RON Signaling Is a Key Mediator of Tumor Progression in Many Human Cancers

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With an increasing body of literature covering RON receptor tyrosine kinase function in different types of human cancers, it is becoming clear that RON has prominent roles in both cancer cells and in the tumor-associated microenvironment. RON not only activates several oncogenic signaling pathways in cancer cells, leading to more aggressive behavior, but also promotes an immunosuppressive, alternatively activated phenotype in macrophages and limits the antitumor immune response. These two unique functions of this oncogene, the strong correlation between RON expression and poor outcomes in cancer, and the high tolerability of a new RON inhibitor make it an exciting therapeutic target, the blocking of which offers an advantage toward improving the survival of cancer patients. Here, we discuss recent findings on the role of RON signaling in cancer progression and its potential in cancer therapy.

Approximately 20 receptor tyrosine kinase (RTK) families have been identified so far in humans (Lemmon and Schlessinger 2010). In addition to their similar structure (sharing extracellular, transmembrane, and intracellular domains), tyrosine kinases conduct similar functions by regulating target protein posttranslational modification through transfer of phosphates from ATP to the hydroxyl group of a tyrosine (Manning et al. 2002). The result of this phosphorylation is activation of intrinsic tyrosine kinase activity, which eventually leads to signal transduction via multiple downstream signaling cascades (Schlessinger 2000).

One of these RTKs with various biological activities is receptor d'origine nantais (RON), which has gained a lot of attention since its discovery in 1993 (Ronsin et al. 1993). RON belongs to the MET proto-oncogene family that, together with the other prototype RTK, MET, constitute the only members of this family in humans (Wang et al. 2006). In animals, though, different orthologs have been identified that are highly homologous to human RON: STK in mice and Sea in chickens, pointing to the conservation of RON through evolution in different species (Hayman 1987; Iwama et al. 1994). Shortly after the discovery of RON, macrophage-stimulating protein (MSP) was identified as the only ligand for RON (Gaudino et al. 1994; Wang et al. 1994). Physiological roles of RON include regulation of the innate immune response during inflammation and promotion of wound healing (Gaudino et al. 1995; Quantin et al. 1995; Correll et al. 1997; Morrison and Correll 2002; Wang et al. 2002).

RON is expressed at low levels in healthy adult tissues of epithelial origin (such as skin, colon, breast, lung, and kidney) and at various levels in macrophages, hematopoietic cells, and osteoclasts (Wang et al. 2006; Meyer et al. 2009; Kretschmann et al. 2010; Fialin et al. 2013). Studies indicate that RON can also be expressed in fibroblasts during pathological conditions (Tong et al. 2011; Benight and Waltz 2012). Expression of RON, however, becomes high in several epithelial tumors such as colon, lung, breast, stomach, ovary, pancreas, and bladder cancers (Maggiora et al. 1998, 2003; Willett et al. 1998; Chen et al. 2000; Okino et al. 2001; Camp et al. 2005; Cheng et al. 2005; Lee et al. 2005). In tumors with mesenchymal origin, such as sarcoma, RON has been less studied; childhood Ewing sarcoma and rhabdomyosarcoma are the only two examples in which RON has been shown to be expressed and activated (Potratz et al. 2010). Within the last few years, data have accumulated to unveil more and more about the roles of RON both in cancer and noncancer settings. Here we discuss recent findings regarding the pathological relevance of RON in cancer progression.

STRUCTURAL AND BIOCHEMICAL PROPERTIES OF HUMAN RON

The *RON* gene, residing on chromosome 3p21, contains 20 exons and 19 introns that encode 1400 amino acids to generate the full-length protein (Ronsin et al. 1993; Angeloni et al. 2000). RON is first translated as a

single-chain cytoplasmic pro-protein. Proteolytic processing results in presentation of the receptor at the cell surface as a disulfide-linked heterodimeric receptor consisting of a 45-kDa extracellular α chain and a 150-kDa transmembrane-spanning β chain that includes a highly conserved intracellular catalytic domain (Gaudino et al. 1994; Wang et al. 1994; Waltz et al. 2001). The extracellular sequences of RON contain several unique structures including the semaphorin (sema) domain, followed by the plexin–semaphorin–integrin (PSI) domain and four immunoglobulin–plexin–transcription (IPT) domains (Chang et al. 2015). The sema domain is responsible for recognizing the receptor ligand, MSP (Wang et al. 2006). All other extracellular domains have specific roles and are often subjected to deletion or truncation under pathological conditions, which results in generation of multiple isoforms with different oncogenic activities. For example, the IPT units are required to maintain the integrity of RON—its activity, proper maturation, and cell surface localization (Collesi et al. 1996; Lu et al. 2007; Zhang et al. 2010). Accordingly, deletion of the first IPT domain causes conformational changes and spontaneous dimerization of RON. This dimerization leads to constitutive activation, resistance to proteolytic degradation, and increased oncogenic potential of RON, as indicated by promotion of epithelial-to-mesenchymal transition (EMT), cell migration, and colony formation (Ma et al. 2010a). Alterations in the IPT units of RON occur with high frequencies in several types of cancer such as colon, pancreas, glioma, and breast (Wang et al. 2000; Zhou et al. 2003; Xu et al. 2004, 2005; Eckerich et al. 2009; Yao et al. 2013b; Chakedis et al. 2016b). Specific oncogenic variants of RON are discussed in detail below.

The intracellular region of Ron consists of the juxta-membrane (JM) domain, the highly conserved kinase domain, and the noncatalytic carboxy-terminal tail (Danilkovitch et al. 1999). The JM domain is involved in regulation of RON stability through recruitment of ubiquitin–protein ligase c-Cbl to phosphorylated Y1017, which results in subsequent ubiquitination and degradation of RON (Penengo et al. 2003; Thien and Langdon 2005; Germano et al. 2006). Alteration of this region, either through mutation or partial deletion, makes RON resistant to c-Cbl-mediated degradation and results in increased stability, constitutive activation, and enhanced oncogenic potential of RON (Wei et al. 2005a). In addition to the regulatory role of Y1017 in the JM domain, an acidic JM-C region has been identified in this domain that is critical for RON autoinhibition. Experimental deletion of this region results in increased receptor autophosphorylation (Wang et al. 2014).

The kinase domain consists of two lobes with several subdomains. The N-lobe contains the α C helix and the P loop, which are essential for ATP recruitment. Y1238 and Y1239 are the two essential tyrosines that reside in the activation loop of the C-lobe and their phosphorylation is the hallmark of RON activity (Gaudino et al. 1994; Danilkovitch and Leonard 1999). These two tyrosines are persistently phosphorylated in oncogenic RON variants

to sustain active downstream signal transduction. There are some other essential residues in the N-lobe, such as K1114 and E1130, which are required for ATP binding to RON; mutation of these residues converts RON to a kinase dead receptor (van den Akker et al. 2004; Wang et al. 2014). In addition to Y1238 and Y1239, there are other tyrosines that contribute to regulation of RON activity. For example, Y1198 is highly conserved among RTKs and its phosphorylation is directly associated with RON activity (Jeffers et al. 1997; Wei et al. 2005b). Mutation of this tyrosine to phenylalanine dramatically reduces RON autophosphorylation (Wang et al. 2014). Y1317 is another conserved tyrosine in the consensus sequence of the kinase domain that forms a putative docking site for SH2-containing molecules. Mutation of this tyrosine abolishes the level of receptor trans-autophosphorylation, pointing to its importance in receptor activity (Santoro et al. 2000).

The carboxy-terminal domain of RON contains two conserved tandem tyrosines, Y1353 and Y1360, known as docking sites (Ponzetto et al. 1994; Iwama et al. 1996; Wang et al. 2002). These sites serve as bridges to transduce signals from the kinase domain to downstream effectors of RON through binding to the SH2 domain of several adaptors, including Gab1 as the key adaptor (Ponzetto et al. 1994; Germano et al. 2006; Chaudhuri et al. 2011). The role of these tyrosines and their necessity for RON signal transduction is somewhat controversial, however. It has been shown that an experimental mutation in the kinase domain of RON (M1254 T) is able to overcome the requirement for Y1353 and Y1360 in promoting oncogenic activity (Santoro et al. 2000). The docking tyrosines in murine RON/Stk have also been shown to be dispensable for constitutive activation of mitogen-activated protein kinase (MAPK) (Wei et al. 2005b). However, in a separate study, these tyrosines were shown to have inhibitory function on the kinase activity of RON when expressed as a competing peptide, suggesting they are important for RON activity (Yokoyama et al. 2005). In our hands, mutation of these two tyrosines to phenylalanine makes the receptor even more competent for activating phosphoinositide 3-kinase (PI3K) and MAPK pathways (N Faham, unpubl.). The apparent discrepancy in the requirement for Y1353 and Y1360 is likely due to the presence of several critical tyrosines in the kinase domain that can compensate as docking sites for transducing the signal to effectors in the absence of the two carboxy-terminal tyrosines (Hanks and Quinn 1991; Songyang et al. 1995; Santoro et al. 2000; Wei et al. 2005a). These observations are in line with a study showing that the multisubstrate docking site of MET is not required for transmitting the signal to RAS and inducing cell scattering (Tulasne et al. 1999). Based on these investigations, it has been suggested that not all signaling and biological activities of MET are mediated through its carboxy-terminal tyrosine residues. In the case of RON, it is clear that deletion of the entire carboxy-terminal tail abrogates downstream signaling and eliminates RON-mediated tumorigenic activities (Lu et al. 2007).

LIGAND-DEPENDENT VERSUS LIGAND-INDEPENDENT RON SIGNALING

RON activation under physiological conditions, where there is basal level of RON, occurs through binding of its ligand, MSP (Danilkovitch et al. 1999; Wang et al. 2006, 2013a; Chaudhuri et al. 2013; Chaudhuri 2014). Hepatocytes are the major source of MSP, which activates RON in a paracrine manner (Bezerra et al. 1993; Yoshimura et al. 1993). Other organs like lungs, adrenal glands, placenta, and kidney can also express MSP, but to a lesser extent (Chang et al. 2015). Under pathological conditions, (e.g., in certain cancers), MSP is overexpressed in cancer cells along with RON and can lead to autocrine activation of RON (Riggins et al. 2006). MSP circulates in the blood in its biologically inactive form (Nanney et al. 1998; Rampino et al. 2002; Kawaguchi et al. 2009), and cleavage by matriptase or other serine-like proteases gives rise to conversion of pro-MSP to the mature dimeric active form (Bhatt et al. 2007; Kawaguchi et al. 2009). Binding of active MSP to the sema domains of RON induces receptor dimerization and subsequent conformational changes in the extracellular domain, which increases MSP binding affinity (Wang et al. 1997; Carafoli et al. 2005; Chao et al. 2012). These conformational changes are critical to trigger RON activation (Yokoyama et al. 2005) and are followed by sequential phosphorylation of regulatory tyrosines in the kinase domain and docking tyrosines in the carboxy-terminal tail (Ponzetto et al. 1994; Danilkovitch et al. 1999).

In the case of RON overexpression (e.g., in tumors), activation can occur independently of MSP by formation of RON homodimers via the sema domain (Chao et al. 2012). It seems that the close proximity of densely expressed RON molecules allows them to transphosphorylate each other without requiring ligand (Danilkovitch-Miagkova 2003). It is unclear, however, whether activation of RON via MSP versus ligand-independent activation due to RON overexpression leads to exposure of different tyrosines and, therefore, differential phosphorylation patterns on the RON receptor. In one study, MSP binding caused increased phosphorylation of Y1360 and not Y1353, compared with auto-activation of RON (Feres et al. 2009). This is in contrast with another study indicating Y1353 as the critical tyrosine for MSP-induced RON function (Chaudhuri et al. 2011). The reason for these discrepancies might be due to analysis of different cell types.

Even though both MSP-dependent and MSP-independent RON activation result in up-regulation of kinase activity and enhanced downstream signaling (Gaudino et al. 1994), there are some differences in these two types of activation with regard to biological outcomes. Based on the evidence so far and examples below, RON does not require MSP for all of its intrinsic functions in cancer cells, but there are certain functions that are MSP-dependent. On the other hand, to our knowledge thus far, MSP appears to be completely dependent on RON to mediate its function (Wang et al. 1994, 1995). For instance, with regard to the intrinsic effect of RON on cancer cells, it has

been shown that MSP is necessary to prevent anoikis in RON-overexpressing epithelial cells under serum-starved conditions. Neither expression of RON alone nor presence of MSP without RON was enough to prevent anoikis in these cells, implying ligand-dependent function (Danilkovitch et al. 2000). We have found that RON overexpression in breast cancer cell lines that contain no detectable MSP is sufficient to promote cancer progression and metastasis when injected orthotopically in immunocompromised mice (N Faham, unpubl.). This is presumably a ligand-independent function because murine MSP is widely believed not to be able to bind and activate human RON. MSP expression in these cells results in a higher incidence of metastasis suggesting that the metastatic potential of RON is enhanced through ligand-dependent mechanisms (Zinser et al. 2006; Welm et al. 2007; Cunha et al. 2014). Similarly, Feres et al. (2009) reported that expression of RON in immortalized human breast MCF-10A cells resulted in protection from cell death and increased spreading and migratory potential, independent of MSP. However, MSP stimulation was required to boost RON-mediated cell migration and proliferation. Another example of MSP independent function of RON was reported in bladder cancer cells under serum-starved conditions, where RON translocated to the nucleus in complex with EGFR and operated as a transcriptional activator of approximately 134 different target genes. Interestingly, neither MSP stimulation nor RON homodimerization or phosphorylation was required for nuclear translocation of RON (Liu et al. 2010). This group has suggested that cancer cells can bypass regular mechanisms of RON activation under stress conditions to confer a survival advantage. In yet separate study, phosphorylation of RON through interaction with integrins and as a consequence of adhesion to extracellular matrix is another example of MSP independent activation of RON, which was mediated by c-Src-FAK pathway (Danilkovitch-Miagkova et al. 2000).

MECHANISMS OF RON ACTIVATION IN CANCER

Activation of RON in tumors is most often due to receptor overexpression, rather than classical MSP binding (Camp et al. 2007; Wang et al. 2007; Yao et al. 2013a). Mutations in the *RON* gene, generation of splicing variants/truncated forms, and, very rarely, increased gene copy number are also documented mechanisms of RON activation in different cancers (Wang et al. 2013a).

Mutation of *RON* (resulting in R1018G, located in the JM domain) has been reported in 11% of gastroesophageal adenocarcinoma, but *RON* is rarely mutated in other cancer types (Catenacci et al. 2011; Yao et al. 2013a). As a result of this mutation, which disrupts the conserved c-Cbl binding motif, RON protein stays stable and active. In addition to mutation, increased copy number is another mechanism of RON activation in gastroesophageal cancer, which has been shown to be a prognostic factor for worse survival (Catenacci et al. 2011).

In contrast to rare gene mutation and amplification events as causes of RON activation, generation of oncogenic splicing variants and truncated forms are common in multiple epithelial cancers (Wang et al. 2006). Approximately nine different nonmutated RON isoforms have been described in various epithelial cancer types including colorectal cancer, glioma, and breast cancer (Gaudino et al. 1994; Zhou et al. 2003; Eckerich et al. 2009; Liu et al. 2011; Yao et al. 2013b). Exon skipping is the most common event leading to splice variants, termed RON Δ 170, RON Δ 165, RON Δ 160, and RON Δ 155 (Collesi et al. 1996; Zhou et al. 2003; Lu et al. 2007). Except for RON Δ 170 which is kinase domain defective, and soluble RON Δ 85, which acts as a dominant-negative isoform without any scattering activity, the rest of the isoforms are constitutively active in the absence of MSP and some have been shown to have cell-transforming potential (Angeloni et al. 2003, 2004; Wang et al. 2006; Ma et al. 2010a,b).

A unique example of a potent, constitutively active, variant of RON is RON Δ 55 (referred to as short form, or sfRON). sfRON lacks most of the extracellular domains, but retains the transmembrane and intracellular domains. In contrast to most of the other RON variants that are generated by exon skipping, RON Δ 55 is produced by an alternative transcription start site within exon 10 of *RON* (Bardella et al. 2004). We have shown that overexpression of this isoform converts slow-growing, nonmetastatic breast tumors derived from MCF7 cells into fast-growing tumors that spontaneously metastasizes from the mammary gland to liver and bones. Mechanistic studies revealed that this phenotype occurs through strong activation of PI3K pathway (Liu et al. 2011). Overexpression of sfRON in ovarian cancer cells also causes activation of PI3K/PDK1 pathway, resulting in EMT and aggressive tumor growth and metastasis (Moxley et al. 2016). Along with these findings, overexpression of sfRON in T47D cells increased their motility and growth rate which was accompanied by increase in EMT-related SLUG expression (Bardella et al. 2004). Oncogenic signaling of sfRON in acute myeloid leukemia, however, has been reported through activation of the Src family kinase Lyn as well as Bcl-2 (Fialin et al. 2013).

Recently, a novel splice variant of RON (termed P5P6) was found in the majority of pancreatic cancers as a result of partial skipping of exon 5 and 6. This isoform is constitutively phosphorylated (in the absence of MSP), activates AKT, and has transforming ability in immortalized pancreatic epithelial cells (Chakedis et al. 2016a). This isoform, together with sfRON, comprises most of the RON protein in pancreatic cancer specimens. Expression of these variants induces markedly different patterns of gene expression than wild-type RON (Chakedis et al. 2016b). It is interesting that even though RON P5P6 is similar to RON Δ 160 (both resulting from complete skipping of exon 5 and 6), RON P5P6 signals through AKT, whereas RON Δ 160 preferentially activates the β -catenin pathway (Xu et al. 2005). Likewise, most RON variants can activate multiple signaling cascades, but with differ-

ent substrate specificity than that of wild-type RON. These distinct features arise from increased catalytic efficiency of the kinase domain, which changes the substrate profile (Santoro et al. 1998; Xu et al. 2005). It would be interesting to characterize signaling pathways downstream from different RON isoforms, either individually or as heterodimer with RON or other RTKs, because not all of these isoforms have been analyzed in detail. Lack of partial or complete domains in these variants leads to generation of different three-dimensional structures that either reside on the cell surface or remain intracellular because of their inability to convert to a two-chain form (Iwama et al. 1996). Structural characterization of these isoforms and their effect on downstream signaling cascades in different tumors may be critical for designing treatment strategies. As some of these RON variants are constitutively active because of either partial or complete deletion of the extracellular domain, they do not require MSP for activation. Therefore, monoclonal antibodies that prevent binding of MSP to RON may be ineffective in cancers harboring these isoforms. Using small molecule inhibitors or antibodies with a different mode of action might have a broader efficacy.

SIGNALING PATHWAYS DOWNSTREAM FROM RON IN CANCER PROGRESSION

It is well accepted that RON mediates several oncogenic functions in cancer cells, including cell proliferation and survival; cell adhesion and spreading; cell dissociation and migration; EMT and matrix invasion; and establishment of metastasis. These features point to the importance of RON in later stages of cancer and RON expression correlates strongly with invasion, tumor stage, and poor prognosis in most, but not all, cancers (Ronsin et al. 1993; Wang et al. 2003, 2006; Lee et al. 2005; O'Toole et al. 2006; Thomas et al. 2007; Welm et al. 2007; Catenacci et al. 2011; Benight and Waltz 2012; Song et al. 2012; Tactacan et al. 2012).

Aggressive cancer phenotypes caused by RON are the result of activation of complex downstream signaling networks including PI3K/AKT, MAPK, JNK, β -catenin, and STAT pathways (Danilkovitch-Miagkova 2003; Yao et al. 2013a). Even though numerous signaling pathways downstream from RON have been described, few studies have focused on the detailed regulation of these pathways in each phenotype.

Regarding tumorigenesis, overexpression of RON in mammary epithelium using a transgenic mouse model induced a tumorigenic phenotype associated with high metastatic burden in lung and liver. Expression analysis of molecules involved in cell cycle progression revealed that RON overexpression led to increased phosphorylation of MAPK and β -catenin, and up-regulation of β -catenin target genes such as cyclin D1 and c-Myc (Zinser et al. 2006). Conditional deletion of β -catenin in the context of RON overexpression resulted in delayed onset of mammary hyperplastic nodules and tumorigenesis, decreased tumor growth, and decreased liver metastasis at the studied time point, revealing a contributing, but not

essential, role of β -catenin in mammary tumorigenesis downstream from RON (Wagh et al. 2012). Gene expression analysis of the A2780 ovarian cell line has shown up-regulation of several MAPK target genes in response to MSP (Chaudhuri et al. 2011). In leukemia and multiple myeloma, RON-induced IL-6 secretion seemed to underlie constitutive activation of Jak/Stat3 pathway and poor prognosis (Del Gatto et al. 1995; Danilkovitch-Miagkova 2003). Signaling in RON-overexpressing gastroesophageal adenocarcinoma cell lines and tissues has been reported to be through STAT3, the inhibition of which resulted in decreased viability of cell lines (Catenacci et al. 2011).

Regarding cell motility and EMT *in vitro*, activation of RON by MSP in noncancerous MDCK cells caused enhanced migration and cell motility through activation of MAPK pathway (Xiangming et al. 2011). In a further detailed *in vitro* investigation, RSK2, a principle effector of the Ras-ERK1/2 pathway, was reported as the main molecule bridging RON signaling to EMT-like biochemical changes such as migration and spindle-like morphology. In this investigation, MSP stimulation of RON in MDCK cells led to phosphorylation of ERK1/2 and RSK2, which resulted in enhanced migration along with diminished E-cadherin and increased vimentin expression—classic features of EMT. Inhibition of RSK2 in these settings reversed the spindle-like morphology and restored E-cadherin expression. Induction of EMT in these cells seems to be collaborative with TGF- β signaling (Wang et al. 2004; Ma et al. 2011). Feres et al. have shown that c-Src activity was essential for MSP-independent RON-mediated migration, cell spreading, and survival in MCF-10A cells; this might be attributed to the involvement of c-Src signaling in adhesion. MAPK and PI3K/AKT pathways, however, contributed to proliferation in the presence of MSP (Riggins et al. 2006; Feres et al. 2009). In a separate study, despite simultaneous activation of MAPK, FAK, and c-Src pathways, MSP exerted its anti-anoikis effect via PI3K pathway (Danilkovitch et al. 2000).

Besides signaling downstream from RON as an individual RTK, cross talk with other RTKs can further diversify the cellular pathways used or can enhance signaling intensity through particular pathways. This phenomenon can happen with or without the associated ligand and can be unidirectional or bidirectional. Interactions of RON with several RTKs including MET, EGFR, IGFR, and PDGFR have been reported (Follenzi et al. 2000; Danilkovitch-Miagkova and Leonard 2001; Peace et al. 2003; Thomas and Theodorescu 2006; Kobayashi et al. 2009; Liu et al. 2010; Benvenuti et al. 2011; Jaquish et al. 2011; Keller et al. 2013). Results of these interactions are sustained active signaling, enhanced cell survival, and increased invasiveness of tumors. These interactions are nicely reviewed elsewhere (Yao et al. 2013a) and are major causes of compensatory signaling and acquired resistance to single targeted therapies in cancer (Potratz et al. 2010; Wang et al. 2013b; Zhao et al. 2013). As mentioned earlier, different RON isoforms can signal distinctly from wild-type RON, and it is possible that

individual or coexpression of these variants further affects other RTK interactions and downstream signaling during tumor progression. So far, it does not appear that a particular signaling pathway can be marked as the “Achilles heel” of RON signaling in all cancers, or even in a single cancer type. Activation of signaling downstream from RON differs greatly based on tissue availability of adaptor and signaling proteins in various cancers, the presence or absence of MSP, generation of RON isoforms, and presence of other RTKs.

CELL-AUTONOMOUS VERSUS NON-CELL-AUTONOMOUS FUNCTIONS OF RON IN CANCER PROGRESSION

Further complexity regarding RON function in cancer arises from its function in the tumor microenvironment. The contributing roles of tumor microenvironment in cancer progression and metastasis are increasingly realized, and the prominent effects of RON in resolving inflammation and promotion of wound healing are opening an exciting new opportunity to consider in cancer therapy. RON is expressed at low levels in certain types of terminally differentiated resident macrophages such as microglia, dermal macrophages, and alveolar macrophages and at very high levels in peritoneal macrophages (Brunelleschi et al. 2001; Suzuki et al. 2008; Okabe and Medzhitov 2014). RON activation promotes polarization of macrophages toward the immunosuppressive alternatively activated (also known as “M2”) phenotype (Correll et al. 1997; Liu et al. 1999; Morrison and Correll 2002; Morrison et al. 2004; Kretschmann et al. 2010; Eyob et al. 2013b). RON does this in part by down-regulating IL-12, and therefore decreasing IFN- γ production by natural killer cells (Morrison and Correll 2002; Wilson et al. 2008). However, there are many other RON-mediated events that suppress inflammation, such as reduction of MHC class II surface expression, decreased STAT1 phosphorylation (in response to decrease in IFN- γ production), up-regulation of STAT3 phosphorylation, increased production of IL-10 and IL-6, and reduction of COX-2 expression through activation of NF- κ B (Zhou et al. 2002; Gunella et al. 2006; Ni et al. 2007; Yu et al. 2009). Interestingly, RON was recently reported to play a protective role in obesity-induced chronic inflammation, through exerting a repair phenotype in a subpopulation of macrophages (Yu et al. 2016). A detailed review on the role of RON in inflammation can be found elsewhere (Wang and Hankey 2013).

Based on reports so far, the non-cell-autonomous, or extrinsic, functions of RON on the tumor microenvironment appear to be dependent on MSP (Morrison and Correll 2002; Morrison et al. 2004; Wilson et al. 2008; Sharda et al. 2011). As a result of RON-mediated immunosuppressive effects, “M2” macrophages fail to present antigen to T cells and instead produce cytokines that inhibit expansion of lymphocytes. They also secrete particular cytokines, angiogenic factors and growth factors that support proliferation and migration of epithelial can-

cer cells (Wyckoff et al. 2004; Mosser and Edwards 2008; Solinas et al. 2009). In some cases, tumors appear to hijack RON function by up-regulating MSP to influence the inflammatory process. For example, we have shown that loss of host RON activity in the presence of tumor specifically prevents suppression of the peripheral CD8⁺ T-cell population. Increased CD8⁺ T-cell activity in this model, followed by production of antitumor factors like TNF- α , leads to reduction in metastatic burden by inhibiting conversion of micrometastases to macrometastases (Eyob et al. 2013a). Inhibition of RON kinase activity by a selective small molecule inhibitor (BMS-777607) caused CD8⁺ T-cell-mediated clearance of micrometastatic tumors and reduced outgrowth of established metastatic nodules in the mouse lungs (Eyob et al. 2013a). Similar results have been shown in a prostate cancer model (Gurusamy et al. 2013).

Another MSP-dependent, extrinsic effect of RON in the cancer setting is promotion of osteolysis through activation of osteoclasts, which are macrophage-derived cells in bones. This feature of RON might play an important role in several pathological conditions, such as osteoporosis and certain metastatic cancers like breast cancer, non-small cell lung cancer, prostate cancer, and multiple myeloma (Kozlow and Guise 2005; Roodman 2010; Sturge et al. 2011; Ibrahim et al. 2013). There are several tumor-derived factors that can mediate osteolytic lesions including TGF- β and PTHrP (Yin et al. 2005; Azim et al. 2012). RON is highly expressed on osteoclasts, but the role of MSP/RON pathway in osteolysis is just now being investigated (Kretschmann et al. 2010; Andrade et al. 2017). Our current work shows that MSP/RON signaling is responsible for bone resorption in breast cancer-mediated bone metastasis and also in osteoporosis. The mechanism of enhanced osteoclasts activity in these settings appears to be through activation of Src signaling and parallel to RANK pathway. This effect of RON strongly relies on the presence of MSP, as RON overexpression in mammary tumors by itself did not cause bone metastasis (AL Welm, unpubl.; Zinser et al. 2006), whereas MSP overexpression in these tumors led to spontaneous bone metastasis through host RON. Furthermore, activation of osteoclasts *in vitro* by MSP-expressing breast cancer cells versus non-MSP-expressing cells has been shown previously (Welm et al. 2007). We also confirmed this exciting novel role of RON/MSP using a RON inhibitor, BMS-777607, which reversed osteolytic lesions in breast cancer mouse models and improved bone turn over markers in human subjects (Andrade et al. 2017). A summary of the current understanding of extrinsic and intrinsic roles of RON, as well as its MSP-dependent and -independent functions in cancer, is presented in Figure 1.

STRATEGIES FOR TARGETING RON FOR CANCER THERAPY

Based on strong associations between RON activity and poor outcomes in cancer patients, the simultaneous intrinsic and extrinsic roles of RON in promoting cancer progression, and its relatively dispensable function in

most normal adult tissues, targeting RON is a ripe opportunity for cancer therapy, particularly in patients whose cancers are strongly addicted to this oncogene. In addition, studies have shown that activation of RON is responsible for emergence of resistance in response to single-agent therapies targeting other RTKs. For example, resistance to lapatinib in HER2-positive breast cancer cells and resistance to IGF1R inhibitor in childhood sarcomas have both been attributed to RON activity (Potratz et al. 2010; Wang et al. 2013b). In pancreatic cancers, RON overexpression is also associated with resistance to gemcitabine (Logan-Collins et al. 2010). In all of these examples, inhibition or silencing of RON restored sensitivity to the original treatment. In another study, knock-down/inhibition of RON sensitized pancreatic cells to histone deacetylase (HDAC) inhibitors (Zou et al. 2013). These data provide further rationale to consider RON inhibition to maximize treatments efficacy in certain cancers.

Various strategies have been reported for targeted therapy based on RON, including monoclonal antibodies and small molecule inhibitors (SMIs), some of which are already in clinical trials (refer to Wang et al. 2010, Chang et al. 2015 and Yao et al. 2013a for detailed descriptions). Monoclonal antibodies have shown efficacy in some preclinical models (O'Toole et al. 2006; Li et al. 2010; Padhye et al. 2011; Yao et al. 2011). However, SMIs might have potential to be used in a more widespread way, given that RON activity does not always depend on MSP (Yao et al. 2013a; Bieniasz et al. 2015). Likewise, it is unclear how anti-RON antibodies might affect signaling when another RTK is involved. Due to the high degree of similarity in the kinase domains of MET and RON, available SMIs often show dual inhibitory effect with slightly different IC₅₀ values (Yan et al. 2013; Yao et al. 2013a; Chang et al. 2015). To our knowledge, BMS-777607 and LCRF-0004 are the only SMIs reported to inhibit RON at lower IC₅₀ than Met (Schroeder et al. 2009; Raeppl et al. 2010, 2015). BMS-777607/ASLAN002 has shown very promising results in preclinical models of breast, pancreatic, prostate, and colorectal cancer and has recently finished phase I clinical trials (Dai and Siemann 2010; Eyob et al. 2013a; Zeng et al. 2014; Bieniasz et al. 2015; Andrade et al. 2017). However, as experienced with other single targeted therapies (Alexander and Wang 2015), resistance has been reported with targeting RON alone, even in cancers that were highly addicted to RON signaling (Sharma et al. 2013; Zhao et al. 2013; Kang et al. 2014). The mechanism lies in compensatory signaling coming from other RTKs like MET, as well as multikinase inhibitory potential of this inhibitor which can lead to induction of polyploidy and resistance to chemotherapeutics (Sharma et al. 2013; Zhao et al. 2013). Mechanistic studies, however, have revealed that this phenotype was attributed to the usage of higher doses of BMS-777607 required for targeting RON, and were due to inhibition of aurora B kinase (Sharma et al. 2013; Zhao et al. 2013; Zeng et al. 2014). More work is needed to determine how and when RON inhibitors should be used and how to design combinatorial treat-

Figure 1. Schematic of intrinsic and extrinsic roles of RON in cancer progression. (A) Secreted macrophage-stimulating protein (MSP) from the liver or tumor cells results in activation of RON in cancer cells in a paracrine or autocrine manner, respectively. Cell-autonomous or intrinsic functions of RON in cancer cells leads to activation of several downstream signaling pathways including phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), β -catenin, Src, and Jak/Stat3 (Danilkovitch-Miagkova 2003; Yao et al. 2013a). Activation of RON in cancer cells can be both MSP-dependent or MSP-independent. However, two major types of RON activation in cancers occurs through protein overexpression and/or generation of splice variants, which are constitutively active and do not depend on MSP for activity (Wang et al. 2006, 2007; Camp et al. 2007; Yao et al. 2013a). Signaling downstream from each variant can be different from that of full-length wild-type RON (Xu et al. 2005; Chakedis et al. 2016a). sfRON and RON Δ 155 are two examples of RON variants that are constitutively active in different cancers (Zhou et al. 2003; Liu et al. 2011; Fialin et al. 2013). Non-cell-autonomous, or extrinsic, functions of RON include (B) immune suppression in tumor microenvironment, through promotion of an alternatively activated phenotype in macrophages (Morrison and Correll 2002; Morrison et al. 2004; Eyob et al. 2013b) and (C) bone resorption through activation of osteoclasts (Kretschmann et al. 2010; Andrade et al. 2017). Based on the reports so far, these extrinsic effects of RON in macrophages and osteoclasts are MSP-dependent (Morrison et al. 2004; Wilson et al. 2008; Sharda et al. 2011; Andrade et al. 2017).

ment strategies in each cancer subtype to circumvent possible resistance.

CONCLUSION

RON is a multifunctional mediator of cancer progression and metastasis for many tumor types. Its dual role in the cancer cells and in the tumor microenvironment, while having no known critically important functions in normal adult tissues, makes it an ideal target for cancer therapy. Many years of basic science research have revealed the function of RON in cancer cells and in the immune system. Published data from multiple laboratories now indicate that inhibiting RON reduces tumor burden and metastatic growth but also boosts the immune response to the tumors. Several inhibitors are now in clinical development, and a continuing understanding of RON function in multiple cancer types should inform thoughtful design of clinical trials on the horizon.

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