Biochimie 142 (2017) 135–143

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

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

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ARTICLE INFO

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

ABSTRACT

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 BRCAness (BRCA-mutant cells) more vulnerable to DNA-damaging mediators, such as c-Met inhibitors.

Contents

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http://dx.doi.org/10.1016/j.biochi.2017.09.001

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 rilotumumab 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 anticancer 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 DSB repair pathways in the management of GC. Additionally, we highlight the significance of linking c-Met and DSBs repair inhibitors with the intention of achieving synergistic therapeutic effects in certain GC patients with BRCAness.

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′-nitronitrosoguanidine), by a chromosomal reorganization that combines two genetic loci, the sequence from the translocated promoter 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-κB [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 knockout* 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