# The Met tyrosine kinase receptor as a therapeutic target and a potential cancer stem cell factor responsible for therapy resistance (Review)

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**Abstract.** The MET tyrosine kinase receptor plays an important role during tumor development and progression being responsible for proliferation, morphogenetic transformation, cell motility and invasiveness. High expression of the MET receptor has been shown to correlate with increased tumor growth and metastasis, poor prognosis and resistance to radiotherapy. Moreover, MET expression and activation has been shown to be associated with therapy resistance. The occurrence of resistance to targeted therapy might be related to the presence of cancer stem cells (CSCs). CSCs are a subpopulation of cells in the tumor that possess the ability of self-renewal, clonogenicity, radioresistance and self-sustained protection from apoptosis. Recently, MET has been postulated as an essential factor supporting the functional stem cell phenotype in some tumors and as a CSC factor is believed to be responsible for therapy resistance. This review presents the results from recent studies identifying MET as a potential marker of CSCs and tumor initiating cells, demonstrating pivotal role of MET in supporting stem cell phenotype and indicating the role of MET in acquiring resistance to antitumor therapy.

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*Abbreviations:* AML, acute myeloid leukemia; CCIC, colorectal cancer initiating cells; CICs, cancer-initiating cells; CSCs, cancer stem cells; EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; GSCs, glioblastoma stem cells; HER, human epidermal receptor; HGF, hepatocyte growth factor; HNSCC, human head and neck squamous cell carcinoma; NOD/SCID, non-obese diabetic/severe combined immunodeficiency; NSCLC, non-small cell lung cancer; RTKs, receptor tyrosine kinases; SCs, stem cells; SCID, severe combined immune-deficient; SF, scatter factor; TKIs, tyrosine kinase inhibitors

*Key words:* MET receptor, c-met, cancer stem cells, targeted therapy, therapy resistance

**Contents**



## Introduction

The major problem in the fight against cancer is metastatic disease and growing resistance to available therapies. Therefore, it is important to understand the mechanisms responsible for the emergence and development of tumors to establish novel molecular-based strategies to enable a more successful destruction of aggressive tumor disease.

One of the well-known factors connected with tumor growth and metastasis is the MET receptor (1). The MET tyrosine kinase receptor together with its ligand, hepatocyte growth factor (HGF) also known as scatter factor (SF), was identified to play a key role during embriogenesis (2-5). At the early stages of development, HGF and MET, are expressed in endoderm and mesoderm and act in an autocrine manner (2). Later, during organogenesis, MET is expressed in epithelial cells of many organs (liver, kidney, lung and skin), whereas HGF in mesenchymal cells (2). Moreover, MET is expressed in some myoblasts and neuronal precursors, and contributes to the development of muscular and nervous structures (2,5). Crucial role of MET during embryogenesis was confirmed in experiments with knockout mice that died in utero at E15 (4). HGF/MET axis is also important in the process of skin, liver and kidney regeneration (6,7).

Ligand-induced MET activation leads to phosphorylation of tyrosine residues (Tyr1230, Tyr1234 and Tyr1235) in the kinase domain of the receptor and allows binding of effector proteins, such as Gab1, Grb2, Shc, PI3K, Src, STAT3 or

PLCγ (8). It activates mainly the RAS-MAPK and PI3K-AKT pathways leading to pleiotropic biological effects on various target cells including the induction of cell proliferation, morphogenetic transformation, cell motility and invasiveness under both normal and pathological conditions (9-11). The last findings also indicate that MET is able to act through c-Abl and p-38-MAPK to induce p53 phosphorylation and promotes cell survival (12).

The MET receptor is considered a good candidate for targeted therapies (13). However, although MET seems to be a very good target in development of new strategies, both *in vitro* and *in vivo* studies have shown that prolonged usage of tyrosine kinase inhibitors results in resistance to treatment and MET has been proposed as a new factor responsible for therapy resistance (14,15). Resistance to treatment is the major limitation and problem of contemporary oncology. This phenomenon may be partially related to the presence of cancer stem cells (CSCs).

The isolation and characterization of CSCs was begun by Lapidot and colleagues (16) who showed that a small population of human acute myeloid leukemic (AML) cells, were capable of initiating human AML after transplantation into severe combined immune-deficient (SCID) mice (16). CSCs as defined by the American Association for Cancer Research (AACR) workshop on CSCs, are a subpopulation of cells in the tumor that have self-renewal capacity and can give rise to heterogeneous cancer cells that comprise the tumor (17). CSCs are defined as cancer-initiating cells (CICs) as well, because of their property of retaining long-term self-renewal ability *in vitro*, and driving clonal expansion in xenotransplantation assays (18,19). CSCs are inherently resistant to radiochemotherapy owing to efficient DNA repair and self-sustained protection from apoptosis (18,20,21). Growing evidence shows that CSCs are responsible for resistance to conventional therapies, and thus, are the most likely cause of tumor recurrence (22). It has been postulated that stemness features of CSCs allow them to escape conventional antitumor therapy and maintain minimal residual disease, resulting in tumor relapse (23). Recently, it has been shown, in samples from patient tumors, that CSC marker expression is associated with a poorer clinical results and may have prognostic value (24-26). However, identifying markers, that could better characterize and isolate a population of CSCs for some tumors, remains challenging and recently, several potential candidates have been proposed.

The MET receptor has been postulated as an essential factor responsible for the functional cancer stem cell phenotype in some tumors and as a CSC factor is believed to be responsible for therapy resistance. The present review provides examples that MET may be a potential cancer stem cell factor responsible for drug resistance and tumor relapse.

## 2. MET receptor in cancer

In the early 1990s it was shown that mouse and human cell lines with overexpression of HGF and/or MET become tumorigenic and metastatic in nude mice and the level of MET and HGF directly correlates with invasiveness and metastatic process (27). Nowadays, it is well documented that deregulation of MET expression and activity is characteristic for multiple cancer types and is a key event underlying tumor progression and metastasis (1). A large number of studies show that HGF and/or MET are frequently expressed in human carcinomas and in other types of solid tumors and in their metastases (1). MET overexpression has been demonstrated in a variety of tumors, including lung, breast, ovary, cervical, kidney, colon, thyroid, liver, gastric carcinomas, glioma and osteosarcoma (28-41). Activating point mutations of *MET* occur in sporadic and inherited human renal carcinomas, hepatocellular carcinomas and several other cancer types (33,35,42).

Moreover, in case of MET and/or its ligand HGF, overexpression or misexpression often correlates with poor prognosis (1,31,33,37). MET was shown to be more frequently amplified in advanced stage of colorectal and gastric cancers suggesting its role in the metastatic process of malignant progression (33,43,44). It was demonstrated for human head and neck cancers that activating mutations of MET are clonally selected during the process of metastasis and its level increased from 2% in the primary tumors to 50% in the metastases (45). Interestingly enough, MET expression may vary within the same tumor. As Pennacchietti and colleagues showed (46) both in carcinoma and sarcoma cells hypoxia promotes the expression of met protooncogene and hypoxic areas overexpress the MET receptor leading to activation of invasive growth (46). It was also shown that MET-positive cells within glioblastoma are located close to the nearest blood vessels (47). MET positive cells co-express glioblastoma stem cell markers, CD133 and CD15, compared with MET-negative cells. Moreover, MET expression was efficient in inducing tumor formation regardless of CD133 expression (47). CD133 glycoprotein has been widely used to purify hematopoietic stem and progenitor cells and it was shown to define a subpopulation of brain tumor cells with significantly increased capacity for tumor initiation in xenograft models (48,49). The authors suggest that MET signaling was responsible for glioblastoma stem cell maintenance, migration and resistance to radiation (47).

The group of Comoglio (50) revealed that MET could be genetically selected for the long-term maintenance of the primary transformed phenotype, and some tumors were dependent on sustained MET activity for their growth and survival (51). Moreover, they proposed that MET overexpression in tumors is not only due to transcriptional induction at single-cell level but also expansion of the stem/progenitor subpopulation of cells inherently expressing MET (52). It has been also shown that cells displaying high *MET* copy number, overexpression of this receptor and ligand-independent constitutive activation, are addicted to this oncogene and responsive to anti-MET drugs (53-56).

## 3. MET receptor as a prognostic marker

High MET expression pattern is currently associated with increased tumor growth rate and metastasis, poor prognosis and resistance to radiotherapy (57-59). MET overexpression has been postulated as a prognostic factor in lung (60,61), breast (62), head and neck (63), gastric (64), ovarian (65) and clear cell renal cell carcinoma (66). MET overexpression is also associated with poor prognosis and tumor invasiveness in glioblastoma patients (67,68). It has been demonstrated that enhanced level of MET in primary colorectal cancer may

predict tumor invasion and metastatic process (69). High MET protein level and its activation, resulting from *MET* amplification, have been reported as associated with a poor prognosis in colorectal and gastric cancers (33,44,64). It was also shown that MET overexpression was significantly associated with worse 3- and 5-year overall survival, progression-free survival and distant metastases in cervical cancer patients (70). Similar results were obtained after a follow-up of 50 months for multiple myeloma patients, where high MET mRNA expression characterized a worse progression-free and overall survival (71). Moreover, co-expression of the MET receptor together with CD47 was proposed as a novel prognostic factor for survival of patients suffering from luminal breast cancer (72). Another study proposed the MET receptor as independent predictor of decreased 5-year survival of patients with invasive ductal breast carcinoma (62). Similar results were obtained by the Edakuni group (73) and showed correlation between co-expression of HGF and MET in breast cancer, histologic grade and reduced patient survival (73). All these examples highlight MET as a prognostic factor whose presence and activity is important for the overall survival and development of metastatic disease in tumor patients.

## 4. Resistance to MET inhibitors

The HGF-MET pathway has been proven to be an attractive drug target for antitumor therapies. Several monoclonal antibodies or small molecules targeting HGF or MET have been discovered and used in monotherapy, in combination with other targeted therapy or with chemotherapy (13). Despite encouraging results involving the use of MET inhibitors in the laboratory and in clinical trials, as well as in studies with other RTK inhibitors, it has been suggested that resistance will develop even in the subset of cancers that initially derive clinical benefits (14,15). Several possible mechanisms of resistance to MET inhibitors such as, *MET* point mutations, amplification or *MET* gene overexpression, activation of MET parallel pathways or amplification of the *KRAS* gene, have been described (74-76). Cepero and colleagues (74) established cell lines resistant to long-term treatment with MET inhibitors and showed that prolonged exposure to increasing doses of c-MET inhibitors leads to amplification, overexpression and activation of wild-type *MET* and *KRAS* in gastric cell lines. Furthermore, they observed strong activation of the mitogen-activated protein kinase (MAPK) pathway (74).

Another mechanism of resistance showed that cells developed resistance by acquired mutation in the MET activation loop or activated epidermal growth factor receptor pathway due to increased expression of transforming growth factor α (75). Two other studies showed that overexpression of HER family members in gastric carcinoma cells and non-small cell lung cancer cells are responsible for acquired resistance to MET kinase inhibitors (76,77). The authors concluded that cells carrying high MET copy number will undergo an oncogenic switch that will create an ERBB tyrosine kinase dependency (76,77).

A recent study revealed the acquisition of secondary resistance to MET monoclonal antibodies. In a very elegant study of Martin and coworkers (78), MET-addicted lung cancer cells continuously treated with MET monoclonal antibody became resistant to treatment, as a result of an increase of *MET* gene copy number and MET overexpression. However, MET antibody resistant cells were sensitive to MET-specific small tyrosine kinase inhibitors (TKIs) and acquired drug-dependence. Moreover, cells resistant to MET TKIs can still be sensitive to treatment with the antibody. The authors suggest that a discontinuous, combined treatment by antibodies and chemical kinase inhibitors may increase the clinical response and bypass resistance to anti-MET targeted therapies through synergistic effect on tumor cells (78). The results demonstrate that despite the acquired resistance to one type of inhibitors, it is possible to use another type and achieve good therapeutic effects. Furthermore, these results show the importance of MET as a therapeutic target.

## 5. MET inhibition overcomes drug resistance

Both *in vitro* and *in vivo* studies have shown that prolonged treatment with tyrosine kinases inhibitors (TKIs) results in resistance to treatment and MET receptor has been proposed as a new factor responsible for resistance to targeted therapies including epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), human epidermal receptor 2 (HER-2) and B-raf (BRAF) inhibitors (14,15). This phenomenon was demonstrated for the first time in lung cancers driven by mutations in the EGF receptor (79). In the study, 22% of patients who developed resistance to gefinitib, selective inhibitor of EGFR kinase, demonstrated amplification of the *MET* proto-oncogene. The amplification of *MET* driven ERBB3 (Erb-B2 receptor tyrosine kinase 3) dependent activation of PI3K, a pathway specific to the EGFR/ERBB family receptors, suggests that *MET* amplification may promote drug resistance in other ERBB-driven cancers (79). It is worth noting, that inhibition of MET signaling restored sensitivity to gefitinib (79,80). Another study reported that MET, as an RTK frequently coexpressed with Her2, in Her2 positive breast cancer, contributes to trastuzumab resistance of Her2-overexpressing breast cancer cells through sustained AKT activation (81).

HGF-MET axis was also shown to be involved in resistance to anti-VEGR therapy. In tumors resistant to inhibitor of VEGF pathway, sunitinib, after treatment with highly selective MET inhibitor, PF-04217903, together with sunitinib, tumor growth was inhibited (82). The study on renal cell carcinoma model demonstrated that the MET receptor is involved in sunitinib acquired resistance (83). Combined treatment with the VEGF and MET inhibitors induced prolonged survival and inhibited tumor growth in mice giving hope for potential therapeutic use in the clinical treatment (83).

In light of these data MET seems to be a very good target for tumors resistant to tyrosine kinase targeted therapies. However, the activity and function of the receptor depend on the cell type and heterogeneity of tumors. Recent studies connect the presence of the MET receptor with cancer stem cell phenotype.

## 6. MET receptor and stem cells

It has been demonstrated that the MET receptor is expressed in stem/progenitor cells in various types of adult normal tissues and maintains stem cell properties. The MET receptor

was considered as a putative pancreatic stem/progenitor cell marker in adult mouse pancreas (84,85). In the developing liver, cells expressing MET can form stem cell colonies *in vitro* and migrate and differentiate into liver parenchymal cells and cholangiocytes when they were transplanted into the spleen or liver of mice subjected to liver injury (86). The essential role of the HGF/MET axis in hepatocyte-mediated liver regeneration, was shown by Ishikawa and colleagues with the use of MET knockout mice (87). In the liver, the MET receptor supported survival, proliferation, sphere formation and differentiation properties of oval cells (87). Another study showed that MET, in cardiac stem cells and early committed cells, is responsible for proliferation, survival, migration and regeneration of the infracted myocardium and improvement of ventricular function (88).

The study by Chmielowiec *et al* (89) underlined a fundamental role of MET during regenerative process in the adult skin. The authors demonstrated that MET signaling not only controls growth and migration of keratinocytes during embryogenesis but is also essential for the generation of the hyperproliferative epithelium in skin wounds (89). It was also demonstrated that MET signaling is a key mechanism in maintaining stem cell niche in brain important for neural stem cell growth and self-renewal (90).

## 7. MET receptor and cancer stem cells

Recently, the MET receptor has been postulated as an essential factor responsible for the functional CSCs phenotype in some tumors. It was reported that MET expression was associated with glioblastoma stem cells (GSCs) identified by prospective isolation from fresh tumors (47) or with neurospheres endowed with specific genetic/molecular features (91). Furthermore, MET was considered to play a central role in maintaining CSC populations in human glioblastoma multiforme (GBM), suggesting a link between MET signaling and CSCs (91,92). Other studies, on GBM cell subpopulations, showed that only cells expressing high level of MET retained clonogenic, tumorigenic and radioresistant properties, features of CSCs (47,91). The authors demonstrated pivotal role of MET in supporting the pool of GBM SCs (47). They used freshly isolated patient-derived GBM cells and provided evidence suggesting that MET plays critical role in SC maintenance, migration and resistance to radiation (47). Subpopulation with high MET level displayed enhanced kinetics growth and was highly tumorigenic *in vivo* as well (47,91). Moreover, only small population of GBM cells has been shown to be positive for the MET receptor and to contain amplification of *MET,* independent of other RTKs (93,94). The study by Li *et al* (95) involved MET as a novel, functional, stem cell marker for pancreatic adenocarcinoma. The authors identified the population with a high expression of MET and suggested that the receptor regulates SCs proliferation, cell renewal and has the ability to form tumors in NOD/SCID mice (95). This study also showed that the use of the MET inhibitor or small hairpin RNAs in pancreatic adenocarcinoma significantly inhibited tumor sphere formation and self-renewal capacity (95). In pancreatic tumors established in NOD SCID mice, MET inhibition decreased tumor growth, reduced the population of CSCs and prevented the development of metastases (95). The study of Sun and Wang (96) on human head and neck squamous cell carcinoma (HNSCC) demonstrated that MET expressing cells have the capacity for self-renewal (96). Furthermore, the MET receptor was responsible for tumor formation and metastatic process in NOD/SCID mice and cisplatin resistance (96). It was also shown that the HGF/MET axis regulates stem- like phenotype in human prostate cancer (97). The study of Gastaldi and coworkers (98) emphasized the role of MET in breast tumorigenesis. The authors showed that MET acts as a critical regulator of luminal cell proliferation and differentiation in the context of murine mammary morphogenesis (98). Moreover, the authors presented that MET is preferentially expressed in luminal progenitors and its activation stimulates clonogenic activity *in vitro*, confers repopulating potential *in vivo* and promotes aberrant branching morphogenesis (98). Table I summarizes the data with reference to MET expression correlated with cancer stem cell phenotype.

Our study on rhabdomyosarcoma showed that silencing of the MET receptor stimulates tumor cell differentiation and activation of MET signaling may be the cause of its development and progression (99,100). We have also demonstrated that cervical cancer cells depend on sustained MET activity for their growth and survival and downregulation of MET decreased tumor growth and forced tumor differentiation *in vivo* (101). Our observation on cervical cancer patient samples revealed that low level of MET accompanied low-grade squamous intraepithelial lesion, whereas increased heavily in high-grade squamous intraepithelial lesion and invasive carcinoma (101) (Fig. 1).

Table I. MET expression and cancer stem cell phenotype.

| Tumor type | Refs. |
|---|---|
| Breast cancer | (98) |
| Colon cancer | (115) |
| Glioblastoma | (47,91,92,103) |
| Head and neck | (96) |
| Pancreatic adenocarcinoma | (95) |
| Prostate cancer | (97) |

Association of MET expression with the stem/progenitor status.

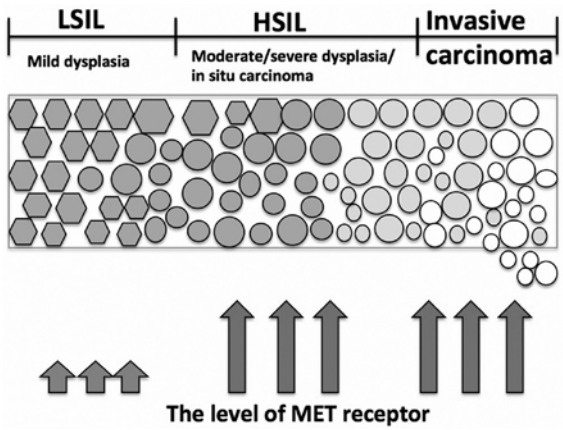


Figure 1. Immunohistochemical staining showed marked increase in the level of MET receptor in samples from cervical cancer patients (101).

Table II. MET expression and cancer stem cell factors.

| Stem cell marker | Function | Tumor type | Refs. |
|---|---|---|---|
| Sox2 | Transcription factor | Glioblastoma pancreatic cancer | (92,104) |
| Klf4 | Transcription factor | Glioblastoma | (92,103) |
| c-Myc | Transcription factor | Glioblastoma | (92) |
| Oct4 | Transcription factor | Glioblastoma | (92,103) |
| Nanog | Transcription factor | Glioblastoma | (92,103) |
| CD49b | $\alpha_2$ integrin | Prostate cancer | (97) |
| CD49f | $\alpha_6$ integrin subunit | Prostate cancer | (97) |
| CD133 | Stem cell biomarker | Pancreatic cancer | (104) |
| CXCR4 | Chemokine receptor | Rhabdomyosarcoma, cervical carcinoma | (99,101) |

Correlation of MET receptor and stem/progenitor factors.

## 8. MET receptor and stem cell markers

The MET receptor not only supports stem-like phenotype of cancer cells but also affects the expression and activity of stem cell markers. It has been shown that MET signaling can regulate glioma subpopulations and expand the pool of stem-like cells. The study of Li and colleagues (92) revealed that MET positively correlates with stem cell marker expression and the neoplastic stem cell phenotype in glioblastoma neurospheres, as well as in clinical glioblastoma specimens. MET expression and activation influences the expression of reprogramming transcription factors known to support embryonic stem cells, Sox2, Klf4, c-Myc, Oct4 and Nanog, known to induce stem-like properties in differentiated cells (92,102). Moreover, MET enhances stem cell characteristics of neurosphere formation and neurosphere cell self-renewal (92). The MET receptor supports the GBM SC phenotype by involving an endogenous dynamic mechanism analogous to cellular reprogramming (92). It was shown that MET-positive cells expressed high levels of stemness transcriptional regulators, Oct4, Nanog and Klf4, when compared to MET-negative cells and the activation of MET signaling increases the expression of the Oct4, Nanog and Klf4 (103). The expression returned to basal levels in response to MET inhibition (103). It was also shown that MET induces a stem-like phenotype in prostate cancer and is expressed together with stem-like markers CD49b and CD49f and (97). Another study reported that cabozantinib, a novel inhibitor of MET, downregulated CSC markers, SOX2 and CD133, induced apoptosis and increased efficacy of gemcitabine, currently used in standard therapy for advanced pancreatic cancer (104).

In our study, we have reported that blocking of the MET receptor could influence expression and function of the chemokine CXCR4 receptor in rhabdomyosarcoma and cervical carcinoma cells (99,101). Cells with decreased MET expression had impaired intracellular signaling and chemotaxis toward SDF-1 gradient, a ligand of the CXCR4 receptor, which was in accordance with decreased expression of CXCR4 (99,101). CXCR4 overexpression and hyperactivation was shown for the first time to correlate with the metastatic ability of breast cancer cells (105). Since that time, the SDF-1-CXCR4 axis has been shown to be involved in the regulation of metastasis to organs that highly express SDF-1 (e.g., lymph nodes, lungs, liver and bones) (106). It was postulated that cancer stem cells and trafficking of normal stem cells involve similar mechanisms regulated partially by CXCR4 (107).

Table II summarizes the study of the correlation between the MET receptor and cancer stem cell markers.

## 9. MET as a CSC factor responsible for therapy resistance

Growing evidence shows that CSCs are responsible for resistance to conventional therapies, and thus, are the most likely cause of tumor recurrence (22). It has been postulated that stemness features of CSCs would allow them to escape conventional antitumor therapy and maintain minimal residual disease, leading to tumor relapse (23). It has been shown for breast cancer (108) and glioma (21) that CSCs survived after radiation, repaired their damaged DNA more efficiently than their non-CSC counterparts and began the process of self-renewal (21,108). Recently, it has been shown, in samples from patient tumors, that CSC marker expression is associated with a poor clinical outcome and may have prognostic value (24-26,109).

The study of Bardelli and colleagues (110) with the use of human colorectal cancer metastases xenografted in mice, demonstrated that amplification of the MET oncogene is a mechanism of both primary and secondary resistance to anti-EGFR therapies. In the study by Jun *et al* (103) the authors used a mouse model of GBM and demonstrated that treatment of EGFR-positive GBM with gefitinib, a TKI, results in the induction of MET expression in a subset of cells that have GSC characteristics. MET signaling was a requisite for initiation and maintenance of the GSC features. The results emphasized the capacity for MET to support the GSC phenotype that involves an endogenous dynamic mechanism analogous to cellular reprogramming (103). It was also presented that MET amplification mediates in developing of EGFR tyrosine kinase inhibitors resistance in EGFR-mutant lung cancer cells (111,112). The authors showed that small population of cells carrying *MET* amplification may pre-exist in EGFR-mutated lung cancers. These cells, not driven by EGFR mutations, can be positively selected by therapy with EGFR inhibitors and sustain resistance to EGFR inhibitors (111). It was demonstrated that the

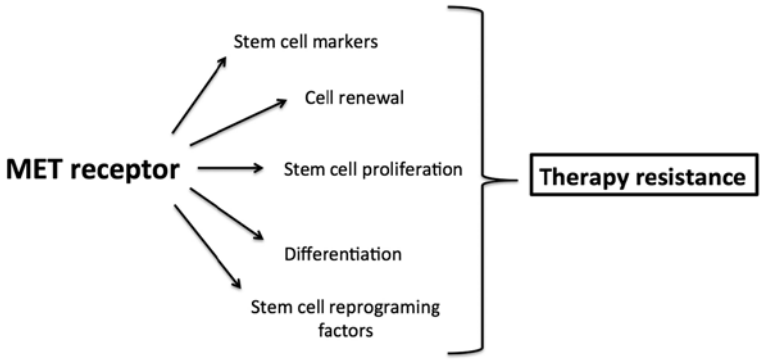


Figure 2. MET receptor as a biological factor responsible for cancer stem cell properties and therapy resistance.

response to specific inhibitors was efficiently counteracted by a variety of growth factors with prominent role of the MET receptor ligand HGF (111,112). BRAF-mutant melanomas or ERBB2-driven carcinomas have been also rescued from drug sensitivity by exposing them to HGF (113,114). Recent study of Luraghi and coworkers (115), showed that effects of EGFR inhibition in sensitive colorectal cancer initiating cells (CCIC) could be counteracted by HGF supporting *in vitro* CCIC proliferation and resistance to EGFR inhibition. It was also shown, for colon cancer, that HGF, secreted by tumor microenvironment, activates β-catenin-dependent transcription and thereby influences CSC clonogenicity and restores the CSC phenotype in more differentiated tumor cells both *in vitro* and *in vivo* (116,117).

All the observations are clinically appealing because combined treatment with an EGFR and MET inhibitor, specifically in patients with evidence of MET amplification at baseline, may lead to extended progression and better outcome.

A study showed that MET amplification together with EMT, and stem cell-like features are observed in non-small cell lung cancer cells with acquired resistance to Afatinib, an EGFR-TKI (118). It was also demonstrated that resistance of non-small lung cancer patients to EGFR inhibitors is due to EGFR T790M mutation and MET amplification (119). Moreover, the patients acquired resistance to the MET receptor inhibitors used as a therapeutic approach in clinical trials. The mechanism of the resistance involved ABCB1 overexpression, which was associated with CSC properties and EMT (119).

Taken together, MET involved in enhancing and maintaining cancer stem cell properties may be responsible for resistance to antitumor therapy (Fig. 2).

## 10. Conclusions

Targeted therapies with compounds inhibiting a specific target molecule opened a new direction in the treatment of cancer. The development of targeted therapies requires the identification of good targets that are known to play a key role in tumor cell growth and survival and are more effective and less toxic than previous standards of care involving cytotoxic therapies (120). Targeted therapy relies on the concept of 'oncogene addiction' that reveals a possible 'Achilles' heel' of cancer cells, wherein they depend on a single oncogenic pathway for sustained proliferation and/or survival (121,122). This means that the inhibition of a single pathway, gene or protein to which they are addicted results in the inhibition of their growth or even their death (121). Unfortunately, targeted therapeutics in cancer has not yet met the high expectations of patients and physicians because some patients relapsed following treatment with specific inhibitors as a result of acquired resistance mechanisms (120,123). CSCs have been shown to be largely responsible for chemoresistant phenotypes in various tumors, thus, the development of new, targeted, effective therapies has become focused on identifying factors that drive and sustain CSCs. The CSC hypothesis predicts that only therapies that efficiently eliminate population of CSCs are able to induce long-term response and stop tumor recurrence. The activation of the MET receptor axis has been directly implicated in acquiring chemoresistance, maintaining clonogenicity and ability to self-renew in various tumor cell populations. In the light of our knowledge MET seems to have two faces: acts as a promising factor for developing personalized cancer therapy and as a factor responsible for cancer stem cell properties and therapy resistance.

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