has additive efficacy combined with chemotherapeutic drugs [63]. A Phase II study (NCT01063517) reported that the olaparib, a PARP inhibitor, when combined with paclitaxel showed a statistically significant survival benefit compared with paclitaxel alone in Asian patients whose tumors had a lower protein expression for ATM with advanced gastric carcinoma. A subsequent Phase III study (GOLD, NCT01924533) assessed the efficacy of olaparib in combination with paclitaxel versus placebo with paclitaxel. It was observed that the overall survival was independent of ATM protein expression status [64].

Based on these findings, clinical studies are examining the application of PARP inhibitors in patients diagnosed with GC and trying to identify reliable predictive molecular factors based on the better understanding of DSB repair pathways [65–67].

4. HGF/c-MET pathway participates in DDR pathways in BRCA-mutated GC

4.1. MET RTK system affects DSB repair in HRR

c-Met holds a crucial role in DDR and especially in signaling pathways which are implicated in DNA repair. HR DSBs repair effectors such as c-Met and RAD51 recombine and V-abl Abelson murine leukemia viral oncogene homolog 1 (ABL) have been suggested [13]. Cells expressing c-Met-mutated variants were treated with c-Met inhibitors. This was accompanied with reduced RAD51 phosphorylation, impairing its' nuclear translocation upon DNA damage [13]. These events cause diminished capacity for DNA repair, as confirmed by the capability of SU11274 to postpone decrease in γH2AX levels, that negatively affects HR-related cellular components [13]. Yu et al. reported that SU11274, a c-Met inhibitor, enhanced the radiosensitivity of DU145 human prostate cancer cell lines mediated by failure of DNA repair capability, abolishment of cell cycle arrest and augmentation of cell death. This research was among the first to prove the success of combining c-Met inhibitors together with radiotherapy in cancer therapeutics [68].

Another study has shown that c-Met inhibition in cancer cells affects the ability to properly execute DSB repair and notably deteriorates HR in a dose-dependent approach, confirming that the observed HR inhibition is c-Met-dependent. More mechanistic insights showed that c-Met inhibition influences the pattern of the RAD51–BRCA2 complex, which is critical for error-free HR repair of double strand DNA damage, apparently upon Rad51 down-regulation and impaired translocation into the nucleus [69]. A synergistic model of interaction between c-Met inhibition combined with ionizing radiation was adequate, to augment γH2AX levels in GTL-16, human gastric adenocarcinoma cells, strongly representing the accumulation of double-strand DNA breaks [70]. Finally, c-Met inhibition diminishes the stimulation of CHK1, ATR and CDC25B in GTL-16 cells as well as nullify an associated DNA damage–intra-S-phase cell-cycle arrest. These data suggest that c-Met inhibition represents a significant damage-checkpoint that might facilitate DNA-defective cells to escape cell cycle arrest before a repair is accomplished [71].

During cellular DSB response, chromatin undergoes rearrangement discriminated by H2AX.Ser139 phosphorylation (γ-H2AX). γH2AX serves as a component between the equilibrium of DNA repair and apoptosis response, through a post-translational change, phosphorylation of tyrosine 142, being able to affect the recruitment to γ-H2AX of functional repair/survival complexes. Combinations of c-Met-targeted therapy and irradiation, increased γH2AX tyrosine phosphorylation levels and pro-apoptotic kinase JNK1 levels, providing an additional link to c-Met inhibitors and DDR machinery [72,73]. Liu et al. have revealed that such combinations can suppress HGF–induced cell proliferation and phosphorylation of the ERK1/2, AKT, and STAT3 [74], enhance the formation of DNA double strand breaks and probably alleviate tumor hypoxia [75]. Baccio and his research team have confirmed that radiation influence the activity and expression levels of c-Met via the ATM-NF-κB signaling pathway resulted in cell invasion. Therefore, c-Met inhibition increase tumor cell radiosensitivity [76]. These results indicate the function of c-Met in the DDR apparatus and the causality of its' targeting, in order to increase cancer cells sensitivity to DNA-damaging mediators.

4.2. MET RTK system could affect DNA repair in BRCA-deficient cancer cells in HRR

PARP inhibitors are successfully eliminated tumors defective in BRCA/2 genes due to the model of synthetic lethality [77–79]. Earlier studies have revealed that PARP inhibitors activate γ-H2AX and Foci formation in PARP1 deficient cells, as a consequence of their deficiency in homologous recombination, are intensely susceptible to PARP inhibitors, resulting in DSBs in S-phase and no longer repaired [80]. This renders BRCA-deficient cells susceptible to agents, for instance, PARP inhibitors, that are provisionally ‘synthetic lethal’ through their principal repair defect [82–84]. Developing drugs, such as an inhibitor of DNA repair that constantly kill cancer cells, in the lack of an exogenous DNA-damaging factor, illustrates a novel model.

Homologous recombination (HR) also plays a critical role in the maintenance of genome integrity. RAD52 is an essential member of the HR pathway [83]. c-Met activation affects Rad51 regulation and translocation into the nucleus [69]. Combinations of RAD52 mutations with mutations in genes like RAD51C BRCA1/2, PALB2 are lethal [83]. Accordingly, small molecule inhibitors of RAD52 might block the biological and chemical functions of RAD52 and the endless growth of BRCA1-deficient cells, representing a potentially important target for GC therapy [85]. The role of c-Met in the other two DSB repair pathways C-NHEJ and alternative NHEJ remains uncertain at the moment. Further research will be needed to sensitize tumor cells to currently DDR.

4.3. DSB repair and c-Met as therapeutic co-targets in BRCA-mutated GCs

Deregulated HGF/MET signaling is observed in an extensive range of malignancies, including GC [2]. While the current findings report that signaling via the cMET protects tumor cells from DNA damage [70], cellular events closely linking MET to the DDR machinery remain currently unknown. New insights into these biological networks evolve as an emerging necessity.

PARP inhibitors are licensed by the FDA for cancer treatment with BRCA mutation carriers. Importantly, recent studies show evidence that BRCA1-deficient cells may develop resistance during this treatment, partly via correcting their defect in HR-mediated DSB repair, or via synthetic viable loss of 53BP1 or through genetic reversion mutations in BRCA1. In addition, phosphorylation of PARP1 at Tyr907 increases PARP1 enzymatic activity and eliminates binding to a PARP inhibitor, capable of developing cancer resistant to PARP inhibitors [61,62,81]. Du et al. have examined the effects of the dual inhibition of c-Met and PARP, against cancer. Both combinations exhibited a synergistic inhibitory effect on clonogenic cell
survival in MDA-MB-231, BT549 and HCC1937 TNBC cells. Notably, combination therapy in xenograft tumor models using MDA-MB-231, significantly abrogated tumor growth, increased apoptosis, reduced cell proliferation and superior DNA damage (γ-H2AX marker) was observed, compared to either inhibitor alone. Also, synergistic cell growth inhibition was assessed in MCF-7/c-Met and c-Met-expressing NSCLC (non-small cell lung cancer) xenograft tumor models. These findings set the hypothesis that this combination therapy may be significantly more effective than PARP inhibition alone, regardless of the cancer stage and type [81].

Francica et al. [86] reported that MET inhibitors, in MET-overexpressing gastric tumors, trigger the ability of cancer cells to fix the damaged DNA and to enhance the effectiveness of the undergoing radiation therapy. Thus, it seems rational to assess whether the synergistic inhibition of DNA DSB repair via HR or NHEJ and c-Met simultaneously, reveals an efficient therapy in BRCA-mutated gastric carcinomas [Fig. 3].

5. Conclusion

c-MET/HGF pathway has become a tempting candidate against GC. In addition to its own unique effects, c-Met promotes cell migration and proliferation by boosting DNA damage repair pathways and escaping cell cycle arrest. Numerous studies have confirmed that a subgroup of GC patients develops BRCA deficiency. Recently, research indicates that BRCA-deficient tumors are more vulnerable to DNA damage since replicating damaged DNA increase the risk of cell death. We, therefore, propose that co-inhibition of HGF/c-Met with DNA damage response proteins may represent a hopeful therapeutic approach for c-Met-expressing gastric carcinomas with BRCA-ness.

Conflict of interest

No potential conflicts of interest were disclosed.

References


C. Mihailidou et al. / Biochimie 142 (2017) 135–143