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The MET Receptor Tyrosine Kinase as a Therapeutic Target in Multiple Myeloma

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Multiple Myeloma (MM) is a progressive and debilitating B-cell disorder typified by the accumulation and dissemination of malignant plasma cells in the bone marrow which subsequently induce osteolytic lesions [1]. Despite recent advancement of new therapies for MM, patients ultimately develop drug resistance and succumb to the disease [2]. This highlights the need to increase our understanding of the disease and to identify new myeloma targets for drug development.

The growth and progression of myeloma is multifaceted and signaling through several cytokine/receptor pathways have been shown to be vital for the pathobiology of this disease [3-6]. Evidence for the MET receptor signaling pathway being an important contributor to the pathogenesis of this disease has been mounting. Both MET and its ligand, hepatocyte growth factor (HGF), are expressed in an autocrine loop in most myeloma cell lines and primary patient samples, as discerned at both the mRNA and protein level [7-10]. This is compounded by the high expression of the proteoglycan, syndecan 1 (CD138), on plasma cells as it binds HGF and boosts HGF-mediated signaling [11,12]. Additionally, malignant plasma cells convert HGF into its active form by secreting HGF-activator (HGFA), a serine protease specific for HGF activation [13].

The effects of HGF/MET signaling on myeloma cells are diverse. It has been shown to promote myeloma-cell growth [3,12,14], and survival [3,15]. Moreover, HGF/MET uniquely signals a morphogenic invasive-growth program [16-18] that is associated with the dissemination of myeloma cells in the bone marrow, leading to disease progression [14,19]. HGF/MET signaling boosts myeloma cell adherence to the bone marrow matrix through enhanced binding to fibronectin and other components of the microenvironment [20]. Additionally, it is involved in the up-regulation of matrix metalloproteinases and urokinase plasminogen activator [21], further enhancing migration and invasion [22]. Characteristically, MET signaling is able to induce angiogenesis by stimulating the production of VEGF and inhibiting thrombospondin 1 expression [23], broadening its support of tumor survival.

In addition to promoting growth and progression of myeloma, HGF/MET signaling may play a role in the focalization of myeloma-related bone disease. HGF levels are increased in patients with extensive bone lesions, and correlates with increases in cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha, involved in osteoclast stimulation [24]. HGF stimulation induces IL-11 secretion from osteoblasts [25], and HGF inhibits bone morphogenetic protein-induced osteoblastogenesis [26].

Clinically, several studies have correlated HGF/MET pathway with myeloma disease parameters. HGF is elevated at diagnosis in the serum and marrows of patients with multiple myeloma [11,27-29] and activated HGFA has been found to be present at high levels in the serum and bone marrow of myeloma patients [30]. Moreover, serum HGF levels tend to be further elevated in patients with advanced stage or aggressive disease [24,28,31-34] and have been associated with a poorer prognosis [27,29,31,35,36]. Similarly, a higher level of *MET* mRNA in MM patients' plasma cells is also associated with a poorer prognosis [37]. Conversely, patients with low HGF levels have been shown to be more likely to achieve high-quality responses [38,39], and the serum levels of a soluble, inhibiting form of MET negatively correlates with disease stage [40], and declining HGF levels are seen in patients who are responding to anti-myeloma therapies [39,41,42].

Targeting the HGF/MET signaling pathway is a rational approach to multiple myeloma therapy. Genetically or pharmacologically depleting *MET* is fatal to myeloma cells [19,43,44], further underscoring the role of MET/HGF axis in myeloma and potential as a therapeutic target. Moreover, a number of translational studies using varying strategies to suppress the HGF/MET axis further bolster the concept of MET being a therapeutic target for MM. PHA-665752, a MET inhibitor, blocked HGF-mediated signaling and inhibited MM cell proliferation, adhesion, and migration [14]. Similarly, an anti- MET Nanobody was shown to not only inhibit MET signaling, growth, adhesion, and migration, but also showed evidence of abolished inhibitory effect of HGF on bone morphogenetic protein-2-induced osteoblastogenesis [45]. NK4, an internal fragment of HGF that acts as a competitive inhibitor, not only inhibited MET signaling and growth in MM cells in culture, but also significantly inhibited the *in vivo* growth of myelomatous tumors in a murine model [46] as does the MET inhibitor, SU11274 [47]. The MET inhibitor amuvatinib was shown to be tumoricidal to primary myeloma cells and cell lines Additionally, these studies suggest that myeloma survival may be dependent on HGF levels [9].

Preclinical studies of the MET inhibitor, tivantinib was also performed in myeloma cell lines and patient samples. Tivantinib is unique in that it is not an ATP-mimetic, but instead is an inhibitor which binds to a part of the MET receptor that is close to the ATP-binding site [48]. This atypical interaction is believed to provide this small-molecule inhibitor with a very unique and high degree of kinase selectivity. In addition to being a kinase inhibitor, recent evidence indicates tivantinib also has activity independent of MET as well [49,50]. The preclinical analysis showed that at clinically achievable concentrations, tivantinib induced apoptosis by >50% in 12 myeloma cell lines [51]. The cytotoxicity in these cells was associated with a loss of MET activity and an inhibition of downstream signaling through the MAPK and PI3K pathways. Tivantinib was equally effective in inducing apoptosis in myeloma cell lines resistant to standard chemotherapy.

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Furthermore, tivantinib also induced apoptosis in primary myeloma plasma cells and demonstrated efficacy in a myeloma mouse xenograft model. Based on the preclinical studies, a small Phase II clinical trial of tivantinib (NCT01447914), was performed in unselected relapsed/refractory myeloma patients [52,53]. In the clinical trial, 16 patients were enrolled and 11 were evaluated for response. Bone disease was not evaluated. In this study, tivantinib was well tolerated. Even though none of these patients had high HGF levels (data not shown), the agent was able to achieve stable disease in 4 of 11 (36%) patients with previously progressing myeloma [53]. Overall, these data demonstrate the promise of targeting HGF/MET signaling axis for the treatment of multiple myeloma and highlights increased need for biomarker testing for selection of candidates for future trials.

Recently, two clinical phase I/II trials (NCT0186629 and NCT01582295) to assess the safety and efficacy of Cabozantinib (XL184) in relapsed/refractory myeloma patients have opened. Cabozantinib is a pan-kinase inhibitor which shows potent activity against MET, vascular endothelial growth factor receptor 2 (VEGFR2/KDR), VEGFR3/FLT4, VEGFR1/FLT1, and RET with IC_{50} values of 1.8, 0.035, 12.2, 6.0 and 9.8 nM, respectively [54]. Additional targets of Cabozantinib include FLT3, TIE2, AXL, TRKB, and KIT with IC_{50} values of 14.4, 14.3, 7.7, and 4.6 nM, respectively. Thus, cabozantinib is able to target both VEGF signaling as well as MET, both important for myeloma progression. The primary assessment in both trials will be to determine safety in a dose escalation study. Patients in NCT01582295 will also be selected for bone disease and an assessment of various markers of bone turnover will also be included in the study, including serum bone specific alkaline phosphatase, osteocalcin, sclerostin, procollagen type 1N propeptide, and urine N-telopeptide. Additionally, changes on whole body FDG-PET/CT scans as well as pain will be monitored.

In conclusion, preclinical studies show strong indication for targeting MET in myeloma for both reducing tumor burden in MET-dependent tumors and for alleviating bone disease. The clinical trial with tivantinib shows promise of MET being a viable therapeutic target. Future clinical trials need to be planned where myeloma patient populations are selected which have high serum HGF levels or possibly high plasma-cell MET levels for targeting this pathway. Additionally, monitoring of bone disease may also prove advantageous for evaluating the treatment benefit. The use of these criteria will allow for a more applicable means to effectively assess MET inhibitors as a therapeutic strategy in myeloma.

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