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MET, a driver of invasive growth and cancer clonal evolution under therapeutic pressure

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Abstract

The MET oncogene, encoding the hepatocyte growth factor receptor, drives invasive growth, a genetic program largely overlapping with epithelial–mesenchymal transition, and governing physiological and pathological processes such as tissue development and regeneration, as well as cancer dissemination. Recent studies show that MET enables cells to overcome damages inflicted by cancer anti-proliferative targeted therapies, radiotherapy or anti-angiogenic agents. After exposure to such therapies, clones of MET-amplified cancer cells arise within the context of genetically heterogeneous tumors and — exploiting an ample platform of signaling pathways — drive recurrence. In cancer stem cells, not only amplification, but also MET physiological expression, inherited from the cell of origin (a stem/progenitor), can contribute to tumorigenesis and therapeutic resistance, by sustaining the inherent self-renewing, self-preserving and invasive growth phenotype.

Introduction

The cancer invasive phenotype — a prerequisite for metastasis — relies on still poorly characterized genetic and molecular mechanisms. It has been noted that mechanisms controlling invasion and metastasis are difficult to unravel, as they are selected in the context of the primary tumor only if they concomitantly confer a growth advantage [1]. Intriguingly, such a dual role is played — among a few genes — by MET, the receptor for Hepatocyte Growth Factor (HGF), also known as Scatter Factor. This tyrosine kinase concurrently transforms cells — thus behaving as a classical oncogene — and drives a genetic program that we like to define as ‘invasive growth’ [2, 3 and 4], a designation later adopted to describe the invasive phenotype of tumors in general [5]. Invasive growth widely overlaps with — or includes as primum movens — the well-known process of epithelial–mesenchymal transition (EMT) [6].

In human cancers, MET is affected by genetic alterations, such as mutations or amplifications, engendering a constitutively active tyrosine kinase, either ligand-independent, or sensitive to otherwise subliminal HGF concentrations [7]. As result, the activated MET oncogene behaves as a cell-autonomous selectable driver of tumor growth. Consistently, MET amplification (i) sustains oncogene addiction, that is dependence for cell proliferation and survival [7]; (ii) is a selectable mechanism of resistance to therapies attacking other regulators of cell proliferation such as Epidermal Growth Factor Receptor (EGFR) [8 and 9].

The role of MET in tumors is not restricted to the relatively rare genetic alterations (1–3% of tumors), but relies on the frequent overexpression of the wild-type gene [4, 7 and 10]. In the latter case, activation of the tyrosine kinase, and the ensuing signaling cascade, requires the ligand HGF [4]. Intriguingly, HGF-dependent MET activity in tumors is expected to recapitulate the physiological outcome of MET signaling that occurs in embryonic and post-natal tissues. During development, HGF controls processes defined as ‘type I EMT’ [6], such as emigration of myoblasts from embryonic somites to the limb buds [11 and 12]. In post-natal tissue regeneration, HGF is essential for wound healing by keratinocytes [13 and 14], a remarkable example of ‘type II EMT’ [6]. Intriguingly, factors governing type I and II EMT often account for ‘type III EMT’ as well, the pathological counterpart of the process, featuring invasion and metastasis. In

this light, dissemination of cancer cells can be seen as the awakening of the embryonic migratory/morphogenic program dormant in post-natal tissues, which can be reactivated in cancer cell subpopulations as part of an adaptive response orchestrated by the microenvironment [6]. Remarkably, MET mutations can render type III EMT cell-autonomous, as suggested by 'cancers of unknown primary origin' (CUPs), enigmatic tumors frequently harboring MET activatory mutations. CUPs are already disseminated at their onset, and display a highly undifferentiated, stem-like phenotype, lacking histological markers of the tissue of origin [15]. Recently, it has been shown that MET controls the physiological and pathological facets of EMT/invasive growth in cells with stem features, where it behaves as a functional marker [16]. Consistently with the notion that factors inducing EMT can sustain the 'stem status' itself [17], and by reassembling the puzzle, MET emerges as a genetic driver of tumor clonal evolution, acting in cancer stem cells, and contributing to both the stem and the invasive phenotype.

MET bypasses inhibition of cell proliferation

MET promotes cell adaptation to an adverse microenvironment, depleted of proliferative/survival cues, nutrients or oxygen, or beset by genotoxic stress, as pointed out by studies in experimental models and patients treated either with conventional therapies or innovative biological agents ('targeted therapies'). The onset of resistance to drugs aimed at either member of the EGFR family, or at downstream signal transducers controlling cell proliferation, highlighted that wild-type MET frequently provides a compensatory signaling pathway, which sustains proliferation and survival, and thus causes 'primary resistance' to such drugs. The protective activity of the HGF/MET pair against EGFR inhibitors (such as small-molecule kinase inhibitors or EGFR antibodies), was first shown in lung adenocarcinoma [8 and 18], and in colorectal cancer [9, 19 and 20]. Recently, a prominent role of HGF emerged from systematic screening of microenvironmental factors that confer resistance to targeting agents [21••, 22•• and 23••]. As a plethora of tyrosine kinase receptors are expressed by cancer cells, not surprisingly many growth factors displayed the ability to counteract the inhibitory effect of drugs targeting a single receptor or intracellular transducer. However, two studies revealed the distinctive role of HGF/MET in protecting melanoma cells from BRAF inhibition [21•• and 22••]. A third study highlighted the ability of MET, and members of EGFR and Fibroblast Growth Factor (FGF) family, to compensate the inactivation of each other [23••]. The interplay among these receptors is particularly intriguing, as EGF and FGF are well known factors for in vitro selection and propagation of stem/progenitor cells [24]. Recently, we have shown that the compensatory interplay among MET, EGFR and FGFR occurs in colorectal cancer stem cells (or 'colorectal cancer-initiating cells'). Indeed, each of the above receptors sustains resistance to inhibition of the other, as shown in a preclinical model reproducing therapy of metastatic colorectal cancer with EGFR antibodies [25]. MET can compensate for EGFR inhibition, through reactivation of the Ras-MAP kinase and PI3-kinase-AKT pathways [26 and 27]. Moreover, MET can sustain an unconventional bypass mechanism that indirectly reactivates EGFR, by promoting the formation of a multi-receptor complex that involves EGFR, AXL and EPH2A, and recruits the intracellular kinase JAK [28].

A growth factor receptor — such as wild-type MET — that bypasses inhibition of an essential proliferative signal — such as EGFR — becomes a cell-autonomous genetic driver of tumor clonal evolution if the two canonical requirements of 'Darwinian selection', chance and necessity, are satisfied: (i) the gene (MET) harbors an activatory mutation, randomly occurred within a heterogeneous cell population (the chance); (ii) the tumor cell population undergoes a selective pressure by inhibitors of proliferative signals (the necessity). Indeed, a significant fraction of lung and colorectal cancer relapsing after beneficial therapy with EGFR inhibitors display MET gene amplification, and strong cell-autonomous acquired (or secondary) resistance. Concomitant emergence of MET amplification and resistance to EGFR inhibitors, is confirmed by in vitro treatment of cell lines with increasing concentration of the drug [9, 29 and 30].

MET and cancer cell heterogeneity

Tumors that recur after anti-EGFR therapy displaying a de novo MET amplification indicate that the treatment positively selected a (minor) MET-amplified subclone already present in the original tumor [8]. This is consistent with the observation that intrinsic genetic heterogeneity is a widespread feature of tumors, a recently emerged issue with important implications for targeted therapy [31]. Interestingly, in glioblastomas, different, intermingled cells harbor

amplification of either MET, EGFR or PDGF receptor in a mutually exclusive fashion [32]. Alternative amplification of one of these tyrosine kinase receptors is consistent with their overlapping role in controlling cell proliferation. Moreover, although a large body of evidence indicates that multiple receptors are concomitantly expressed in the same cell to provide a redundant, robust circuit of cell proliferation control, it is emerging that, conversely, wild-type MET and receptors of the EGFR family may be even expressed in a mutually exclusive way. Alternative expression of MET or ERBB2/HER2 has been observed in breast cancer [33], reflecting the coexistence of different subclones. Expression of MET and EGFR is usually mutually exclusive in cancer stem cells (neurospheres) isolated from glioblastoma [16]. These studies indicate that targeting one single receptor in tumors may easily result in positive selection of cells lacking such receptor.

MET sustains radioresistance

As part of the invasive growth program, MET not only restores the proliferative signal, but it exerts an effective anti-apoptotic activity that protects from cell and DNA damaging agents. This response arises either during targeted or conventional cancer therapies such as radiotherapy. In the latter case, MET plays an essential role as it is activated by genotoxic stress. Indeed MET is transcriptionally induced by ionizing radiation, through a signaling pathway entailing the ATM kinase, involved in detection of DNA double strand breaks, and the transcription factor NF-κB. The upregulated MET plays a dual role, by concomitantly promoting invasion and protecting from apoptosis. Consistently, in tumors xenografted in mice and treated with radiotherapy, MET inhibition results in increased cell death and tumor regression [34]. It was further shown that MET inhibition prevents formation of the RAD51-BRCA2 complex, required for DNA repair by homologous recombination [35].

Concerning the cell response to DNA damage, an intriguing interplay between MET and p53 recently emerged. Loss-of-function mutations of p53, well-known to confer tolerance to DNA damage, activate MET by acting at multiple levels, including: (i) accumulation of MET mRNA by a dual mechanism, involving loss of the MET targeting miR-34, and activation of transcription factor Sp-1 [36]; (ii) stimulation of MET protein endocytosis through Rab-dependent receptor recycling [37]; endocytosis, on its turn, increases MET intracellular signaling [38]. As result, mutant p53 increases MET activity, leading to cell motility and invasive growth [36 and 37]. From these studies one could infer that the normal p53 protein represses the MET pathway. However, another study suggests that, on the contrary, activation of intact p53 involves MET as an arbiter of the cell fate binary decision between cycle arrest and apoptosis. After activation with the synthetic molecule Nutlin-3, p53 induces reversible cell cycle arrest, which is converted into cell death by MET (or ATM) inhibition [39]. By further elaborating, we speculate that, in cells experiencing radiation-induced DNA damage, p53 and MET are concomitantly activated, and MET prevents the p53-dependent apoptotic response, thereby prolonging cell cycle arrest and increasing the chance of DNA repair.

Taken together, the above studies suggest that MET effectively protects cells from death induced by DNA damage in the presence of normal p53, and can be even more active in case of p53 mutation. As in the case of resistance to EGFR inhibitors, MET sustains primary radioresistance and can drive clonal selection under the pressure of radiotherapy. This was observed in mouse models of radiation-induced glioblastoma, where the most significant oncogenic event — possibly induced by DNA damage and then selected — was MET amplification [40].

MET promotes escape from angiogenesis inhibition

Last but not least, MET was shown to sustain intrinsic resistance to, and to promote side-effects of antiangiogenic therapy. VEGF antibodies are currently used to treat many cancer types with modest benefits, and have been associated with progression toward invasion, for example, in glioblastoma [41 and 42]. Tumor escape from angiogenesis inhibition, and progression, have been observed in animal models, MET being recognized as a major culprit [43]. Indeed MET is transcriptionally induced by Hypoxia Inducible Factor in cells suffering from compromised vascularization [44]. Consistently, in a mouse model of pancreatic neuroendocrine tumors (RIP-Tag2 mice), it was shown that treatment with VEGF inhibitors (antibodies or small molecules) impaired tumor growth but concurrently increased hypoxia, MET expression, invasion, and metastasis, which were prevented by concomitant administration of VEGF and MET inhibitors

[45 and 46•]. Interestingly, in the same model, MET was found to be overexpressed not only in hypoxic tumor cells, but also in the lymphatic endothelium, and MET inhibition resulted in markedly decreased lymphangiogensis and lymph node metastasis [47]. Evidence that MET is activated in hypoxic cells, and can promote EMT and metastasis, stems mostly from pharmacological inhibition of the VEGF pathway, mimicking treatments currently in use, but it comes also from mice genetically engineered and pharmacologically targeted in order to disrupt perivascular stromal cells, that is, pericytes [48]. Finally, to explain MET activation during anti-angiogenic therapy, a mechanism alternative to transcriptional induction by hypoxia was discovered in glioblastoma cells treated with VEGF antibodies. This treatment results in the release of MET from an inhibitory heterocomplex including VEGFR and a tyrosine phosphatase, which is followed by MET signaling activation, and induction of the EMT/invasive growth phenotype [49•].

MET relies on signaling partners in addicted cells

Transmembrane and intracellular molecules that cooperate with the MET receptor in transducing the invasive growth signal were extensively characterized in the past [4]. In recent years, the picture of this signaling network has been enriched by the discovery of partners that interact with MET in cells harboring amplification, and are crucial to sustain MET addiction, and, possibly, clonal evolution under therapeutic pressure. Among these partners, the best-known is RON, the MSP receptor, structurally homologous to MET and endowed with similar signaling properties driving invasive growth (Figure 1) [50]. RON is transphosphorylated by MET, and is required to unleash the MET full oncogenic potential in MET-amplified cells [51]. A recently identified partner of MET is ROR1, an orphan receptor with intriguing structural homologies with HGF in the extracellular domain, and with MET in the intracellular domain, but devoid of catalytic activity (Figure 1) [52]. ROR1 is a privileged substrate of MET in cells harboring MET amplification, and can redirect invasive growth signaling toward proliferation or invasion, based on MET trans-phosphorylation of different tyrosine residues [53]. Another new interactor, Tensin-4, stabilizes MET exposure at the cell surface, promoting intensity and duration of the signal: its loss favors MET degradation and death of cells harboring amplification [54]. Finally, STAT3, previously characterized as an essential mediator of MET signaling in physiological invasive growth (branching morphogenesis) [55], has been recently shown to be critical to sustain the proliferative program of MET-amplified cells [56], and to sustain MET-mediated resistance of colorectal cancer to MEK inhibitors [57].

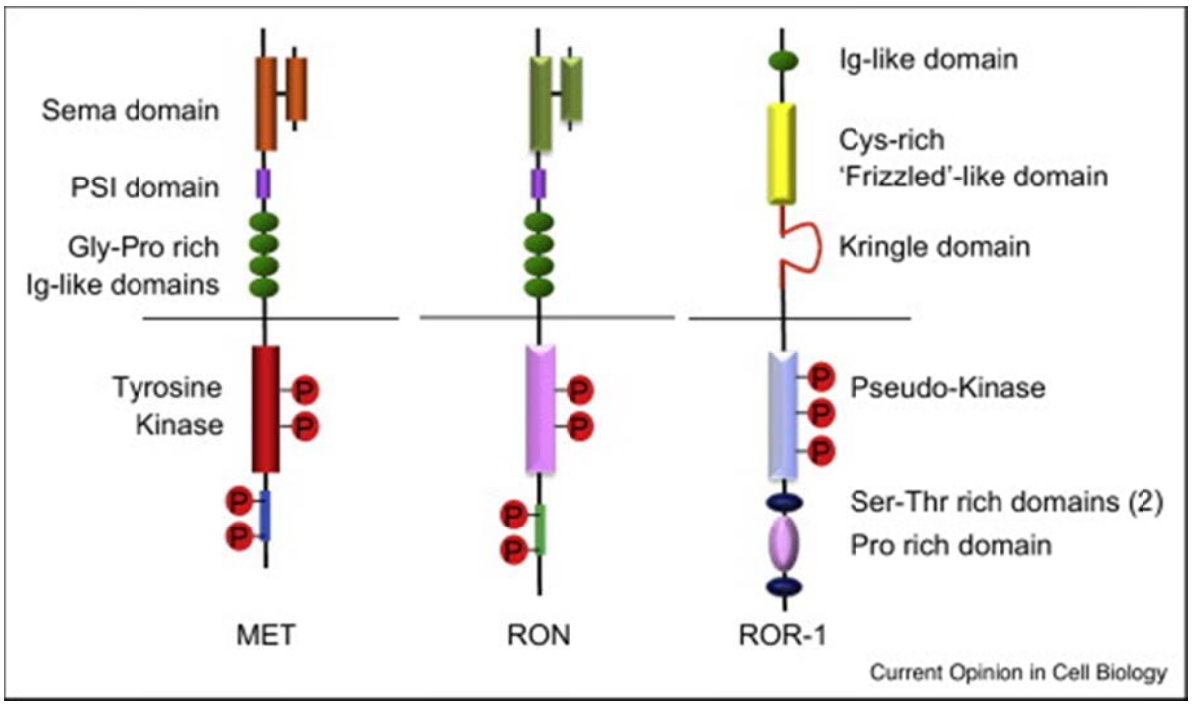

Figure 1.

MET, RON and ROR-1 cooperate in oncogenic signal transduction. MET (the HGF receptor) and RON (the MSP receptor) share ample structural homology. Both include an extracellular α-chain disulphide-linked to a membrane-spanning β-chain. The extracellular region

includes (i) the N-terminal Sema domain of 500 amino acids, encompassing the whole α-chain and part of the β-chain, homologous to domains found in semaphorins and their receptors plexins; (ii) the PSI (Plexin-Semaphorin-Integrin) domain, named after the three families that display this sequence including 50 amino acids and four disulphide bonds; (iii) four Immunoglobulin-like (Ig) domains rich in glycine (Gly) and proline (Pro). The intracellular portion includes a tyrosine kinase domain containing two tyrosine residues (Tyr1234 and Tyr1235 in MET) that, when phosphorylated (P), positively modulate the catalytic activity, which is weaker in RON than in MET. The carboxy-terminal tail contains two tyrosines (Tyr1349 and Tyr1356 in MET) acting as a multifunctional docking site for the recruitment of several transducers and adaptors. ROR-1, a privileged substrate for MET, is an orphan receptor including and extracellular portion that contains three domains, among which a cystein (Cys) rich domain displays homology with the wnt receptor frizzled, and a 'kringle' domain displays homology with the MET ligand HGF. The intracellular region includes a domain homologous to tyrosine kinases, but devoid of catalytic activity (pseudo-kinase), and sequences involved in signal transduction: two serine and threonine (Ser-Thr) rich domains, and a proline (Pro) rich domain.

MET regulates normal and cancer stem cell phenotypes: 'inherence'

In several tissues, MET expression has been previously associated with cells of the stem/progenitor compartment, rather than with differentiated cells [3]. Recently, mechanistic insights into the ability of this receptor to sustain the specific properties of stem/progenitor cells have been provided. Genetically modified mice revealed that MET and HGF are essential not only for liver development [58], but also for post-natal regeneration, especially after injury, which involves reactivation of the stem/progenitor compartment: these cells, also known as 'oval cells', unlike mature hepatocytes, express MET [59 and 60]. Interestingly, it has been shown that, in oval cells expanded in vitro, MET and EGFR sustain self-renewal and binary cell fate decision, promoting respectively hepatocyte or cholangiocyte commitment through alternative signaling pathway: MET via AKT and STAT3, EGFR via Notch [61]. A recent study on the mouse mammary epithelium revealed that MET is specifically expressed in luminal progenitors, and showed that HGF retains cells in the stem/progenitor state, preventing differentiation toward the mature luminal phenotype [62]. Interestingly, this may have pathogenetic implications for human basal-like breast cancer that likely derives from transformation of luminal progenitors [63], retains stem-like features, and express significant levels of wild-type MET [64]. In this context, MET can be envisaged as a driver of tumor stemness, and a marker of expansion of a luminal progenitor population that is restrained to further proceed toward differentiation. This evidence suggests that MET (and possibly other cellular oncogenes) play a dual role in oncogenesis: (i) in the mutated, amplified or otherwise genetically altered form, MET generates and maintain the transformed phenotype, and drives clonal evolution; (ii) in the wild-type form, MET contributes to maintain - in the cancer stem cell - the phenotype 'inherent' in the stem/progenitor cell of origin. We like to call the latter phenomenon 'inherence', and point out that it can be essential to confer 'replicative immortality', a hallmark of cancer still elusive in its essence [65].

The 'inherence' paradigm is exemplified by MET in glioblastoma stem cells. The oncogene is expressed in neural stem cells and switched off after differentiation, while it persists after transformation of neural stem/progenitor cells into glioblastoma stem cells [66 and 67]. Consistently, MET can be used as a marker to prospectively isolate glioblastoma stem cells from the whole tumor tissue [68•], and it is expressed in cultures enriched in glioblastoma stem/progenitor cells (neurospheres) [69• and 70•]. Notably, MET is specifically expressed in the neurosphere cell subpopulation which retains self-renewing and tumorigenic properties, and generates a heterogeneous population, including also cells that lose stem properties along with MET expression [70•]. Most importantly, in glioblastoma stem cells, MET behaves as a functional marker, sustaining the stem-status by inducing a set of 'reprogramming transcription factors' [69•]. Interestingly, among these, KLF4 concomitantly sustains stem reprogramming and EMT. This was observed after KLF4 transduction into differentiated cells to generate 'induced pluripotent stem cells' [71], and after HGF stimulation [72]. Consistently, MET expression has been preferentially associated with a glioblastoma subtype characterized by a gene expression pattern typical of mesenchymal cells [70• and 73]. The ability of MET to control transcription factors involved in both stem reprogramming and EMT adds relevant mechanistic explanation to the well-known association between the two biological process [17].

Conclusions

Three decades after its discovery [74 and 75] the MET oncogene, expressed in normal and cancer stem cells, appears to be a key player in cancer onset and progression. The oncogenic role is sustained both by wild-type MET and by a genetically altered, constitutively activated form. The first governs invasive growth, a physiological program largely overlapping with epithelial–mesenchymal transition, and associated with the stem phenotype; the second drives the transformed phenotype (Figure 2). In both instances targeting MET can be beneficial for cancer therapy, as MET inhibition may result in prevention of invasion and metastasis, interference with cancer stem cell properties and — in MET-addicted cells — growth arrest and tumor regression. Owing to its properties MET is often selected as a driver of tumor clonal evolution under therapeutic pressure (e.g. anti-EGFR targeted therapy, ionizing radiation, and anti-angiogenic agents, Figure 2), suggesting MET inhibition by targeted therapy to prevent resistance.

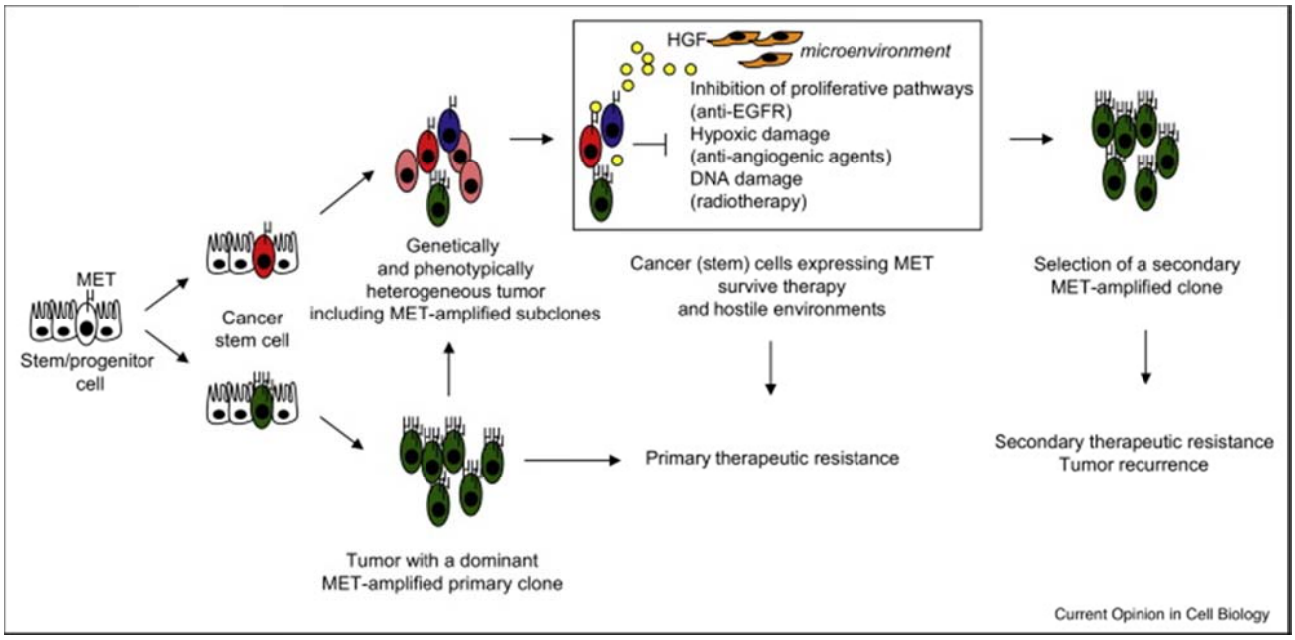

Figure 2.

MET in cancer stem cells and mechanisms of clonal evolution. MET is expressed in the stem/progenitor compartment of many tissues. MET amplification can occur in these cells and drive transformation into cancer stem cells and emergence of a primary clone. Alternatively, or in addition, in cancer cells transformed by other oncogenic events, wild-type MET stimulated by HGF secreted by the microenvironment can promote invasive growth and stemness, and sustain primary resistance to several targeted and conventional therapeutic agents. In the context of genetically heterogeneous tumors, subclones of MET amplified cells can be positively selected by therapies and drive recurrence of a secondary resistant tumor.

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• of special interest

•• of outstanding interest

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