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Ron receptor tyrosine kinase signaling as a therapeutic target

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Abstract

Introduction—Since its discovery nearly 20 years ago, the Ron receptor tyrosine kinase has been extensively studied. These studies have elucidated many of the major signaling pathways activated by Ron. In the context of the inflammation and cancer, studies have shown that Ron plays differential roles; Ron activation limits the inflammatory response while in cancer, Ron activation is associated with increased metastases and poor prognosis.

Areas Covered—This review discusses the current literature with regard to Ron signaling and consequences of its activation in cancer as well as its role in cancer therapy. Further, we discuss the mechanisms by which Ron influences the inflammatory response and its role in chronic inflammatory diseases. Finally, we discuss Ron's connection between chronic inflammation and progression to cancer.

Expert Opinion—The complex nature of Ron's signaling paradigm necessitates additional studies to understand the pathways by which Ron is functioning and how these differ in inflammation and cancer. This will be vital to understanding the impact that Ron signaling has in disease states. Additional studies of targeted therapies, either alone or in conjunction with current therapies are needed to determine if inhibition of Ron signaling will provide long term benefits to cancer patients.

Keywords

Ron receptor; MST1R; hepatocyte growth factor-like protein; Met receptor

2. Introduction

Ron is a tyrosine kinase (TK) receptor of the Met proto-oncogene family. Also known as macrophage stimulating 1 receptor (MST1R), identification of the receptor was first reported in 1993, wherein Ronsin *et al.* described the receptor and its homology with c-Met [1]. Since this initial report, there have been more than 300 papers that focus on Ron in both

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Declaration of Interest

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normal and diseased states with Ron activation, through its pleiotropic downstream signaling partners, inducing diverse effects on cellular function. Although Ron and Met are the only two members of this receptor tyrosine family, the receptors share only 34% overall homology. However, the tyrosine kinase region of the receptors are quite similar with 80% homology [2]. The Ron receptor is also evolutionarily conserved, with homologs to the receptor found in multiple mammalian species including mouse [3, 4] and rat [2] as well as non-mammalian species such as puffer fish [5] and sea urchin [6]. The Ron receptor is encoded on human chromosome 3p21.31 and is synthesized as an 185kD precursor protein. This proform is then cleaved into the 35kD extracellular alpha chain and the 150kD beta chain, which has extracellular, membrane spanning and intracellular domains. The extracellular portion of the beta chain is then disulfide linked to the alpha chain forming the mature receptor.

The only reported ligand for Ron is hepatocyte growth factor-like (HGFL), also known as macrophage-stimulating protein (MSP). Although originally identified by its domain structure as similar to hepatocyte growth factor (HGF), the ligand for Met, HGFL and HGF share only 45% homology and the ligands are not cross reactive [7]. HGFL is also found on human chromosome 3p21.31 and, similar to Ron, is evolutionarily conserved. The protein is produced mainly in the liver and secreted into the circulation as an 80kD proform that can be cleaved by proteases in the coagulation cascade [8] as well as membrane bound proteases. The resulting cleavage fragments form a 50kD alpha subunit that is disulfide linked to the 35kD beta chain. The beta chain of HGFL mediates binding of HGFL to the Ron receptor while the alpha chain is known to regulate the activity of Ron [9, 10]. Upon stimulation with HGFL, Ron forms homo- or heterodimers and autophosphorylates. This phosphorylation activates multiple signaling pathways including PI3-K/Akt, MAPK, Ras, Src and β -catenin signaling, leading to multiple, cell-type specific changes that will be discussed in the following sections.

1.1 Ron expression patterns and identification in cancer

Ron is expressed early in development, with fetal liver expression as early as embryonic day (e)12.5 and in other sites such as adrenals, spinal ganglia, skin, lung and bone around day e13.5-16. By e17.5, expression is seen in the liver, central nervous system, bone, gastrointestinal tract and kidney [11, 12]. Additional evidence to Ron's role in development comes from studies performed in the mammary gland. Ron is expressed in the developing mammary gland [13] and is important during maturation; genetic deletion of Ron in pre pubertal mice causes an increase in branching morphogenesis and accelerated ductal elongation [14].

In adult tissues, Ron expression has been found in brain, adrenal glands, epithelium of the gastrointestinal tract, testis, kidneys [11] and ovaries [15]. However, most of the studies on Ron in adult tissues have been reported in cancer related models or in human tumor samples. For example, a panel of more than 300 human tumor samples representing 6 cancer types was examined for Ron expression. The tissues tested include breast, lung, prostate, pancreas, gastric and colon. This analysis found >65% of each tumor type was positive for Ron expression, with 100% of breast cancer tissues expressing Ron [16]. The majority of cancer

models indicate that Ron is highly expressed in the epithelial cells of the tumor [16]. In addition to the numerous cancers in which Ron overexpression has been identified, recent reports indicate that Ron is also upregulated in human gliomas [17], melanoma [18] and Merkel cell carcinoma [19]. Merkel cell carcinoma is a neuroendocrine tumor of the skin; the addition of these 3 cancer subtypes suggest Ron is also playing a role in both neurological and skin cancers, expanding its role to most known cancer subtypes.

Numerous studies of Ron in the context of cancer and inflammation have been completed and a detailed description of their findings is too exhaustive for this review. As such, the reader is directed to review Wagh *et al.* for an extensive analysis of historical findings [2]. However, the wealth of research about this receptor has led to several well established findings including (i) that Ron and its ligand HGFL are important factors in tumorigenesis, (ii) that Ron and HGFL are key determinants in metastatic activities, and (iii) that the function of Ron and HGFL in innate immunity is to suppress the inflammatory response. Given the numerous on-going clinical trials involving receptor tyrosine kinase inhibitors in the treatment of cancer, it is paramount to understand their biology and potential clinical efficacy. Therefore, the purpose of this review is to discuss the current findings with regard to Ron and HGFL in cancer therapy and Ron's role in the relationship between inflammation and cancer.

1.2 Identification and function of the Ron ligand

The ligand for Ron has multiple gene names stemming from its discovery in different model systems. In 1976, macrophage-stimulating protein, MSP, was first reported as a component in serum that was capable of enhancing the chemotactic response of mouse peritoneal macrophages [20]. Then in 1991, the gene sequence for HGFL was first published and named based upon its sequence identity to hepatocyte growth factor (HGF), the ligand for the Met receptor. When MSP was later purified and sequenced, it was found to be identical to HGFL [21]. The receptor for HGFL was subsequently established to be Ron [7, 22]. Based on the reported HGFL induced functions in macrophages, Ron expression has been identified on several resident macrophage populations including peritoneal and alveolar macrophages, but not in circulating monocytes [23]. Multiple reports indicate that the role of HGFL stimulated Ron activation in macrophages is to limit the inflammatory response, shown by a reduction in nitric oxide production and cytokine/chemokine responses following macrophage activation [24–28].

2. Ron and Cancer

2.1 Activation

Many advances in the understanding of Ron's role in cancer cell functions have been recently published. First, the dimerization and subsequent phosphorylation of Ron has been shown to occur by both HGFL-dependent and independent mechanisms. For example, Feres *et al.* found that breast cancer cell migration and proliferation were HGFL-dependent functions. However, this study also found that activities such as enhanced cell spreading and survival occurred in the absence of HGFL [29]. Importantly, these activities were ligand independent as no other ligand has been identified for Ron. Additional studies using

pancreatic cancer cell lines found that Ron is able to form heterodimers with insulin-like growth factor-1 receptor (IGF1R). This signaling was described as unidirectional where IGF1 must bind to IGF1R to stimulate activation of this heterodimer and suggests that Ron is required for the migration of cells via IGF1R stimulation [30]. Other studies have shown that Ron is able to form heterodimers with epidermal growth factor receptor (EGFR); however, this signaling was bidirectional, where activation of either receptor causes transphosphorylation and downstream signaling [31]. Finally, multiple truncated isoforms of Ron have been found and their biological roles studied [17, 32–35]. Short-form (sf)-Ron is an N-terminally truncated form of Ron that confers susceptibility to Friend virus and is required for normal IFN γ production in concanavalin A treated mice [36, 37]. The 165kD Ron isoform (Ron) was shown to drive an invasive phenotype in early reports examining gastric cancer cell lines [33]. However, the mechanism for this phenotype was unknown. A report by Zhang *et al.* found that both Ron and the newly discovered Ron165.e11p are maintained as single chain proteins and cannot be processed and exported to the cell surface. These truncated Ron isoforms are retained in the cytoplasm and become constitutively activated, signaling through known downstream targets such as Akt and leading to epithelial to mesenchymal transition (EMT) [38]. These studies suggest that signaling of Ron through both HGFL dependent and independent mechanisms plays a role in tumorigenesis and that successful targeting of this receptor system for cancer therapy will require a more complete understanding of these signaling pathways.

2.2 Signaling

Numerous signaling pathways activated by Ron have been previously described [2]. However, additional studies detailing the fine regulation of these pathways are still an active area of investigation. For example, recent studies using MDCK cells expressing Ron have found that ribosomal S6 kinase 2 (RSK2), an intermediate in MAPK/ERK signaling, was directly phosphorylated by activation of Ron via HGFL; this activation leads to its dissociation with Erk1/2. Dissociation was followed by nuclear accumulation of RSK2 and the subsequent increase in EMT markers such as decreased E-cadherin and increased vimentin [39]. Others confirmed these results with regard to Ron and EMT, where HGFL stimulation of MDCK cells stably expressing Ron leads to loss of epithelial markers and increased mesenchymal markers through a similar pathway [40].

Although the role of β -catenin signaling downstream of Ron has been published [41], additional reports have expanded our understanding of the interactions of Ron and β -catenin. For example, work by our group supported the initial findings of Danilkovitch-Miagkova *et al.*, which described the signaling cascade induced by Ron-mediated β -catenin activation [41]. This is an HGFL dependent event whereby activation of Ron by ligand stimulation leads to β -catenin nuclear localization and subsequent increases in c-myc and cyclin D1 [42]. Further, we demonstrated the important requirement for β -catenin in mammary tumorigenesis, as loss of β -catenin leads to a delay in mammary hyperplasia and reduced the metastatic burden in mice that overexpress Ron in the mammary epithelium [43]. Additionally, work in the prostate has supported the role of Ron in β -catenin activation where overexpression of Ron leads to accumulation of β -catenin protein and increased pErk [44]. This signaling paradigm is similar to that described in mammary tumors [45]. Taken

together, these data support the role of β -catenin activation by Ron signaling. A summary of the current understanding of Ron signaling in cancer is presented in Figure 1.

2.3 Angiogenesis

The role of Ron in angiogenesis has been expanded as well. Ron expression in human prostate cancer cell lines can be correlated with production of angiogenic chemokines such as CXCL-1 and CXCL-8 through activation of the NF- κ B-dependent pathway. Overexpression of Ron in these cell lines led to increased microvessel density via recruitment of endothelial cells following orthotopic prostate injection [46]. Others have confirmed the role of Ron in angiogenesis in pancreatic cancer indicated by augmentation in VEGF expression with Ron activation [47]. However, Logan-Collins *et al.* was unable to confirm increased VEGF expression in pancreatic tumor lysates in Ron sufficient tumors compared to Ron deficient tumors [48]. Although these data provide some information for the role of Ron in angiogenesis, additional studies are needed to fully comprehend the role of Ron in angiogenesis. As angiogenic inhibitor therapies are part of the standard of care in cancer treatment [49], a thorough understanding of Ron's role in this process will be necessary for effective combination therapy.

2.4 Migration

An elegant study in pancreatic cancer cell lines recently reported the mechanism of action for Ron associated migration. Previous reports have shown that Ron associates with $\alpha 6 \beta 4$ integrin and is important for localization of this complex to lamellipodia in keratinocytes. Activation of Ron by HGFL in this system leads to keratinocyte spreading, migration and subsequent wound healing [50]. In the recent study [51], the authors found that Ron activation via HGFL interrupts the binding of plectin and integrin B4 (ITGB4) in hemidesmosomes in pancreatic cancer cells. This dissociation is mediated by PI3K downstream of Ron and appears to occur in a cyclic fashion, where Ron cycles between bound and unbound to plectin on the cell membrane, which allows for assembly and disassembly of the hemidesmosome. This action is suggested as the way by which pancreatic cancer cells are able to migrate over the extracellular matrix. This study provides a novel mechanism to explain how cancer cells can migrate through tissue although additional studies are needed to confirm this observation. It is possible that this mechanism is central to migration of all types of cancer cells or could be a cell type specific phenomenon.

3. Ron and Cancer Therapy

3.1 Current Therapies

Studying changes in Ron activation during treatment with currently available therapies provides additional insight into its role in therapeutic resistance. Logan-Collins and coworkers [48] found that knockdown of Ron using shRNA transfection in pancreatic xenografts delayed acquired gemcitabine resistance compared to Ron expressing xenografts. While 50% of the acquired resistance in the Ron knockdown group was attributed to re-expression of Ron, activation of other kinases (Met and EGFR) played a role in the other 50%, suggesting that kinase switching plays a major role in gemcitabine resistance. The

concept of kinase switching and its role in cancer resistance is well known. A recent review of mechanisms of resistance to imatinib therapy in chronic myeloid leukemia discusses the ability of the Bcr-Abl fusion gene to activate multiple downstream targets, including those activated by Ron (PI3K, Ras, Src) [52]. More work is needed to understand the role of kinase switching in solid tumors and how Ron is related to this process.

Additional studies have examined the association between Ron and tamoxifen resistance. First suggested in 1998 by the discovery of an ER binding site in the promoter region of Ron [53], recent work has found an important connection between Ron activation and tamoxifen cytotoxicity. Using both human and mouse breast cancer cell lines, McClaine *et al.* found that HGFL stimulated Ron activation led to a reduction in tamoxifen cytotoxicity [54]. This study also found increases in cyclin D1 expression in these cells along with increased ERE-driven luciferase expression after Ron activation. Given that elevated Ron is associated with poor prognosis in many cancer types [55–57], these results strongly suggest that Ron may be augmenting ER signaling and driving tamoxifen resistance.

3.2 Targeting Ron for Therapy

There has been a flourish of activity from different groups working to develop Ron related therapeutic modalities. Two antibody based methods have been reported: one is the development of TK specific antibodies as a treatment while the other uses Ron for targeted delivery of cytotoxic agents. The antibody foretinib is a TK inhibitor against Met, Ron and VEGFR designed to inhibit both proliferation and angiogenesis. While constructed to target Met and VEGFR, initial studies found potency against Ron as well [58]. Originally named EXEL-2880, this antibody was shown to tightly bind to Met's active conformation and form a salt bridge that protects the antibody from degradation. EXEL-2880 was shown to inhibit migration, invasion, anchorage dependent growth and endothelial tube formation by reducing phosphorylation of Met in the melanoma tumor cells as well as lung and liver metastases in animal models [58]. Phase I dose escalation studies in patients with confirmed metastatic or unresectable solid tumors determined the optimal delivery schedule and safety profile [59]. Additional secondary endpoints included examining outcomes in a subset of patients. These indicated a decrease in phosphorylated (p)Ron and pAkt, as well as reduced proliferation and increased apoptosis. Currently multiple studies are listed as ongoing or completed on the clinicaltrials.gov website that use foretinib alone or in combination with other established therapies in several different solid tumors. Long-term studies are a likely next step to determine if foretinib treatment either alone or in combination can prevent recurrence of distant metastases.

The second area of therapeutic research is using a Ron antibody for directed drug targeting. The rationale for this work is that as Ron is expressed on a large percentage of solid tumors, by delivering chemotherapeutic agents directly to the site of tumor activity, one can reduce off targeting effects and allow more of the cytotoxic agents to access the tumor. A series of papers by M.H. Wang and colleagues have documented the development of antibodies for this purpose. These antibodies (Zt/g4, Zt/f2, Zt/c9) are used to create immunoliposomes that transport doxorubicin (Dox) or 5-fluorouracil (5-FU) to the tumor. This group has shown that uptake of Dox delivered by these immunoliposomes is dose and time dependent and that

the antibody itself has no effect on Met or EGFR protein levels [60]. Further, Zt/g4 impairs tumor growth and sensitizes tumor cells to gemcitabine as shown by reduced colony formation as well as cell number [60]. Zt/g4 is effective at killing both breast and colon cancer cells [61] as well as purified pancreatic cancer stem cells [62] *in vitro*. Finally, they show that the Zt/f2 antibody inhibited tumor growth *in vivo*. Antibody delivery alone reduced tumor volume by 51%, whereas the addition of 5-FU immunoliposomes reduced tumor volume by 80%. Mechanistically, the authors showed that binding of Zt/f2 to Ron caused antibody-Ron complex internalization and subsequent degradation by the proteasome [63]. This series of papers represents a novel approach by which Ron can be utilized for cancer therapy. It will be interesting to follow the progression of preclinical models to human clinical trials in this scenario.

4. Ron and innate immunity

4.1 Mechanism of Action

As with Ron and cancer studies, many reports on the role of Ron in macrophage driven inflammation have been published in multiple chronic inflammatory models. HGFL dependent activation of Ron leads to inhibition of the classically activated M1 macrophage pro-inflammatory phenotype though inhibition of iNOS and inflammatory cytokine production and promotion of M2 anti-inflammatory phenotype as evidenced by increased arginase 1 production [64, 65]. The activation of Ron by HGFL in primary peritoneal macrophages is through the NF- κ B pathway [64]. This study also found that activation of macrophages by lipopolysaccharide (LPS) treatment leads to production of two isoforms of Ron; full length and a short form (sf-Ron) version that lacked most of the extracellular binding domain. The authors suggest that the production of the truncated Ron in response to LPS signaling represents a negative feedback mechanism by which the inflammatory response is limited [64]. Data supporting this concept has already been reported. Using a construct that allowed only the production of full length Ron, Wetzel *et al.* investigated the importance of sf-Ron in a model of acute liver injury. Loss of sf-Ron leads to more severe disease by histological and serum markers of liver injury [37].

Other macrophage subtypes implicate Ron in LPS-mediated NF- κ B signaling. HGFL pretreatment of alveolar macrophages led to a decrease in TNF α production mediated by reduced NF- κ B activation and increased I κ B levels. Ron was also found to regulate Adam17, the metalloproteinase responsible for releasing TNF α from membrane surfaces. Adam17 message and protein levels are increased in alveolar macrophages from Ron deficient mice [66]. Further, a myeloid cell specific knockout of Ron in alveolar macrophages demonstrated similar results with increased TNF α production and lung injury. Taken together, these studies indicate that Ron is playing a major role in limiting the innate immune response via myeloid cell regulation.

4.2 Ron and Chronic Inflammatory Diseases

Ron is increasingly shown to play a role in many common chronic inflammatory conditions. In rheumatoid arthritis, synovial fibroblasts (RASf) treated with HGFL had reduced expression of cytokines such as MIP-1, MCP-1, iNOS, COX-2 and RANTES after LPS

stimulation [67]. The authors also found decreases in activation of pathways known to be downstream effectors of Ron in RASF cells after pretreatment with HGFL. Interestingly, this report did not show that Ron was expressed on synovial fibroblasts and no study to date has done so. However, our own recent findings suggest that Ron is expressed in fibroblasts associated with prostate cancer (unpublished). Clearly, additional studies are needed in fibroblast cells to verify the presence of Ron as well as studies to further elucidate its role in rheumatoid arthritis pathology.

Studies of Ron in the pathology of inflammatory bowel disease (IBD) are ongoing due to the association of chromosomal aberrations in the 3p21 region in IBD patients. Multiple studies have identified single nucleotide polymorphisms (SNP) in the 3p21 region. Genome wide association studies (GWAS) studies have found an association with multiple SNPs located within the MST1R (Ron) gene and IBD [68, 69], including two SNPs that are predicted to cause amino acid changes (non-synonymous SNP) [69]. Other GWAS studies report an association between HGFL and IBD [69–72]. Interestingly, a different GWAS study in primary sclerosing cholangitis, an inflammatory bile duct disease that occurs concurrently with IBD in a subset of patients [73], also found an association with the same non-synonymous SNP (R689C) located in the beta chain of in HGFL as those reported for IBD. Computational analysis of the R689C SNP suggested that the arginine to cysteine conversion will negatively impact the ability of HGFL to bind to the Ron receptor [70]. However, a report published in early 2012 created a HGFL protein expressing the R689C mutation. By examining the ability of activated THP-1 cells to migrate and proliferate in response to wild type or mutant HGFL, they found that cells stimulated with the mutant protein were able to migrate and proliferate more efficiently than those stimulated with wild type HGFL [74], suggesting that not only does R689C HGFL bind to the Ron receptor, but binds in a way that over stimulates Ron. However, it should be noted that no binding, Ron activation or mechanistic studies have been completed using this HGFL mutant protein. Given the conflicting results of these two studies, we look forward to additional reports describing the effect of R689C on HGFL binding.

5. How does Ron connect inflammation and cancer?

Clearly, the function of Ron activation relates to the cell type that is expressing it. In cancer studies, the epithelial cell has been implicated with respect to the effects of excessive Ron signaling, with increased proliferation and migration among other results leading to aggressive and metastatic phenotype. However, in the immune compartment, Ron signaling seems to be involved in limiting the inflammatory response. A study by Stuart and Kulkarni *et al.* [75] demonstrates the cell specificity phenomenon. Using primary hepatocytes and Kupffer cells from Ron wild type (TK+/+) and Ron tyrosine kinase domain knockout (TK–/–) mice, the authors found exaggerated TNF α production as well as increased NF- κ B activation from TK–/– Kupffer cells when stimulated with LPS compared to control TK+/+ Kupffer cells. Interestingly, when TK+/+ hepatocytes were exposed to either conditioned media from the TK–/– Kupffer cells or TNF α directly, they had a significant increase in cell death compared to the TK–/– hepatocytes, suggesting that loss of Ron desensitizes hepatocytes to the excess of inflammatory mediators produced by the TK–/– Kupffer cells. Further, using mice with a conditional loss of Ron in hepatocytes or myeloid cells, the

authors showed that loss of Ron in hepatocytes alone is protective while loss in the myeloid compartment was detrimental in response to inflammation. These results provide support for the differential role of Ron in epithelial and immune cells. As inflammation is quickly becoming recognized as an important contributor to cancer development [76], understanding how Ron functions in both compartments within the context of cancer will be necessary for efficient targeting in therapy.

In addition to immune cells and epithelial cells, recent data suggests that Ron is expressed in synovial fibroblasts in RA patients [67]. Fibroblasts constitute a major proportion of stromal cells that provide growth signals to tumor cells within the microenvironment. Our own data indicates that prostate associated fibroblasts express Ron; therefore, determining the contribution of Ron in fibroblasts will be important in understanding the link between inflammation and cancer.

Finally, some of the inflammatory conditions to which Ron has been associated (RA and IBD) have been associated with increased cancer risk. In fact, a meta-analysis of the literature published between 2001 and 2011 found strong associations between 23 autoimmune and chronic inflammatory diseases and increased cancer risk [76]. The authors reported association of IBD with not only gastrointestinal cancers, but also small increases in lung, skin, endocrine and reproductive organ cancers. A diagnosis of RA was associated with an increased association with gastrointestinal, lung, skin, endocrine, breast and reproductive organ cancers [76]. Further, drugs used to treat both RA and IBD are also anti-cancer therapies. Methotrexate, a mainstay of cancer treatment, is a known antifolate drug that works by inhibiting DNA replication in dividing cells. This drug is also frequently used in the treatment of moderate IBD and RA. In these diseases, methotrexate is proposed to work through multiple mechanisms (reviewed in [77]), including inhibition of aminoimidazolecarboxamidoribonucleotide (AICAR) transferase, which leads to an increase in the anti-inflammatory metabolite adenosine.

These data provide a solid connection for chronic inflammation and cancer risk and specifically suggest that Ron may be a mediator for this connection.

6. Expert Opinion

Major progress has been made in the past few years in our understanding of the Ron receptor TK and its ligand HGFL. Many of the signaling paradigms critical for Ron's roles in both inflammation and cancer have been elucidated. However, given the complexity with which Ron functions, more discoveries are necessary. For example, we now understand that Ron can be activated via HGFL dependent and independent mechanisms, and the mechanism of activation profoundly affects downstream cellular activities. A greater understanding of the degree of interdependence of these pathways on each other will be necessary if we are to successfully target Ron for therapy in either cancer or inflammatory conditions.

Determining what role Ron plays in cancer stem cells (CSC) will be required as well. Padhye *et al.* indicated that Ron was expressed on pancreatic cancer stem cells purified from a cell line [62], however this is the only known report. As targeting the CSC population is

critical to prevent recurrence, understanding the role of Ron in this discrete cell population is important. As Ron overexpression in cancer is linked with poor prognosis [55–57], it is distinctly possible that Ron plays a role in the therapy resistant phenotype seen in CSC. A recent review on the CSC paradigm suggested that evidence supports the idea that the CSCs responsible for invasion, metastasis and therapeutic resistance have a mesenchymal like phenotype [78]. Ron is known to be a major driver of the EMT phenotype. Further, many of the signaling pathways that lie downstream of Ron activation have also been implicated in maintenance of the CSC populations (reviewed in [78]). Taken together, these ideas necessitate further investigation of the role of Ron in CSC.

Additional studies of HGFL in the context of disease are required to understand the contribution this ligand has to Ron activation. Although primarily produced in the liver and secreted, preliminary evidence from our group suggests that Ron overexpressing tumor cells can produce their own HGFL that acts in an autocrine or paracrine fashion to further stimulate Ron signaling within the tumor microenvironment. Also, we know from functional studies of HGFL R689C that mutations in HGFL itself can directly influence the function of Ron. These results suggest that targeting HGFL in the tumor microenvironment may be a viable therapeutic option that has yet to be explored.

Additionally, a better understanding of the role of Ron in the association between inflammation and cancer is needed. Studies of Ron's involvement in chronic inflammatory conditions such as inflammatory bowel disease are ongoing. Additional research in models of chronic inflammatory associated cancers will help determine the role of Ron in progression from a chronic inflammatory state to cancerous stage. For example, coupling the APC min mouse model with a chemical colitis model such as dextran sulfate sodium induces colorectal cancer in approximately 40% of treated animals (reviewed in [79]). The use of APC min mice will be especially interesting because these mice develop sporadic adenomatous polyps due to increased β -catenin signaling. Early work in this model showed that loss of APC leads to up regulation of c-myc and cyclin D1. Further, this work also found female APC min mice are susceptible to both spontaneous intestinal and mammary tumor formation [80]. However, work from our group suggested that Ron is not required for the formation and growth of adenomas in APC min mice [81]. These data examined only adenoma formation and did not include the use of an inflammatory inducing agent such as DSS. Therefore, investigation of the APC min mouse is still an attractive model for exploring the role of Ron at the intersection of cancer and inflammation.

Finally more studies are needed to determine if targeted therapy, either through inhibition of Ron signaling or by antibody directed delivery of cytotoxic agents, will provide long term benefits to cancer patients. It is well accepted that distant metastases and acquired resistance are a major causes of cancer related mortality, it will be interesting to see if Ron targeted therapy is able to reduce these occurrences. Given the results of Ron's role in tamoxifen and gemcitabine resistance and the prospect of kinase switching, multiple targeted therapies will be necessary in order to completely abrogate the ability of the tumor cells to evade treatment.

In summary, more studies on the role of Ron in cancer progression and inflammation are needed to fully understand the impact that Ron signaling has in disease states. Targeting Ron in cancer therapy is likely to provide benefit to patients, especially when used in conjunction with other approved therapies. Combining these therapies may lead to a reduction in metastatic disease and therapeutic resistance, improving the outcomes for many people affected by multiple cancer types.

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Figure 1. Schematic of the known signaling partners of Ron

A) HGFL dependent and independent Ron signaling. HGFL dependent Ron signaling impacts a variety of cell functions and induces multiple downstream effector pathways, including FAK [82] and JNK [83, 84], in which we have little information on the signaling intermediates. Activation of NF-κB is facilitated by IκB phosphorylation and dissociation, leading to chemokine production [46]. Activation of VEGF is mediated MAPK [47] via SRC [85]. PI3K activates AKT signaling with increased survival as one consequence [82]. Additionally, Ron was found to facilitate plectin/integrin B-4 (ITGB4) via PI3K phosphorylation of ITGB4 in a cyclic fashion, which is proposed as a mechanism by which migration occurs [51]. The best-characterized signaling cascade is activation of Erk. Ron signals through son of sevenless (SOS) and Ras [86], which activate RAF and MEK [54], leading to activation of Erk. Erk activation can activate multiple pathways, including the phosphorylation and nuclear translocation of RSK, which leads to EMT [39]. Alternatively, Erk phosphorylates β-catenin, leading to nuclear translocation and increases in c-myc and cyclin D expression [44]. For HGFL independent activation, Ron activates FAK and leads to increased cell spreading and survival [29]. **B)** Truncated versions of Ron (murine mRon, 165 [33] and 165.e11p [38]) are constitutively phosphorylated within the cytoplasm, which leads to activation of the AKT and Erk1/2 pathways and an EMT phenotypic change [38]. **C)** Ron can form heterodimers with other tyrosine kinases. Recent work demonstrated that Ron form heterodimers with IGF1R. Stimulation of IGF1R by ligand leads to phosphorylation of both receptors, IGF1R mediated activation of Stat3 and increased migration; however, HGFL binding of Ron is unable to activate this signaling cascade [30]. This unidirectional signaling is unique to the Ron:IGF1R heterodimer, whereas receptor binding to either Ron or EGFR can lead to phosphorylation of Ron:EGFR heterodimers and induce migration [31].