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MSP-Ron signalling in cancer treatment

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ABSTRACT

Macrophage stimulating protein (MSP)/HGF-linked protein (HGFL) was simultaneously discovered as a protein stimulating macrophage activity and hepatocyte growth factor (HGF) family protein. MSP is produced by epithelial cells, and its receptor, Ron

(Recepteur d'origine nantais), is expressed in stromal cells. Ron and Met, an HGF receptor, are also both family receptors. However, HGF is produced by stromal cells, and Met plays some roles on epithelial cells. Therefore, HGF-Met and MSP-Ron signallings show a reciprocal correlations under physiological condition. Although HGF-Met is a well-known signalling promoting cancer, RON overexpression was also observed in some human cancers that originated from epithelial cells, and SP-Ron signalling has important activities in cancer development. MSP induces invasion, metastasis, and drug resistance of cancer cells. Moreover, Ron interacts with Met and the EGF receptor, and they exert various effects in cooperation to achieve malignancy. Ron could be an important target of cancer therapy using monoclonal antibodies and small chemical inhibitors. In this review, we focus on the roles of MSP in cancer development and therapies against MSP-Ron-signal-positive cancers.

Key words: MSP, Ron, cancer, therapy

Abbreviation: HGF - hepatocyte growth factor, HGFL - HGF-linked protein, HIF - hypoxia-inducible factors (HIF), MSP: macrophage stimulating protein, Ron - Recepteur d'origine nantais, STK - stem cell-derived tyrosine kinase

1. INTRODUCTION

Macrophage stimulating protein (MSP) was discovered as serum protein promoting mouse macrophage motility, and later identified as HGF-liked protein (HLP) (Kato, 2016). Similarly to HGF, MSP is characterized by kringle domains (highly conserved triple disulfide loop structures) in the α-chain, and a serine protease domain in the β-chain, but are devoid of enzymatic activity because of amino acid substitutions in the catalytic triad. The conversion to mature MSP could also be mediated by proteolytic enzymes associated with the cell membrane from resident or exudate peritoneal macrophages. Thus, MSP activation is regulated in tissue homeostasis and in disease pathologies, such as inflammation and cancer progression. MSP mediates its biological activities through a receptor tyrosine kinase, RON (Recepteur d'origine nantais) /STK (stem cell-derived tyrosine kinase) (Kato, 2016). RON belongs to a family of receptor tyrosine kinases that includes Met, and MSP-induced dimerization leads to its autophosphorylation and kinase activation.

2. RON EXPRESSION IN CANCER

RON genes generate two transcripts: 5.0-kb and a 2.0-kb mRNA in humans (Gaudino et al., 1994). The longer transcript encodes the full-size receptor, and the short transcript has a partial extracellular domain followed by the transmembrane and intracellular sequences (also known as RonΔ55). A short *Ron* mRNA is expressed in human lung, ovary, and gastrointestinal tract tissues and also in several human ovarian, breast, pancreas, and lung cancers and leukemia.

3. MSP-RON SIGNALLING IN CANCER

MSP-Ron has various functions including innate-immune responses and anti-inflammation summarized previously (Kato, 2016), and its roles in cancer development is focused on in this review. Some human tumor types and cell lines show an increased expression of MSP and Ron (Leonis et al., 2007, Sugie et al., 2016). A high expression level of Ron is positively correlated with a poor prognosis in various human cancer types, and Ron overexpression in breast and bladder cancers is particularly associated with decreased patient survival (Sugie et al., 2016). To define the significance of Ron activation, Ron transgenic mice have been generated, and the activities of the MSP-Ron pathway in tumor initiation and progression were reported based on loss-of-function analysis (Yao et al., 2013). MSP-RON signalling in stromal cells including bone marrow-derived cells promotes tumor growth and metastasis by suppressing anti-tumor host immunity, which is elicited by both cancerous cells and surrounding stromal cells in coordination (Yao et al., 2013). Furthermore, MSP-RON activation promotes metastasis by triggering MBD-dependent DNA methylation gene reprogramming (Cunha et al., 2014). Some cancer cells are dependent on MSP-RON signalling for their growth and survival (Wang et al., 2009, Logan-Collins et al., 2010). Specific small interfering RNA (siRNA)-mediated knockdown of RON expressions decreased cell proliferation and migration, and increased apoptosis in various cancer cell lines. Aberrant RON expression and activation have prognostic values for patient survival through the generation of active forms such as RONΔ160, which lead to the persistent

activation of downstream cascades (Yao et al., 2013). Amplification and a point mutation in RON have been reported and several RON isoforms have been observed in several cancer samples and established cell lines (Catenacci et al., 2011). In addition to single RON activities, functional crosstalk between RON and other signalling proteins such as MET and EGFR, which provide a mechanism underlying drug resistance, has emerged as an additional mechanism for RON activation (Wang et al., 2013, Zou et al., 2013).

It is known that tumor hypoxia is associated with radiosensitivety and chemoresistance, and the underlying mechanism is cellular insensitivity regulated by hypoxia-inducible factors (HIF), which impairs drug uptake, transport, and metabolism. Ron expression was increased in response to hypoxia (Prislei et al., 2010). Under hypoxia, RON plays important roles in chemoresistance. Especially, RON activates nonhomologous end joining DNA repair by interacting with Ku70/DNA-PKcs and inhibiting RON activity to increase cancer cell chemosensitivity (Chang et al., 2016). Nuclear Ron interacts with the hypoxia-inducible factor HIF-1α in a manner that relies on RON tyrosine kinase activity, binds to the c-Jun promoter, and causes activation (Chang et al., 2014). Thus, the ability of anti-RON mAb to direct doxorubicin cytotoxicity could be developed for attenuating hypoxia-acquired drug resistance in various cancer cells (Guin et al., 2011).

Lapatinib-resistance is a major problem for HER2-positive breast cancer treatment by the PI3K/AKT signalling pathway, and thus both small-molecular RON inhibitors and Ron-targeted siRNA effectively restored lapatinib sensitivity by inhibiting PI3K/AKT activation (Wang et al., 2013). Moreover, increased Ron expression led to resistance to doxorubicin, paclitaxel, and cisplatin in ovarian cancer cells, and to tamoxifen in breast cancer involving the MAP signalling pathway (Prislei et al., 2010, McClain et al., 2010). The insulin-like growth factor-1 receptor (IGF1R) is emerging as a promising therapeutic target in human cancers, and IGF1R-blocking antibodies show marked antitumor activity. However, acquired resistance is observed in the high-risk childhood sarcoma Ewing family tumor and rhabdomyosarcoma, and Ron was identified as a modifier of IGF1R inhibitor activity (Potratz et al., 2010).

The splicing isoforms RONΔ160 and RONΔ155 are the naturally occurring RON variants that have tumor growth and invasion activities (Zhou et al., 2003, Zhou et al., 2015). Furthermore, the short-form (SF)-RON was expressed in human acute myeloid leukemia (Fialin et al., 2013). SF-RON over expression in epithelial cells results in an aggressive phenotype *in vitro* characterized by faster growth, motility, anchorage, contact independence, and an altered morphology. It is known that Ron leads to unresponsiveness to the Met inhibitor in MET-positive gastric cancer. SF-RON was frequently upregulated in MET-positive gastric cancer, and only SF-RON, not full-length RON, conferred MET inhibitor resistance (Wu et al., 2015).

4. CANCER THERAPY TARGETING HGF-MET AND MSP-RON

Various strategies have been demonstrated to block RON activity, and the blocking of MSP-Ron signalling should prove to be clinically significant in targeted human cancers either alone or in combination therapy (Leonis et al., 2007). Soluble fragments of the Ron-sema domain, small molecule inhibitors, have also been developed. Soluble and secreted molecules representing the sema domain of Ron act in a dominant-negative manner, inhibiting MSP-responsive cancer cells (Angeloni et al., 2004). The expression of these fragments actually occurs in various cancer cells, which antagonize the RON-mediated tumorigenic activities (Leonis et al., 2007, Angeloni et al., 2004). Furthermore, antibodies (e.g., IMC-41A10 and IMC-RON8) that bind to RON with high affinity and effectively block interaction with MSP, downstream signalling, cell migration, and tumorigenesis (Zou et al., 2013, O'Toole et al., 2006). Recently, Church et al. reported an interesting strategy for cancer therapy. The small-molecule analog for a "hinge" region within the putative dimerization domain in both HGF and MSP inhibits their signalling activities including proliferation, migration, and invasion in *in vitro* assay (Church et al., 2016). In the future, the MSP-RON pathway will become a more important target in treatment of various cancers.

5. SUMMARY/CONCLUSION

1. Some human tumor types and cell lines show an increased expression of MSP and RON. MSP secreted from tumor and stromal cells promotes tumor growth and metastasis by suppressing anti-tumor host immunity.
2. MSP-RON signaling plays important roles on growth, migration and survival, and induces invasion, metastasis, and drug resistance of cancer cells.
3. Aberrant RON signalling derived from short-form of Ron have prognostic values for patient survival and result in an aggressive phenotype characterized by faster growth, motility, anchorage, contact independence, and an altered morphology
4. Various strategies to inhibit MSP-RON signalling should prove to be clinically significant in human cancers either alone or in combination therapy. The MSP-RON pathway will become a more important target in cancer treatments.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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