Therapeutic Considerations for Ron Receptor Expression in Prostate Cancer

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Abstract

Introduction: The Ron receptor tyrosine kinase was initially discovered as a protein which played a critical role in regulating inflammatory responses. This effect was primarily determined through studies in various macrophage populations. Since its initial discovery, a role has emerged for Ron as a driver of cancer within epithelial cells. After numerous publications have detailed a role for Ron in promoting tumor initiation, growth, and metastasis, Ron has been designated as an emerging therapeutic option in a variety of cancers.

Areas Covered: This review discusses the current literature regarding the role of Ron in prostate cancer and places special emphasis on the role of Ron in both epithelial cells and macrophages. Whole body loss of Ron signaling initially exposed a variety of prostate cancer growth mechanisms regulated by Ron. With the knowledge that Ron plays an integral part in regulating the function of epithelial cells and macrophages, studies commenced to discern the cell type specific functions for Ron in prostate cancer. A novel role for Ron in promoting Castration Resistant Prostate Cancer has recently been uncovered, and the results of these studies are summarized herein. Furthermore, this review gives a summary of several currently available compounds which show promise at targeting Ron in both epithelial and macrophage populations.

Outlook: Sufficient evidence has been provided for the initiation of clinical trials focused on targeting Ron in both macrophage and epithelial compartments for the treatment of prostate cancer. A number of therapeutic avenues for targeting Ron in prostate cancer are currently available; however, special consideration will need to take place knowing that Ron signaling impacts multiple cell types. Further understanding of the cell type specific functions of Ron in prostate cancer will help inform and shape future clinical research and therapeutic strategies.

Keywords

receptor tyrosine kinase; RON receptor; prostate cancer; hepatocyte growth factor-like protein

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Disclosure of potential conflicts of interest: The authors declare no conflicts of interest.

1. Introduction

Receptor tyrosine kinases are becoming increasingly prevalent medicinal targets as new information is uncovered revealing their importance in multiple diseases. Specifically, in cancer, receptor tyrosine kinases have been implicated as drivers of disease and there has been success targeting these proteins, such as the use of the monoclonal antibody trastuzumab to target HER2 in breast cancer (1). One such receptor that is receiving increased attention recently due to seminal findings regarding its crucial role in multiple cancers, such as pancreatic, breast, and prostate, is the Ron receptor/MST1R. The Ron receptor is a member of the Ron and c-Met family of cell surface receptor tyrosine kinases and is primarily expressed on epithelial cells and macrophages, although low levels of expression have been detected in other cell types (2–4). Ron and c-Met are the only two members of this family and the two receptors share some similarities in structure and function. Despite these similarities, a number of specific roles have emerged between the two receptors.

The only known ligand for Ron is Hepatocyte Growth Factor Like protein (HGFL), named due to the structural similarities to the ligand for c-Met, HGF, and the two are believed to have evolved from a common ancestor (5). HGFL is produced primarily by hepatocytes and secreted in the blood in a pro-form. Following cleavage, HGFL forms a heterodimer capable of binding to Ron (6–8). Both the Ron receptor and HGFL have been highly associated with multiple cancers (9–12). Specifically, in prostate cancer Ron was highly expressed in over 85% of primary tumors and in 100% of prostate cancer metastasis (13). The exceptionally high correlation with disease progression is one reason why Ron is the focus of numerous studies for the treatment of prostate cancer. With approximately 30,000 deaths annually in the United States from prostate cancer, the identification of novel targets to treat this disease is a crucial task that needs to be completed, and the Ron receptor is an up and coming therapeutic option (14).

1.1 Ron Structure and Function

The Ron receptor is located on chromosome 3p21.31 in humans and has homologs in several other organisms, such as rat (15), chicken (16), feline (17), mouse (15, 18), xenopus (19) and zebrafish (20). Structurally, the Ron receptor originates as an 185kDa precursor protein, which is cleaved into a 35 kDa extracellular alpha chain that is disulfide linked to a 150 kDa transmembrane beta chain. The extracellular portion of Ron contains a Sema-PSI domain required for ligand binding, while the intracellular portion possesses the kinase domain responsible for signal transduction (21). Ron activation results in receptor dimerization leading to autophosphorylation of kinase domain residues Y1238 and Y1239 and subsequent phosphorylation of Y1353 and Y1360, which induces the activation of multiple downstream signaling cascades (22). Recently, it has been discovered that the intracellular portion of Ron contains an acidic region of the juxtamembrane domain responsible for auto-inhibition; however, phosphorylation of Y1198 in the kinase domain relieves this inhibition and facilitates activation (23). A number of splicing and truncation variants have been identified for Ron, which produce differing effects on function/activation of the receptor (24). One isoform of Ron, known as short form Ron (sf-Ron/ RON 55), is heavily prevalent in

pancreatic cancer and is constitutively phosphorylated, has transforming activity, and is resistant to many therapies targeting the extracellular portion of Ron (25). Structural variants, such as sf-Ron, will need to be taken into consideration during the development of therapeutics targeting Ron signaling.

Initially the ligand for Ron, HGFL, was identified as a protein which induced changes in macrophage shape and spreading (26). Further work indicated that not only did HGFL treatment impact mechanical characteristics of the cell, but it also limited inflammatory responses. HGFL treatment of macrophages reduced nitric oxide production following treatment with a variety of stimuli (27). Shortly thereafter, crosslinking studies were performed to determine that HGFL was binding to Ron at the cell surface (28). Ron was further implicated in mediating inflammatory response as it was determined that Ron signaling deficient mice (TK–/–, lacking Ron tyrosine kinase domain) have a defect in the ability to regulate nitric oxide levels and incur greater tissue damage following inflammatory responses (29). The regulation of inflammatory responses through Ron signaling is a critical aspect of effective wound healing.

Ron has been shown to have both HGFL-dependent and HGFL-independent functions. Overexpression of Ron specifically in the mammary epithelium was sufficient to drive breast cancer, although, overexpression of Ron in the mammary epithelium of HGFL knockout mice produced tumors with a significant delay in mammary tumor formation (30). In this context, HGFL loss in the tumors altered cell signaling patterns, with decreased NF-κB activation and reduced β-catenin expression. It is interesting to note that genetic knockout of HGFL did not completely prevent tumor formation, indicating that there are HGFL independent functions of Ron that remain oncogenic when Ron is overexpressed. In another breast cancer study, HGFL independent functions of Ron were reported that enhanced cell spreading and survival (31). These reports suggest that Ron activation may function in the absence of HGFL possibly through a yet to be discovered ligand or through cross talk with other receptors. The ideal candidate as an alternative ligand for Ron would be HGF, however, despite having similar structural domains as HGFL, HGF does not appear to activate Ron (32). Ron activation through potential alternative ligand(s) is a current area of investigation. Receptor crosstalk has been reported between Ron and a number of receptors, such as c-Met (22), PDGFR-β (33), IGF1-R (34), Plexins (35) and EGFR (36), making receptor cross-talk another viable option to explain HGFL independent Ron oncogenic function.

2. Ron in Prostate Cancer

2.1 Ron-Dependent Signaling Mechanisms in Prostate Cancer

Numerous studies within the past decade have expanded upon the role of the Ron receptor in prostate cancer. Our group was the first to demonstrate that Ron is critical for prostate tumor growth (13, 37). We showed that whole-body genetic ablation of Ron signaling in the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) mouse model leads to decreased prostate tumor growth (37). Accompanying this research was the discovery of several tumor cell-intrinsic processes regulated by Ron to promote prostate cancer. Prostate tumors isolated from Ron-deficient TRAMP mice exhibited markedly increased tumor apoptosis

and decreased microvessel density compared with controls (37). Similarly, loss of HGFL in TRAMP mice led to increased prostate tumor cell death, and this was at least in part due to down regulation of a Ron-STAT3-Bcl2-dependent pro-survival mechanism (38). Thus, Ron signaling provides a survival advantage to prostate tumor cells. Interestingly, neither loss of Ron nor HGFL in TRAMP mice led to changes in tumor cell proliferation, whereas loss of Ron in the polyoma middle T antigen model of breast cancer led to a significant decrease in cellular proliferation (37–39). These studies suggest that Ron provides different oncogenic functions across cancers from different tissues.

Ron has also been identified as an important regulator of tumor-associated macrophages (30, 38, 40, 41). Whole-body loss of Ron signaling in mouse models of breast and prostate cancer leads to increased localization of F4/80-positive macrophages within tumors coupled with altered expression of macrophage activation markers (30, 38). This suggests Ron regulates macrophage recruitment and activation within the tumor microenvironment to promote cancer. As these *in vivo* studies cannot differentiate the contributions of Ron signaling in individual cell compartments to modulation of tumor-associated macrophages, further investigation into cell type-specific mechanisms is necessary to gain a full understanding of the complex roles of Ron in maintaining a pro-tumorigenic microenvironment.

2.2   Epithelial-Specific Roles for Ron in Prostate Cancer

Many studies have demonstrated the importance of epithelial-specific Ron signaling in supporting tumorigenesis in a variety of epithelial cancers. Loss of Ron signaling diminishes tumorigenic activities of several established and primary thyroid (42), colorectal (43–45), and pancreatic (46) cancer cell lines. Furthermore, epithelial-specific overexpression of Ron in the lung, breast, and pancreas induces adenocarcinomas with metastasis in mammary and pancreatic models (47–49). Recent work has similarly uncovered the functions of prostate cancer epithelial specific Ron signaling. Knockdown of Ron in human prostate cancer cell xenografts in immunodeficient mice revealed that loss of Ron in prostate tumor epithelial cells significantly reduces tumor growth (13). Conversely, overexpression of Ron in prostate epithelial cells is sufficient to induce prostate cancer in mice (50). Taken together, this work demonstrates that epithelial Ron expression promotes murine and human prostate tumor growth *in vivo*. Interestingly, Ron overexpression selectively within prostate epithelial cells was associated with changes in both cell proliferation and cell death (50). This contrast in phenotype between whole-body and cell type-specific modulation of Ron signaling may suggest Ron signaling across multiple cell types communicates within a tumor, however further examination is needed to delineate these mechanisms.

While the role of Ron in cancer cell metastasis has been characterized in several cancers, such as breast (12, 39, 49, 51–53) pancreatic (9, 34, 54), and lung (55), few studies have addressed the importance of Ron in prostate cancer cell migration, invasion, and metastasis. Initial *in vitro* studies have suggested an important role for epithelial Ron in regulating some of these phenotypes. Jiang *et al.* showed that inhibition of Ron activation with a neutralizing antibody reduced PC-3 cell migration while stimulation with recombinant HGFL increased cell migration (56). A second study revealed consistent results with these findings by

demonstrating that knockdown of Ron in PC-3 and DU-145 cells attenuates cell migration and invasion. Moreover, treatment with HGFL was sufficient to induce migration and invasion. In these models, ERK1/2 was shown to mediate HGFL-induced cell migration and invasion, suggesting this pathway plays a key role in Ron-mediated prostate cancer cell metastasis (57). These data suggest that epithelial Ron signaling is an important promoter of prostate cancer cell migration and invasion; however additional studies are needed to test the role of Ron in prostate cancer metastasis *in vivo* and expand upon the mediating mechanisms.

Prostate cancer epithelial-specific Ron expression has also been established as a key regulator of the tumor microenvironment. Ron in human prostate cancer cells positively regulates production of angiogenic chemokines through activation of NF-κB (13). Furthermore, Ron expression in these cells was deemed necessary for endothelial cell recruitment and prostate tumor vascularization. Studies performed using TRAMP mice support the role of Ron signaling in angiogenesis, as loss of Ron or HGFL leads to decreased prostate tumor microvessel density as measured by CD31 staining (37, 38).

2.3 Macrophage-Specific Roles for Ron in Prostate Cancer

Continuing the investigation into cell type specific functions for Ron has led to multiple discoveries regarding the role of Ron in macrophages to promote prostate cancer. Research has uncovered that Ron is expressed primarily on tissue resident macrophages and terminally differentiated macrophages, but Ron expression is markedly lower in circulatory monocytes (4, 58–61). This observation was also supported in prostate tumor tissue with Ron expression detected in tumor resident macrophages in an orthotopic model of prostate cancer (41). Using a model of breast cancer, Ron expression was connected specifically to a subset of tumor associated macrophages that express Tie2 (62). The significance of macrophage specific Ron expression for prostate tumor growth was first directly examined when mice harboring a myeloid specific deletion of the Ron tyrosine kinase domain (LysMCre TKf/f) were orthotopically injected with syngeneic murine C2RE3 prostate cancer cells. In this model, mice with a myeloid specific Ron loss developed significantly smaller prostate tumors and exhibited increased tumor cell apoptosis compared to transplantation into Ron proficient counterparts (41). Interestingly, prostate tumors in Lys-M-Cre TKf/f mice had an increase in the number of tumor-infiltrated macrophages. This observation was consistent with whole body loss of Ron signaling in both prostate and breast cancer murine models (30, 38), suggesting that macrophage-specific Ron expression is at least partly responsible for regulate macrophage tumor infiltration.

Research regarding Ron expression in macrophages has established that Ron is capable of promoting a M2 macrophage phenotype, as Ron expression promotes arginase expression and inhibits inducible nitric oxide synthase (iNOS) expression (30, 41, 62–64). Macrophage activation can be characterized as a continuum between M1 and M2, with M1 traditionally being inhibitory toward tumor growth and M2 being tumor promoting (65). M2 macrophages are anti-inflammatory in nature and are known to promote angiogenesis and matrix remodeling in cancer (65, 66). Thus, loss of Ron in macrophages suppresses the M2

phenotype and produces a macrophage that is capable of infiltrating tumors and suppressing tumor growth.

Macrophages are known to impact the function of other cells within the tumor microenvironment. Given that Ron in macrophages has been shown to suppress inflammatory responses in several injury and infection models, macrophage Ron signaling may play a crucial role in regulating the tumor microenvironment (7, 60, 67–70). Moreover, Ron activation in macrophages suppresses TLR4 signaling, which could limit the activation of neighboring immune cells within the tumor thereby suppressing tumor immune surveillance (71). Indeed, myeloid specific loss of Ron resulted in reduced cytotoxic T-cell function in prostate tumors (41). This result is consistent with what was observed in a murine model of breast cancer, where T-cells isolated from Ron signaling deficient mice had increased proliferation rates, increased expression of T-cell activation markers, and increased *in vitro* cytotoxicity when co-cultured with breast cancer cells. Furthermore, the increased cytotoxic T cell response seen in tumor-bearing Ron deficient mice was correlated with reduced tumor growth and metastasis (30). Taken together, these studies implicate Ron signaling in macrophages as a key regulator of the antitumor immune response.

2.4   Ron in Castration Resistant Prostate Cancer

Ron signaling had been established as a critical player in prostate cancer growth and development, but until recently the role of this signaling pathway had not been evaluated in the most deadly form of prostate cancer, Castration Resistant Prostate Cancer (CRPC). Ron mRNA and protein expression in patients was determined to be elevated in hormone refractory prostate cancer samples relative to hormone naïve samples (72, 73). Further, recent data from our laboratory has shown that Ron is functionally important for the development of castration resistance in several murine allograft and human xenograft mouse models (73). The ability of Ron to promote castration resistance is, at least in part, dependent on activation of β-catenin, NF-κB, and the androgen receptor. Activation of β-catenin through Ron in prostate cancer had yet to be detected, however, in breast cancer Ron has been shown to activate β-catenin for promotion of growth and in the regulation of cancer stem cells (49, 74, 75). Under androgen deprivation, Ron activation of the androgen receptor appears to be dependent on β-catenin and NF-κB. Interestingly, Ron has been reported to have differential effects on the androgen receptor depending on the presence or absence of androgens. When androgens are present, the relationship between Ron and the androgen receptor may be inhibitory (72). However, under androgen deprived conditions the relationship appears to be mutually active as Ron overexpression was shown to induce activation of the androgen receptor (72, 73) and re-expression of the androgen receptor in PC-3 cells was shown to induce transcription of Ron (72).

Understanding the differential effects of Ron on the androgen receptor is critical for the treatment of patients with CRPC, because the majority CRPCs have low levels of androgens due to treatment with androgen deprivation therapy. Additionally, several androgen receptor variants have been uncovered which play pivotal roles in prostate cancer, most notably AR-variant 7 (76). Further studies should focus on determining if Ron expression alters androgen receptor variant expression, and if so under what conditions. Moreover, reports

have shown that macrophage androgen receptor expression plays an important role in the development/initiation of prostate cancer (77). With this information, understanding the impact that Ron inhibition may have on macrophage function and on androgen receptor signaling in during the treatment of CRPC patients may prove to be crucial. CRPC is a devastating disease with limited treatment options and these initial studies established the scientific underpinnings for targeting Ron in CRPC.

3 Available Therapeutic Options for RON

3.1 Small Molecules

Possessing an intracellular kinase domain has made targeting Ron with a small molecule inhibitor (SMI) a realistic possibility. As such, several inhibitors have been developed that show efficacy against Ron. Specifically, Foretinib (EXEL-2880) is a SMI with high specificity against Ron, c-Met, and VEGF and was shown to reduce proliferation in cancer cells (78). A clinical trial with Foretinib has yet to be completed for prostate cancer; however, a phase II clinical trial was completed in Triple Negative Breast Cancer showing a clinical benefit rate of 46% (79). Recent pre-clinical work in prostate cancer cell lines indicates that Foretinib treatment may be beneficial in prostate cancer as treatment suppressed metastasis and reversed epithelial to mesenchymal transition (57).

Another intriguing SMI is the compound known as ASLAN002/BMS-777607. ASLAN002 is a dual Ron/c-Met tyrosine kinase inhibitor, but is one of the few compounds available that has preferential action against Ron over c-Met (80). A phase 1 clinical trial of ASLAN002 recently completed in patients with metastatic solid cancers and showed that the inhibitor is well tolerated and suggested that a phase 2 clinical trial begin with the treatment of 300mg twice daily (81). Recently, preclinical work from our laboratory with ASLAN002 illustrated that treatment in combination with castration therapy for castration resistant prostate tumors in a murine model of CRPC inhibits tumor growth (73). Additionally, bone metastases are frequent occurrences in metastatic prostate cancer patients and work by Andrade *et al* showed that treatment with ASLAN002 limits cancer-mediated bone destruction in murine models (82). The numerous reports demonstrating that ASLAN002 is safe and possibly effective at treating prostate cancer warrants further clinical study regarding use of this compound in prostate cancer patients.

A more recently developed inhibitor for Ron/c-Met is Merestinib/LY2801653 (83). Preclinical work with this compound showed its ability to inhibit cancer cell proliferation and cell scattering, and showed potent in vivo antitumor effects in xenograft mouse models (83). Merestinib recently completed a phase 1 clinical trial to determine tolerability in humans and the results have yet to be released (trial I3O-MC-JSBA, NCT01285037). Each of these SMI compounds targeting Ron has the potential to benefit prostate cancer patients. However, knowing that Ron promotes prostate cancer through its expression in both epithelial cells and macrophages, further research into how treatments should be targeted in patients is warranted.

3.2 Antibodies

A number of monoclonal antibodies have been generated toward the Ron receptor, with some making progress in clinical trials. Monoclonal antibodies against Ron can be used to directly target Ron signaling in cancer or they can be fused to a cytotoxic agent and used to guide that agent toward the tumor with Ron overexpression. Narnatumab/IMC-RON8 is a fully humanized monoclonal antibody that binds with high affinity to Ron, subsequently preventing the association of Ron with HGFL. A phase 1 clinical trial of Narnatumab has completed, determining that Narnatumab is well tolerated and provides limited antitumor activity (84). This study produced less than ideal results, however, with only 1 patient reaching the trough concentration at which Narnatumab produced antitumor activity in animal models.

A different approach to target Ron has been used by M.H. Wang's group, where these investigators developed three antibodies that target the Maturation Required Sequence of Ron located on the extracellular domain of this receptor. These antibodies are known as Zt/g4, Zt/f2, and Zt/c9 and rather than preventing ligand binding, this interaction induces receptor internalization and degradation (45, 85, 86). The induction of receptor internalization has been exploited by this group as a means to transport cytotoxic compounds inside the cell. These antibodies have been successfully coupled to doxorubicin, 5-fluorouracil, Gemcitabine, as well as other compounds, and have show preclinical efficacy (45, 85, 87). These proofs of concept studies establish the utility of Ron antibodies in cancer therapy, although none of these current antibodies have been tested in preclinical models for the treatment of prostate cancer. Furthermore, no studies have examined the impact of antibodies targeting Ron in the epithelial versus macrophage compartments.

4. The Outlook of Ron in Prostate Cancer

Significant progress has been made detailing the important role of Ron in prostate cancer since Ron was initially discovered. This progress has laid a solid groundwork for future studies to catapult the idea of the treatment of Ron signaling for prostate cancer into mainstream therapeutics. New areas of research will need to focus on the different possibilities for Ron to be used as a biomarker and the mechanism for directly targeting Ron in patients with prostate cancer. As a biomarker, plasma levels of HGFL have already been shown to correlate with prostate cancer progression and Ron expression shown to correlate with Gleason score and response to hormone therapy (72, 88). As a direct target, several compounds outlined previously are already available to begin testing in patients. Additionally, a major problem with treating prostate tumors is that they are known to have low immunogenicity, making many immunotherapies ineffective. Knowing that macrophage loss of Ron impacts macrophage infiltration and alters T-cell function provides a basis for changing that constraint. Although not in prostate cancer, it has recently been shown that Ron inhibition in breast cancer enhances response to anti-CTLA-4 immunotherapy in murine models (89). This suggests that Ron inhibition may be able to suppress antitumor immunity in prostate cancer to increase immunogenicity and sensitize tumors to immunotherapies.

With the number of studies demonstrating that Ron can impact the prostate tumor microenvironment, it is imperative to determine what role the tumor microenvironment plays in regulating castration resistant prostate cancer. Specifically, Ron has been shown to alter endothelial cells, macrophages, and T-cells of the prostate tumor microenvironment making these cell types a primary focus. If Ron produces significant changes to the tumor microenvironment to promote CRPC, then coupling Ron to other therapies, such as immunomodulatory agents, may prove effective in Ron overexpressing CRPC tumors. Lastly, as Ron has been linked to therapeutic resistance in prostate cancer, and Ron has been shown to regulate stemness in breast cancer, studies should be performed which focus on the ability of Ron to regulate stemness in prostate cancer to drive therapeutic resistance. Producing research focused in these areas will enhance our ability to discern what patients will benefit from Ron directed therapy and what method will be best suited for targeting Ron in prostate cancer.

Acknowledgments

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