

Review Article

The Role of Mineralocorticoid Receptor Signaling in Genitourinary Cancers

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Abstract. A steroid hormone receptor, mineralocorticoid receptor (MR), is well known to play a critical role in maintaining normal homeostasis in the body primarily via regulating ionic and water transports. Indeed, MR antagonists have been prescribed to the patients as diuretic drugs. Meanwhile, emerging evidence has indicated that MR signaling, with or without functional interplay with glucocorticoid receptor or androgen receptor, contributes to modulating the development and progression of several types of neoplasms including genitourinary malignancies. This review summarizes the available data suggesting the involvement of MR signaling in renal cell carcinoma, prostatic adenocarcinoma, urothelial carcinoma, and other malignancies, and highlights potential underlying molecular mechanisms.

Keywords: Antagonists; mineralocorticoid receptor; prostatic adenocarcinoma; renal cell carcinoma; urothelial cancer.

1. Introduction

In spite of considerable advances in diagnostic technologies as well as treatment strategies, the prognosis for patients with genitourinary malignancy, such as renal cell carcinoma, prostatic adenocarcinoma, or urothelial carcinoma, remains largely unimproved during the last few decades. Further research is therefore required to better understand the molecular mechanisms responsible for the development and/or progression of genitourinary cancers. This may in turn provide novel targeted therapy.

In addition to various known risk factors for genitourinary neoplasms, some intrinsic factors have been demonstrated to involve their tumorigenesis. Specifically, a steroid hormone receptor, androgen receptor (AR), is known to be a crucial transcriptional regulator in prostate cancer and still represents its central therapeutic target [1, 2]. Recent

studies presumably conducted based on striking sex-specific differences in the incidence of renal cell carcinoma and urothelial carcinoma [3] have also indicated an important role of AR signaling in their outgrowth [2, 4, 5]. Similarly, another steroid hormone receptor, glucocorticoid receptor (GR), has been shown to function as a tumor suppressor in several types of malignancies, especially in castration-resistant prostate cancer [6, 7]. Moreover, the functional interplay between AR and GR signals has been documented [6–10].

The mineralocorticoid receptor (MR) also belongs to the steroid-inducible transcriptional factor superfamily. Clinically, MR antagonists, such as spironolactone, eplerenone, canrenone, finerenone, and mexrenone, have been used as diuretic agents for the treatment of, for example, hypertension, heart failure, chronic kidney disease, and primary aldosteronism [11]. It is noteworthy to mention that

not only mineralocorticoids but also some of glucocorticoids (primarily as agonists) and other steroids, including progesterone (as an antagonist), have binding affinity for the MR [12, 13]. Specifically, natural glucocorticoids, such as cortisol and corticosterone, and some of synthetic glucocorticoids clinically used, such as prednisone and prednisolone, have relatively strong and weak mineralocorticoid potency, respectively, while other potent synthetic glucocorticoids, including dexamethasone and betamethasone, have no or little agonist activity at the MR [14]. Additionally, spironolactone possesses anti-androgenic and progestational activities via binding to the AR and progesterone receptor (PR), respectively, while other steroidal anti-mineralocorticoids, particularly eplerenone and finerenone, specifically bind to the MR [12]. Meanwhile, emerging evidence has suggested that mineralocorticoids and MR antagonists contribute to modulating the development and progression of various types of malignancies. In this article, we review the available data indicating the involvement of MR signaling particularly in genitourinary cancers and discuss potential underlying molecular mechanisms.

2. Mineralocorticoids, MR, and Their Physiological Functions

Mineralocorticoids are a class of corticosteroids, including aldosterone which is the major physiological mineralocorticoid. As is the case with other steroid hormone receptors, the MR undergoes conformational changes upon binding to ligands, dissociates from the heat-shock proteins, homodimerizes, and translocates to the nucleus where it directly interacts with various hormone response elements in the promoter of target genes, resulting in the regulation of their transcription [13] (see Figure 1). Downstream targets/pathways of MR signaling include serum and glucocorticoid-regulated kinase 1 (SGK1), angiotensin II receptor type 1 (AGTR1), and insulin-like growth factor-1 receptor (IGF1R), as well as epidermal growth factor receptor (EGFR)/mitogen-associated protein kinases (MAPK)/phosphatidylinositide 3-kinases (PI3K)/Akt and protein kinase C- ϵ (PKC ϵ) [13]. The transcriptional activity of the MR has been shown to be regulated by various interacting proteins (*i.e.* co-regulators comprising co-activators and co-repressors) a subset of which specifically binds to the MR and others of which function as common mediators of the nuclear receptor superfamily [15, 16]. The MR is also known to functionally interact with GR, and the heterodimer regulates transcriptional responses [*e.g.* FK506-binding protein 5 (FKBP5), PER1] different from those mediated by MR homodimers [13, 17]. In addition, the functions of the MR versus GR (or AR) in cells expressing both receptors appear to be complex and are influenced by the availability of steroids that selectively bind to only one receptor or two receptors [12, 13].

The MR is expressed in a variety of normal tissues, such as the kidney, heart, colon, brain, and adipose tissue, whereas

gene profiling by microarray analysis has demonstrated that MR expression is generally low or rarely observed across the panel of 60 cancer cell lines, including those derived from the kidney, colon, and central nervous system [18]. Physiologically, activation of the MR by binding of aldosterone leads to the induction of the expression of molecules that regulate ionic and water transports mainly via sodium channels, sodium-potassium pump, and SGK1. This results in the reabsorption of sodium and subsequent increases in extracellular volume and blood pressure, as well as potassium excretion. Thus, mineralocorticoid-mediated MR signals play a key role in maintaining normal homeostasis in the body. In addition, diverse functions of the MR involving the modulation of inflammatory responses, oxidative stress, and steroid biosynthesis, as well as apoptosis, cell adhesion and migration, and fibrosis/epithelial-to-mesenchymal transition (EMT), in non-neoplastic cells, have been suggested [13, 19–21]. Aldosterone has also been shown to modulate the expression of vital molecules, such as cyclooxygenase (COX)-2 [13, 22], in normal tissues.

3. MR Signaling and Renal Cancer

The expression of the MR has been demonstrated in the distal nephrons, particularly principal cells and some subtypes of intercalated cells, in non-neoplastic kidneys [23, 24]. Correspondingly, an immunohistochemical study showed that MR signals were detected in 18 (90%; 1+: 5 cases; 2+: 5 cases; 3+: 8 cases) of 20 chromophobe renal cell carcinomas and 13 (95%; 1+ 5 cases; 2+: 5 cases; 3+: 3 cases) of 14 renal oncocytomas, but in none of 84 clear cell renal cell carcinomas or 14 papillary renal cell carcinomas [23]. In this study [23], however, the relationship between the levels of MR expression in chromophobe renal cell carcinomas and their clinicopathological characteristics (*e.g.* tumor stage, prognosis) was not assessed. Clear cell renal cell carcinomas were confirmed to exhibit extremely low levels of MR gene expression by a quantitative polymerase chain reaction method [23]. A study, using ligand binding assays, also displayed significantly lower binding activities of [³H]-aldosterone in renal “adenocarcinoma” than in non-neoplastic normal renal tissue [25]. Two other studies showed that MR gene expression was further down-regulated in advanced stages of clear cell renal cell carcinoma [26, 27]. In one of the studies [27], low expression of the MR gene was shown to associate with worse outcomes in all patients ($n = 181$; progression-free survival: $P < 0.001$; overall survival: $P < 0.001$), those with pT1 disease ($n = 108$; progression-free survival: $P = 0.033$; overall survival: $P = 0.007$), or those with \geq pT2 disease ($n = 73$; progression-free survival: $P = 0.006$; overall survival: $P = 0.023$). Multivariate analysis further identified low MR expression as a prognosticator for progression [hazard ratio (HR) = 1.71, $P = 0.051$] and overall survival (HR = 2.21, $P = 0.014$) [27]. In addition, the expression of 11 β -hydroxysteroid dehydrogenase type II,

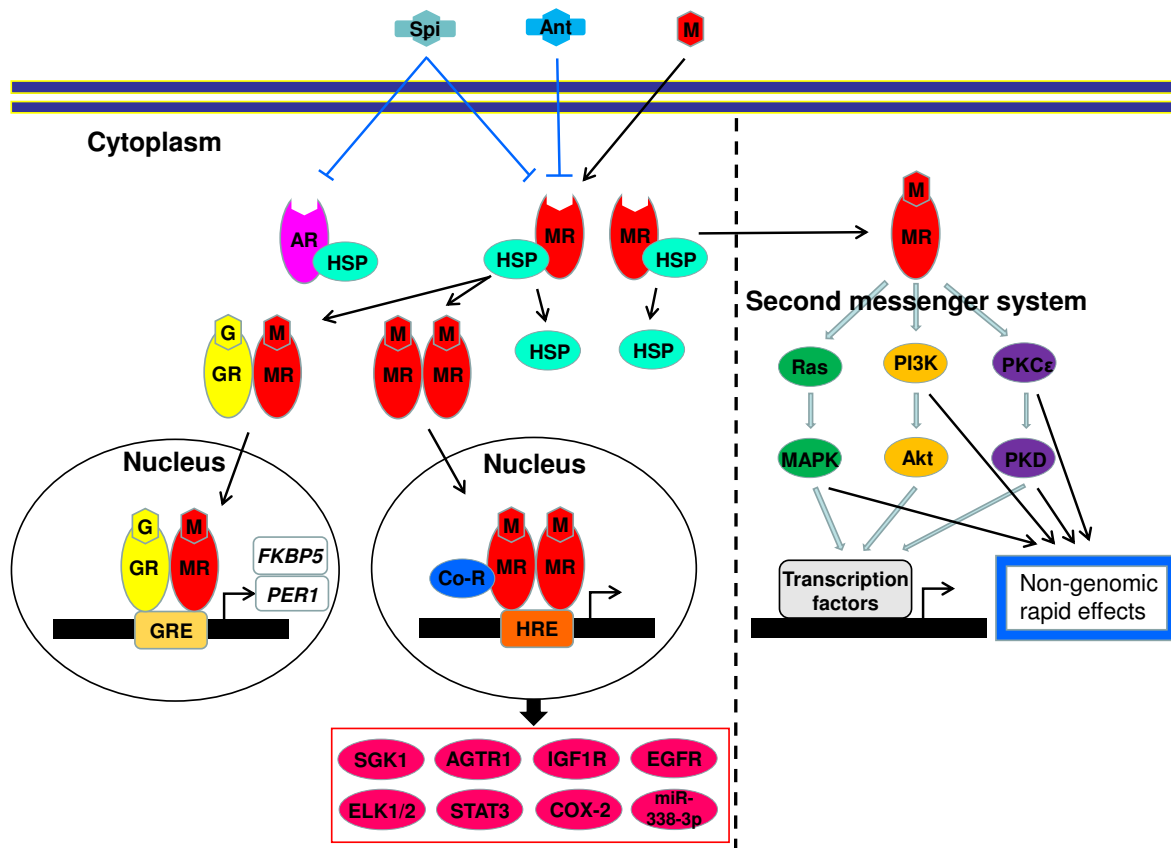


Figure 1: Schematic illustration of mineralocorticoid receptor-mediated signaling pathways particularly in neoplastic cells. Ant, mineralocorticoid receptor antagonist; AR, androgen receptor; C, corticosteroid; Co-R, co-regulator; G, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HRE; hormone response element; HSP, heat shock protein; MR, mineralocorticoid receptor; Spi, spironolactone.

an enzyme which prevents glucocorticoid binding to the MR by converting cortisol to cortisone, has been detected in 2% of clear cell renal cell carcinomas, 0% of papillary renal cell carcinomas, 95% of chromophobe renal cell carcinomas, and 100% of renal oncocytomas [23].

The microarray gene profiling analysis revealed that 2 of 6 renal cancer cell lines moderately expressed the MR, while other 4 showed low/negative expression [18]. In cell line models, the impact of MR activation on tumor growth has been assessed. Inconsistent with MR expression data in surgical specimens, treatment with spironolactone significantly inhibited cell proliferation of a clear cell renal carcinoma line RCC4 [28], although the suppressive effect of spironolactone through the AR pathway could not be completely excluded. Moreover, in multiple renal cancer cell lines, aldosterone up-regulated and spironolactone down-regulated the expression of K-RAS4A [28] which is known to control cell proliferation potentially via the EGFR/PI3K/Akt pathway. These *in vitro* findings suggest a stimulatory role of MR signaling in renal cell carcinoma. By contrast, a more recent study showed that overexpression of MR in 786-O and

ACHN renal cancer lines resulted in significant inhibition in cell proliferation, migration, and invasion, as well as tumor growth in xenograft-bearing mice along with the increased expression of Ki-67, EZH2, and CD31 [27].

Epidemiological evidence indicates that hypertension represents an established risk factor for renal cancers, especially clear cell renal cell carcinoma [29, 30]. Furthermore, this elevated risk has been shown to associate with the activity of the renin-angiotensin-aldosterone system (RAAS) [28]. Indeed, in a retrospective study involving 5,207 patients, suppression of the RAAS by angiotensin-converting enzyme (ACE) inhibitors ($n = 1,559$) for the treatment of hypertension reduced the risk of developing renal cancer (HR for incidental tumor = 0.72; HR for fetal tumor = 0.65), whereas other anti-hypertensive agents, including calcium-channel blockers ($n = 1,416$), diuretics ($n = 2,099$), and β -blockers ($n = 2,681$), exhibited no significant impact on the risk (HR for incidental tumor = 1.10; HR for fetal tumor = 1.03) [31]. An *in vivo* experiment using a mouse xenograft model for renal cancer supported the observations in the cohort study by demonstrating the suppressive effect

of ACE inhibition on tumor growth [32]. Thus, conflicting evidence exists as to whether activation of MR signaling is associated with the promotion versus suppression of the development/progression of renal cell carcinoma.

4. MR Signaling and Prostate Cancer

A population-based retrospective case-control study involving 48,984 men with hypertension was recently conducted to compare the risks of developing prostate cancer in those treated with 6 types of anti-hypertensive drugs, including ACE inhibitor, angiotensin II receptor blocker, calcium channel blocker, diuretics, spironolactone, and thiazole [33]. Of these medications, spironolactone was found to significantly reduce the incidence of prostate cancer [odds ratio (OR) = 0.88; $P < 0.001$]. These observations may suggest that MR inactivation results in the inhibition of prostate carcinogenesis, while anti-tumor properties of spironolactone via the non-MR pathway (e.g. retinoid X receptor γ (RXR γ) [34], AR) have been separately indicated. Meanwhile, MR protein expression was confirmed in all 4 human prostate cancer cell lines examined [35]. MR gene expression was shown to be comparable between normal prostate and prostate cancer tissue specimens [35] and was detected 1 of 2 lines included in the cell panel for the expression profiling [18].

In contrast to epidemiological evidence described above [33], MR antagonists, including spironolactone and eplerenone, were shown to induce the proliferation of AR-dependent LNCaP prostate cancer cells, while a non-steroidal antagonist PF-03882845 had no significant effects on their growth [36]. Additionally, in prostate cancer xenograft-bearing mice resistant to the treatment with an ERG inhibitor, the expression of the MR and its target genes, such as *FKBP5*, *SGK1*, *TNSI*, and *TSC22D3*, was significantly up-regulated [37]. These conflicting data suggest that MR activation is associated with the suppression or induction of prostate cancer progression.

MR signals have also been suggested to modulate sensitivity to an AR signaling inhibitor enzalutamide that is often used for the treatment of castration-resistant prostate cancer. In AR-positive castration-resistant prostate cancer cell lines, aldosterone treatment significantly induced the cytotoxic effects of enzalutamide [35]. Correspondingly, MR knockdown via siRNA transfection in C4-2 prostate cancer cells resulted in considerable reduction in sensitivity to enzalutamide as well as enzalutamide-mediated apoptosis, although cell proliferation without enzalutamide treatment was similar between control-siRNA and MR-siRNA sublines [35]. Interestingly, in this study [35], MR knockdown was also found to significantly increase the expression of AR gene and a downstream target *prostate-specific antigen* gene, suggesting potential interplay between MR and AR signals in prostate cancer cells.

Another anti-androgenic medication abiraterone acetate has been given to patients with metastatic castration-resistant

prostate cancer, usually in combination with prednisone or prednisolone in order to protect from abiraterone-induced mineralocorticoid excess. A recent retrospective study [38] demonstrated clinical evidence suggesting that prednisone can be replaced with eplerenone (50 mg/day) which effectively prevents the adverse effects related to mineralocorticoid excess. Meanwhile, there was no significant difference in the prognosis between prostate cancer patients treated with abiraterone plus prednisone versus eplerenone. However, this study provides no real insight into the possible role of MR in prostate cancer progression.

5. MR Signaling and Bladder Cancer

A case-control study described above [33] additionally showed a significantly lower risk of developing bladder cancer in female patients treated with spironolactone (OR = 0.81, $P < 0.001$), but not in male patients (OR = 1.03, $P > 0.05$), implying a suppressive role of MR antagonists in the development of urothelial cancer. However, this effect of spironolactone might be mediated through the AR pathway whose activation is known to induce urothelial tumorigenesis [5] or the modulation of RXR γ [34], although no significant effect in male patients is unexplainable.

It has been documented that the expression of the MR gene is down-regulated in bladder cancer [39]. To the best of our knowledge, however, there are no preclinical studies assessing the impact of MR activation/inactivation on the development and progression of urothelial cancer. Instead, various glucocorticoids even with similar glucocorticoid potency have been shown to have differential effects on the growth of bladder cancer cells [10, 40]. Because natural or synthetic glucocorticoids have mineralocorticoid activities with varying degrees, these findings may imply the involvement of glucocorticoid-mediated MR signaling in bladder cancer progression. Further studies are required to confirm whether mineralocorticoids and/or anti-mineralocorticoids modulate the growth of urothelial cancer cells via the MR pathway.

6. MR Signaling and Non-urological Cancers

Previous studies have indicated the involvement of MR signaling in several non-urological malignancies, including breast, colorectal, liver, and lung cancers. The down-regulation of MR gene expression in some of these malignancies has also been documented [39, 41, 42], suggesting its function as a tumor suppressor. In addition, loss of the MR gene locus was detected in a subset of leukemias [43]. Prognostic significance of MR expression in liver [42] and lung [44] cancers have also been reported. By contrast, it was demonstrated that the expression levels of the MR gene were higher in lymph node-positive cervical cancers than in NO tumors [45], implying tumor progression promoted via MR activation.

In a breast cancer line, aldosterone inhibited cell proliferation in a dose-dependent manner, increased/decreased the proportion of cells at G1-G0/S phases, respectively, and induced cell adhesion [46]. Another study using leukemia cells showed that aldosterone could antagonize the stimulatory effect of an MR antagonist ZK91587 at low doses (e.g. 0.3-0.75 μM) on their proliferation, while aldosterone alone at 10 μM did not significantly inhibit cell growth [47]. MR overexpression/silencing in liver cancer lines was also shown to result in decreases/increases in cell proliferation and xenograft tumor growth, as well as increases/decreases in apoptosis, respectively, via regulating the expression of miR-338-3p [42]. Furthermore, in liver cancer cells, miR-766 was found to induce their proliferation and metastasis by targeting the MR [48]. Similarly, in pancreatic cancer cells, miR-135b-5p promoted their migration and invasion as well as EMT by targeting the MR [49]. An inverse association between MR activity and angiogenesis via the expression of vascular endothelial growth factor receptors has also been indicated in colorectal cancer [41, 50].

7. Conclusions

Physiological functions of MR signaling have been much more extensively investigated. While MR antagonists, including spironolactone, have been clinically used primarily as diuretic agents, the involvement of MR signaling in the development and/or progression of neoplastic diseases remains far from being fully understood. Nonetheless, most of clinical/preclinical findings currently available suggest the role of MR as a tumor suppressor. This is supported by MR expression data indicating its down-regulation in several types of malignancies, compared with corresponding non-neoplastic tissues. However, it needs to be considered whether the cell type of origin of the tumor expresses the MR and whether MR expression or its loss is a bystander effect rather than a driver.

Figure 1 illustrates the current knowledge on the activation of MR and related signaling pathways in cancer cells. Accordingly, clinical use of MR antagonists may be harmful to cancer patients in terms of their unfavorable effects on tumor progression. However, conflicting evidence indicates that inactivation of MR or treatment with MR antagonists is associated with the inhibition of tumor growth. Anti-tumor activities of MR antagonists via the non-MR pathways have also been suggested. Moreover, the close relationship between the MR and GR/AR/PR suggests possible mechanisms including overlapping interactions where changes in co-regulators or pioneer factors may modulate responses at the genomic or signaling levels, with gain of function or perhaps assumption of function in some “very hormone-dependent” cancers. Further investigation of MR signals and MR agonists/antagonists, as well as their interplay with other signaling pathways, is thus necessary to precisely determine the functional role of mineralocorticoids/MR in

genitourinary and non-urological malignancies, which may in turn provide novel preventive and/or therapeutic options against these diseases.

Competing Interests

The authors declare no competing interests.

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